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PARTICIPATION IN ACTIVITY AND RISK FOR INCIDENT DELIRIUM

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Abstract

Objectives—To examine the mediating role of activity participation between educational attainment and risk for incidence delirium; and to examine the contribution of participation in specific activities to the development of delirium.

Design and Setting—Prospective cohort study. An urban teaching hospital in New Haven, Connecticut, USA.

Participants—Drawn from two prospective cohort studies of 779 newly hospitalized patients aged 70 and older without dementia.

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Author Contributions:

Under the direction of RNJ, FMY constructed the research questions, designed the study, conducted the analyses, and wrote each draft of the manuscript until completion for submission; SKI provided the initial idea, designed and acquired the data, provided guidance and interpretation of the analyses, and edited each draft of the manuscript. MAF, ERM, and DKK all contributed to the editing of each draft of the manuscript. RNJ revised each draft critically for important intellectual content, particularly with regards to methodology. All authors have read and approved the final manuscript.

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None.

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Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x
Personal Relationship		x		x		x		x

Authors can be listed by abbreviations of their names.

Measurements—The main outcome was delirium measured by the full Confusion Assessment Method (CAM) algorithm, which consisted of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness, as rated by trained clinical interviewers.

Results—Bivariable results indicated a significant relationship between both education and the development of delirium (odds ratio, 0.92 [95% confidence interval (CI), 0.88 to 0.97], and between activity and delirium (odds ratio, 0.60 [95% CI, 0.46 to 0.79]. In multivariable analysis, activity mediated the relationship between education and risk for delirium. Considering each activity separately, multivariable logistic regression analysis showed that regular exercise significantly lowered the risk for developing delirium (odds ratio, 0.76 [95% CI, 0.60 to 0.96].

Conclusion—Among older persons without dementia, activity participation before hospitalization is a mediator between education and incidence of delirium. Specifically, we found that participation in regular exercise was found to be significantly protective against delirium.

Keywords

delirium; acute confusional state; activity; exercise; cognitive reserve

INTRODUCTION

Delirium is a common, life-threatening clinical syndrome that is preventable. The prevalence of delirium at hospital admission is between 14 to 24 percent, and the incidence of delirium ranges from 6 to 56 percent after hospital admission.¹ Delirium is associated with poor outcomes, such as longer hospital stays, institutionalization, and death, which are costly for the patient, caregivers, hospitals, and the federal government.^{1,2} Given its high prevalence and incidence, and its association with poor outcomes, finding mechanisms to prevent delirium remains a high priority.

Recent findings suggest that older hospitalized patients with higher educational attainment are at a reduced risk for developing delirium, which can be explained by cognitive reserve theory.^{2,3} Cognitive reserve refers to the capacity of the mature adult brain to buffer the effects of neurological disease or injury. Factors that have been hypothesized to enhance cognitive reserve include measures such as higher educational attainment, higher occupational status, higher intelligence scores, and higher literacy levels.⁴ Observational studies have suggested that persons with higher educational levels are more resistant to dementia.⁵ The neuroprotective effects of cognitive reserve may be important in acute cognitive impairment, like delirium, as well as in more chronic states, like dementia.

There are no studies to date that have examined the role of activities in delaying the clinical manifestations of delirium under the cognitive reserve theory. However, cognitive reserve and physical activity have been studied extensively in patients with dementia and Alzheimer's disease.⁶ Given that delirium and dementia demonstrate substantial overlap and pathophysiological similarities in cholinergic deficiency and cerebral metabolism,^{1,7} the role for physical activity in delirium would not be surprising. Previous studies provide some preliminary evidence to support the relationship between activity and delirium before and during hospitalization among patients admitted to surgical⁸ and medical services.^{9,10} Before surgery, Marcantonio and colleagues⁸ used the Specific Activity Scale (SAS)¹¹ to find a three-fold greater odds of developing delirium among patients with limited physical functioning than those with higher physical functioning. During hospitalization, lower delirium rates have been found among older patients who adhere to a multicomponent intervention.⁹ Inouye and colleagues¹⁰ found that higher adherence to performing physical activities or the mobility

intervention (walking and active range-of-motion exercises) and cognitively stimulating activities (therapeutic activities) three times daily significantly reduced the risk of delirium.

