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Boston University

Original Research Article

Paternal Occupation and Delirium Risk in Older Adults: A Potential Marker of Early-Life Exposures

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Abstract

Background and Objectives: Delirium is a common disorder among older adults following hospitalization or major surgery. Whereas many studies examine the risk of proximate exposures and comorbidities, little is known about pathways linking childhood exposures to later-life delirium. In this study, we explored the association between paternal occupation and delirium risk.

Research Design and Methods: A prospective observational cohort study of 528 older adults undergoing elective surgery at two academic medical centers. Paternal occupation group (white collar vs. blue collar) served as our independent variable. Delirium incidence was assessed using the Confusion Assessment Method (CAM) supplemented by medical chart review. Delirium severity was measured using the peak CAM-Severity score (CAM-S Peak), the highest value of CAM-S observed throughout the hospital stay.

Results: Blue-collar paternal occupation was significantly associated with a higher rate of incident delirium (91/234, 39%) compared with white-collar paternal occupation (84/294, 29%), adjusted odds ratio OR (95% confidence interval [CI]) = 1.6 (1.1, 2.3). All analyses were adjusted for participant age, race, gender, and Charlson Comorbidity Index. Blue-collar paternal occupation was also associated with greater delirium severity, with a mean score (*SD*) of 4.4 (3.3), compared with white-collar paternal occupation with a mean score (*SD*) of 3.5 (2.8). Among participants reporting blue-collar paternal occupation, we observed an adjusted mean difference of 0.86 (95% CI = 0.4, 1.4) additional severity units.

Discussion and Implications: Blue-collar paternal occupation is associated with greater delirium incidence and severity, after adjustment for covariates. These findings support the application of a life-course framework to evaluate the risk of later-life delirium and delirium severity. Our results also demonstrate the importance of considering childhood exposures, which may be consequential even decades later.

Translational Significance: Little is known about the impact of lifetime exposures on delirium risk. We used paternal occupation, a potential marker of childhood socioeconomic status (SES) in the 1930s–1940s, to capture formative early-life exposures in a cohort of older adults. We found that blue-collar paternal occupation was associated with greater delirium incidence and severity. Early-life factors such as childhood SES may contribute a better understanding of sensitive periods for later-life delirium risk. Increased awareness of life-course mechanisms may improve delirium treatment and prevention strategies.

Keywords: Cognitive reserve, Life-course analysis, Social determinants of health, Social exposome, Socioeconomic status

Background and Objectives

Up to one in three adults aged 70 and older will experience delirium during their lifetime (Marcantonio, 2017). Delirium is an acute neurocognitive disorder, characterized by cognitive and behavioral changes including inattention, disorganized thinking, disorientation, and altered level of consciousness (American Psychiatric Association, 2013). This neurocognitive disorder is often preceded by a disruptive medical event or condition, such as acute illness, hospitalization, or major surgery, and increases risk of hospital complications and duration of hospital stay (Marcantonio, 2017). The onset of delirium often triggers a series of costly health events requiring facility placement or home care and rehabilitation services (Inouye et al., 1999). As a result, significant increases in health care spending are attributable to this condition (Leslie et al., 2008). The majority of delirium prevention strategies focus on addressing age-related comorbidities and risk factors measured later in life (Jones et al., 2006). Few studies have considered the role of delirium risk factors over the life course.

Arias et al. (2022) have proposed a novel conceptual framework for the impact of social determinants of health on delirium. This framework is based on the premise that environmental and social factors may increase risk for delirium by influences that increase brain vulnerability across the life course. Arias et al. (2020) have already demonstrated that a person's neighborhood of residence, as measured by the Area Deprivation Index (ADI), contributes to delirium risk with a twofold increased risk of delirium for those living in the most disadvantaged neighborhoods. Life-course epidemiology facilitates the study of early-life exposures that may substantially influence cognitive health decades later. Early-life risk factors can either build or diminish cognitive reserve, the neurobiological substrate that confers resilience to disease (Arenaza-Urquijo & Vemuri, 2020; Jones et al., 2006). Researchers posit that cognitive reserve accumulates over time and influences the response to brain injury or disease (Jones et al., 2006). As a result, the cognitive reserve theory may provide a link between environmental influences and clinical outcomes.