In this study, we examine the effects of education and self-reported participation in activities and the risk for delirium among newly hospitalized older adults without dementia. Our aims were: 1) to examine whether the relationship between education and delirium was mediated by activities; and 2) to examine the contribution of participation in specific activities to the development of delirium.

We hypothesized that the level of physical, social, and cognitive activities mediate the protective effect of education against delirium. In addition, we predicted differential effects of specific activities on the risk for delirium in older adults without dementia. Previous literature supports hypotheses that both cognitively stimulating activities and exercise promote optimal cognitive functioning.

METHODS

Setting and Patients

This study utilized the most current data available, collected between 1989 to 1998, with both a standardized rating for delirium status and indicators for activity participation in an older cohort without dementia. Participants were from the New Haven, Connecticut area, and drawn from two different studies that are described in detail elsewhere,^{9,12} but are briefly noted below. While there were some baseline difference between the two cohorts, combining the samples appeared justified due to the similarities in the aims, inclusion and exclusion criteria, and study methods. Both studies were approved by the institutional review board of Yale University School of Medicine to obtain informed consent for participation from the patient, or those with significant cognitive impairment, from the closest relative or legal guardian.

The first study consisted of 525 medical patients aged 70 and older admitted to an acute care hospital in New Haven, Connecticut during the period of November 1989 through July 1991. Patients who were enrolled in the study were evaluated at admission and discharge, and on alternate days throughout their hospital stay for the presence of delirium using the full Confusion Assessment Method (CAM) criteria.¹³ For this analysis, we excluded those with dementia at baseline (N=105). We also excluded patients who refrained from answering one or more activity questions (N=15), yielding a final sample of 404 hospitalized older adults.

The second study included 469 persons (aged 70 years and older) admitted to the general medicine service of the same hospital, between March 1995-April 1998.⁹ Patients were assessed daily until discharge for the presence of delirium using cognitive assessment and the full CAM instrument.⁹ As in the first study, we excluded 92 older adults with dementia (19.6%) and 2 adults who refrained from answering one or more activity questions (0.4%), resulting in 375 older adults available for the analysis.

We excluded those with dementia at baseline to minimize its confounding effects and allow us to isolate the effects of education and activity on delirium. Moreover, older adults with dementia at hospital admission were excluded from the analysis because there was a significantly higher proportion who participated less than one time per month in each activity, except for attending religious services, than those who did not have dementia. This secondary analysis pooled the two studies described above, in order to increase the power of the current study, as shown in our previous study.³

Primary Outcome Measure

Delirium Assessment—The full CAM algorithm was used to determine the presence of delirium, which consisted of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness, as rated by trained clinical interviewers. Each of these features was rated by the interviewers based on observations made during their structured interviews and cognitive assessment, which included the Mini-Mental State Examination¹⁴ and the digit span test.¹⁵ The CAM instrument provided a standardized rating for delirium, which has been validated against geropsychiatric diagnoses, with a sensitivity of 94–100% and specificity of 90–95%.¹³

Definitions of Study Variables

Sociodemographic variables and Charlson comorbidity index—In addition to age (centered at mean age of 79.6 in analytic models) and sex (reference group is men), level of educational attainment was collected from the patients during baseline interviews conducted within 48 hours of hospital admission. Patients were asked to report on the total years of formal education that they completed. Educational attainment was treated as a continuous variable in our analytic models representing years of education. Comorbidity was characterized with the Charlson comorbidity index, a weighted sum of comorbid illnesses, which was categorized as scores of 0, 1, and 2 or higher.¹⁶

Activity—Patients were asked the following stem question for 11 specific activities: “Think back to a typical month before your current illness, and tell me how often you have done each of these things. How many times during a typical month have you...?” The specific activities are shown in Table 3. We excluded the “other than watching TV” activity category because it provided no information about activity patterns and was not highly correlated with the rest of the 10 specific activities. These items were adapted from ones used in the New Haven Epidemiological Population Studies of the Elderly.¹⁷ The respondent’s answers were scored as graded responses (0, less than 1 time per month; 1, 1–4 times per month; and 2, more than once a week).

Statistical analyses

The analysis took place in three steps using the Mplus version 4.1 software.¹⁸ First, we examined the factor structure of the activity indicators using both exploratory factor analysis (EFA) and confirmatory factor analysis (CFA).¹⁹ EFA and CFA models were conducted using polychoric correlation coefficients and the weighted least squares mean and variance adjusted (WLSMV) estimator. Model fit was assessed with the root mean square error of approximation (RMSEA)²⁰ and the comparative fit index (CFI).²¹ The RMSEA provides a measure of discrepancy per model degree of freedom (df) and approaches zero as model fit improves, with adequate model fit suggested at values less than 0.06.²² The CFI ranged between 0 and 1; values greater than 0.95 generally indicate adequate model fit.²³ Other, more commonly used fit indices for structural equation modeling (SEM) applications are not currently available for models that include ordinal dependent variables.²⁴

We performed SEM to examine whether the activity factor mediates the relationship between educational attainment and delirium while adjusting for the background variables of age, sex, and comorbidity. Mediation analyses give an estimate of the strength and significance that a variable (or mediator) explains the relationship between an independent and dependent variable.²⁵ For instance, mediation of activity and delirium by education is determined by comparing the effect of path c with (Model 5) and without path a (Model 4) (Figure 1). We first examined two separate logistic regressions models: Model 1 was a bivariable regression between education and the risk for developing delirium; and Model 2 was the risk for developing delirium regressed on latent activity. The latent activity variable is continuous,

indicated by the 10 categorical activity items within a factor analytic model, measured by per standard deviation (SD) increase. In Model 3, we estimate both education and activity as predictors for the risk of developing delirium; Model 4 added the background variables (age, sex, and the Charlson comorbidity index) to Model 3. Model 5 was the mediation analysis using multivariable regression of Model 4 with a simultaneous estimation of the pathway between education and the risk for delirium development through activity. That is, both delirium and latent activity are viewed as dependent upon educational attainment.

Finally, we used logistic regression to examine the odds ratios for the graded response of individual activities in predicting the cumulative risk for delirium. First, we examined 10 separate multivariable logistic regression models for each individual activity on the risk for developing delirium, while controlling for sociodemographic characteristics and comorbidity. For example, we regressed delirium on only the “exercise regularly” activity, while controlling for age, gender, education, and comorbidity. Then, while we controlled for these same variables, we regressed delirium on only the “garden or yard work” activity. The final equation (Model 2) was also a multivariable logistic regression, but consisted of the risk for developing delirium regressed on all ten activities and control variables. All analyses were conducted using the maximum likelihood estimator.

RESULTS

Patient characteristics are presented in Table 1. In both studies, the age range of the participants was 70 to 99 years old. The range of education across studies was no formal education (zero or unknown years of education) to graduate level (20 years of education). Patients with missing values for educational attainment were included in the lowest educational level, since they often had no formal education in the United States. Alternative methods for handling this missing information were explored (imputing the mean and maximum likelihood estimation methods), and these alternative approaches did not affect the results.³ The majority (65%–68%) had a Charlson comorbidity score of 2 or greater,¹⁶ indicating a high degree of comorbidity as expected in a hospitalized older sample.

The single factor CFA model fit statistics ($\chi^2 = 82.36$, $df = 31$, $p < 0.001$; CFI = 0.93; RMSEA = 0.05) for the activity items fit reasonably well by some indices (RMSEA < 0.06) but not others (CFI < 0.95). Our *a priori* two-factor model with cognitive and social activity factors fit better ($\chi^2 = 58.64$, $df = 29$, $p < 0.001$; CFI = 0.96; RMSEA = 0.04) but had cross loadings and undesirable measurement properties (i.e., Heywood case or factor loading greater than 1). Thus, we examined the model fit after dropping the cross-loadings, and found that the two-factor model without cross-loadings was a worse fitting model ($\chi^2 = 174.44$, $df = 30$, $p < 0.001$; CFI = 0.80; RMSEA = 0.08). The EFA solutions identified optimally fitting multiple factor solutions, but with factors suggested beyond a first principal factor were indicated by only one or two items with salient loadings (greater than or equal to 0.40). Generally, more than two indicators are needed to identify a latent factor. Therefore, we decided to simultaneously examine a general continuous latent activity factor and each individual categorical observed activity item in predicting their effects on delirium within SEM.

The logistic regression odds ratios (OR) (95% confidence intervals, CI) results based on the structural equation model are presented in Table 2 and labeled corresponding to pathways in Figure 1. Bivariable results indicated that higher levels of education (per year of education, OR = 0.92, 95% CI [0.88, 0.97]) predicted lower cumulative risk for delirium (Model 1). More engagement in activity also predicted lower risk for delirium in a separate bivariable regression analysis (per SD increase in latent activity, OR = 0.65, 95% CI [0.46, 0.79]) (Model 2). In a multivariable analysis, we found that both attaining more education and engaging in activities protected against the risk for developing delirium (Model 3). We also found that both education

and activity significantly predicted lower risk for delirium while controlling for sociodemographic characteristics and comorbidities (Model 4). In Model 5, we found that activity participation mediated the relationship between education and risk for delirium. By including education as a significant predictor of activity level in the comprehensive model, the direct effect of education on delirium risk is no longer significantly different from zero (fully standardized parameter estimate -0.038 (Standard Error (SE)= 0.031 , $p < .05$), with an effect size reduction of 65% relative to the effect in Model 4).

In the multivariable logistic regression analyses of delirium regressed on control variables and each individual activity, we found the following decreased delirium risk was significantly associated with the following three specific activities: “exercise regularly”; “read books, magazines, newspapers”; and “visit relatives or friends” (Table 3). Upon examining all the other activities in one model with control variables, the only activity that was a significant independent contributor to lowering delirium risk was “exercise regularly” (OR= 0.76 , 95% CI [0.60 , 0.96]). We observed a dose-response relationship of exercise participation and delirium risk. Relative to persons who participated in exercise less than once per month, those who did so between 1–4 times per month had an odds ratio of 0.76 (95% CI [$.21$, 2.72]) and those participating 5 or more times had an odds ratio of 0.57 (95% CI [$.36$, $.92$]).

DISCUSSION

This study examined whether activity participation among older persons free of dementia mediated the association of educational attainment and cumulative risk for delirium, while adjusting for demographic factors and comorbidities. Our hypothesis that activity mediated the relationship between education and delirium was confirmed, as persons without dementia who were engaged in higher levels of activity before hospitalization had a markedly lower cumulative risk for delirium, even after adjusting for demographic factors and comorbidities. Of the individual activities examined, only participation in regular exercise was found to be independently and significantly protective against delirium.

Activity participation is potentially modifiable, and our results suggest that more activity participation is protective against delirium risk. Activity participation may signal one mechanism by which education, as a reserve capacity indicator, confers neuroprotection. Thus, higher baseline or pre-morbid activity level, including both cognitively-stimulating activities and physical exercise, prior to hospital admission may enhance an individual's ability to withstand the stress of acute illness and hospitalization. Alternatively or in addition, activity participation and engagement in exercise may mark a subset of patients in greater health at baseline, capturing residual differences in health not represented by our included control variables. Based upon this study and complementary results in other fields showing neuroprotective effects of physical activity, we believe it is reasonable to consider testing physical activity interventions as a preventive strategy for the development of delirium among older adults without dementia facing hospitalization. The clinical importance of this finding is that regular exercise is a relatively straightforward intervention for older adults, and has been shown to protect against functional decline.²⁶ The relationship between cardiovascular fitness and executive functioning has been demonstrated in both cross-sectional studies²⁷ and in a six-month randomized controlled trial.²⁸ In addition, the relationship between physical activity and cognitive function has been demonstrated in animal models.²⁹

The mechanism by which regular physical exercise improves cognitive functioning in older adults appears to operate through increases in both gray and white matter volume in the prefrontal and temporal cortices, where age-related brain volume loss occurs.³⁰ Therefore, older patients who engage in regular exercise may experience less neural decline and higher maintenance of brain volume, and may also better withstand common precipitants of delirium.

Previous studies have demonstrated the effectiveness of mobility interventions during hospitalization in preventing delirium.¹⁰ However, the positive effect of delirium prevention as demonstrated by Inouye and colleagues is arguably due to a multifaceted intervention that also included other interventions, such as therapeutic activities. Future studies will be needed to determine the frequency and types of regular exercise prior to admission that have beneficial effects for delirium prevention. In addition to increases in neuronal tissue, a recent study reported that physical activity can also lead to an increase in brain vascularization, causing an increase in cerebral blood flow, which may delay cognitive declines associated with aging.²⁹ The reason for these beneficial effects, the authors hypothesize, is due to the vascular plasticity of the brain and the ability to grow new capillaries from preexisting vessels, brought on by increases in physical activity.²⁹

The main limitation to this study is that it is observational and causal claims are limited. Thus, while we did our best to adjust for likely confounders in our sample, such as age and comorbidity, it is possible that unmeasured factors mediate the association between activity and delirium risk, or that the implied effect of activity participation represents residual confounding and insufficient control of baseline cognitive and functional status. The generalizability may also be limited, given that our two samples are representative of the urban New Haven, Connecticut areas. However, the cohort relationships are still internally valid within these two samples. We also have limited details regarding the duration, frequency, type, and intensity of the specific activities. For example, the types of exercise for the “exercise regularly” question can be broadly interpreted and may cause bias. Although the data collection was conducted during the last decade (1989–1998), this is the only available study with a prospective state-of-the-art delirium assessment³ that contains information regarding activity involvement among older adults prior to the development of delirium. The fit statistics mentioned for the factor analytic approach are based on a limited information approach to model estimation, and were not available for the maximum likelihood logistic regression models we used for subsequent SEM steps. Hence, the model fit was not ideal for the a priori two factor model.

Our study results suggest that activity participation, particularly physical exercise, may be protective against delirium in persons without dementia. Future research is needed to test the effectiveness of exercise interventions for prevention of delirium, or for shortening its duration and poor outcomes. Studies will be needed to evaluate the types of activity, as well as the timing, duration, and intensity of such activity, which will be most beneficial to prevent or delay the incidence of delirium. For example, it might be worth examining whether a short-term exercise program or targeted exercise programs (“prehabilitation”) could reduce the risk of delirium, which commonly complicates hospitalization and surgery in older persons. Given the poor outcomes and high mortality rates associated with delirium, such an intervention may hold substantial implications for the care of our rapidly aging population.

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For “yes” x mark(s): give brief explanation below:

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Figure 1.

This is a depiction of the proposed reserve model through the education-activity-delirium pathway using a path diagram for structural equation modeling. This schematic conceptual representation shows how we simultaneously examine the latent variable of activity, depicted by an oval, and observed variables of education, age, sex, and comorbidity in predicting delirium, depicted by rectangles. The indicators for activity are also observed variables, depicted by the rectangle labeled "activity involvement." Paths labeled "f" indicate the factor measurement model of latent activity as measured by observed activity items. Paths labeled "c," "b," and "d" are direct relationships of delirium on education, activity, and other background variables modeled, in respective order, using logistic regression. Path "a" is a linear regression of activity on educational attainment (included in Model 5). Mediation of the activity and delirium relationship is determined by comparing the effect of delirium regressed on education (path "c") with and without path "a," which represents activity regressed on education.

Table 1

Characteristics of hospitalized participants from two studies of delirium (N=779).

Characteristic	Study 1 (N=405)	Study 2 (N=375)
Age (Mean (years old), $\pm$ SD)	78.5 (5.8)	79.8 (6.4)
Sex (reference: male) (n, (%))	189 (46.7)	149 (39.7)
Educational Attainment (Mean (years), $\pm$ SD)	11.4 (3.7)	11.3 (3.6)
Charlson Comorbidity Index		
0 (n, (%))	47 (11.6)	45 (12.0)
1 (n, (%))	81 (20.0)	86 (22.9)
2 or more (n, (%))	276 (68.2)	244 (65.1)

Abbreviations: SD, standard deviation.

The effects sociodemographic characteristics, activity, and comorbidities for the cumulative risk delirium presented as odds ratios (N=779).

Characteristic	Model 1 Delirium regressed on education only	Model 2 Delirium regressed on activity only	Model 3 Delirium regressed on education and activity	Model 4 Delirium regressed on control variables	Model 5 Delirium regressed on control variables with activity regressed on education [†]
Corresponding path- way in Figure 1					
Education (years)	c	0.92 [*] (0.88, 0.97)	-----	0.95 [*] (0.90, 1.00)	0.96 (0.91, 1.02)
Activity (per SD increase)	b			0.68 [*] (0.51, 0.91)	0.68 [*] (0.51, 0.91)
Female sex(reference=male)	d1		0.60 [*] (0.46, 0.79)	1.17 (0.78, 1.76)	1.17 (0.78, 1.77)
Age (years)	d2			1.02 (0.98, 1.05)	1.02 (0.99, 1.05)
Charlson score(per point)	d3			1.42 [*] (1.01, 2.02)	1.43 [*] (1.01, 2.02)

SD, standard deviation

^{*} p<.05

[†]Model 5: Activity regressed on education (parameter a in Figure 1), b=0.12, (95% confidence interval, 0.09 to 0.15)

Table 3

Cumulative risk for delirium presented as odds ratios (95% confidence intervals) for activity items (N=779).

Activity	Model 1 Individual activity items with control variables [†]	Model 2 All activity items with control variables [‡]
Exercise regularly	0.72 ** (0.58, 0.91)	0.76 * (0.60, 0.96)
Work in garden or yard	0.99 (0.75, 1.29)	1.07 (0.81, 1.43)
Work at a hobby	0.90 (0.71, 1.14)	0.94 (0.74, 1.20)
Go out for entertainment	0.88 (0.67, 1.16)	1.07 (0.80, 1.45)
Read books, magazines, newspapers	0.77 * (0.59, 1.00)	0.81 (0.62, 1.06)
Work at a job (paid or unpaid)	0.79 (0.57, 1.09)	0.83 (0.59, 1.17)
Play cards, games, or bingo	0.85 (0.65, 1.11)	0.88 (0.66, 1.17)
Go to religious services or activities	0.86 (0.63, 1.17)	0.97 (0.70, 1.34)
Visit relatives or friends	0.71 * (0.53, 0.93)	0.74 (.54, 1.03)
Participate in any group	1.05 (0.78, 1.41)	1.27 (0.92, 1.77)
Education (years)		.95 (.89, 1.00)
Sex (reference: male)		1.13 (0.74, 1.72)
Age (years)		1.02 (0.99, 1.05)
Charlson comorbidity score		1.43 * (1.02, 1.99)

*
p<.05**
p<.01[†] Model 1: Multivariable logistic regression of individual activity with control variables (education, sex, age, and Charlson comorbidity index) on risk for delirium[‡] Model 2: Multivariable logistic regression of all activities on risk for delirium with control variables