Childhood socioeconomic status (SES), which encompasses early-life influences, such as parental occupation, income, or wealth, is a predictor of health outcomes

in later life (Luo & Waite, 2005). Potential mechanisms through which childhood SES affects later health have been proposed by Cohen et al. in their study on childhood SES and adult health, whereby childhood socioeconomic status likely influences physical environmental exposures, including in the home, neighborhood, and school. These exposures may go on to affect adult physical health outcomes through psychological, behavioral, and physiological mechanisms. The importance of this model is that adult health outcomes cannot be explained by adult health indicators alone (Cohen et al., 2010). For instance, childhood SES may capture formative exposures such as neighborhood environment, quality of formal and informal education, and access to financial resources in childhood or adolescence. Life-course epidemiologists refer to the timing of formative exposures as “sensitive periods,” in which “an exposure has a stronger effect on development and subsequent disease risk than it would at other times” (Kuh et al., 2003). The sensitive period model does not preclude effects of the exposure at other times throughout the life course. In both the National Survey of Health and Development Birth Cohort Study (5,362 participants) and the Whitehall II Occupational Cohort Study (10,308 participants), the sensitive period model demonstrated that more advantaged SES at multiple life points was associated with higher cognition in adulthood. The authors emphasized the importance of considering each period of the life course in relation to adulthood cognitive ability (Landy et al., 2017). Building on this body of work, we examined SES as an exposure and childhood as a commonly accepted sensitive period (Nelson & Gabard-Durnam, 2020).

One approach to understanding socioeconomic disparities in health is comparing occupational strata, such as white-collar versus blue-collar occupation (Väisänen et al., 2020). White-collar workers typically have college degrees and work in professional, administrative, or managerial jobs, whereas blue-collar workers typically have a high school degree or less and work in manual jobs such as manufacturing. Previous studies have found a decline in the prevalence of chronic diseases with increasing occupational status, including specifically hypertension, heart disease, diabetes, asthma, and chronic obstructive lung disease (Clougherty et al., 2010; Cullen et al., 2006). In

the 1930s–1940s, the father’s occupation often influenced the socioeconomic status of the entire family (Goldthorpe, 1983). Due to the age range of our sample, participants were likely children during the 1930s and 1940s, so in this study, we explored the association between paternal occupation category (white collar vs. blue collar) and delirium incidence and severity. Applying the life-course framework, we examined paternal occupation as a potential marker of childhood SES (Chen et al., 2002; Cohen et al., 2010; Salonen et al., 2009). Our work builds on previous studies demonstrating associations between childhood SES and validated cognitive measures of memory, language, executive function, and attention (Fors et al., 2009; Greenfield & Moorman, 2019). These studies found that early socioeconomic disadvantage was significantly associated with cognitive difficulty in middle and late life (Fors et al., 2009; Greenfield & Moorman, 2019). This study addresses an important gap in the literature, as the association between childhood SES and acute changes in cognition has not been systematically investigated (Arias et al., 2022). Given that delirium is a preventable risk factor for subsequent cognitive decline, understanding the contribution of early exposures to delirium may assist with developing interventions that can potentially alter cognitive trajectories (Fong et al., 2009). We hypothesized that this relationship might extend to delirium incidence and severity. Our goal was to apply this novel and unique perspective to examine a potential early-life risk factor for delirium.

Research Design and Methods

Study Population

The Successful Aging after Elective Surgery (SAGES) study is an ongoing prospective cohort study of older adults undergoing major elective surgery. The study design and methods have been described in detail previously (Fong et al., 2015; Schmitt et al., 2015). In brief, eligible participants were age 70 years and older, English speaking and able to communicate verbally, scheduled to undergo elective surgery at two Harvard-affiliated academic medical centers with an anticipated length of stay of at least 3 days, and available for in-person follow-up interviews. Eligible surgical procedures were as follows: total hip or knee replacement, lumbar, cervical, or sacral laminectomy, lower extremity arterial bypass surgery, open abdominal aortic aneurysm repair, and open or laparoscopic colectomy. Surgical procedures selected for inclusion were known to carry a higher risk of delirium and scheduled at least 6 days prior to surgery to allow adequate time for the baseline assessment (Schmitt et al., 2012). Exclusion criteria included evidence of dementia, delirium, prior hospitalization within 3 months, legal blindness, severe deafness, terminal condition, history of schizophrenia or psychosis, and history of alcohol abuse or withdrawal. Dementia screening occurred at three levels: initial medical record review, telephone

recruitment, and baseline interview. Participants were also excluded if they failed a capacity assessment of informed consent understanding, or if they scored below 69/100 on the Modified Mini-Mental during the baseline interview (Schmitt et al., 2012). A total of 560 patients met all eligibility criteria and were enrolled between June 18, 2010 and August 8, 2013. Participants who were missing data on paternal occupation ($n = 32$, 6%) were excluded from this analysis, resulting in a final sample size of 528 individuals for the present study (Supplementary Figure S1, Supplementary Table S1). Written informed consent for study participation was obtained from all participants according to the procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women’s Hospital, the two study hospitals, and Hebrew SeniorLife, the study coordinating center, all located in Boston, MA.

Study Procedures

Data collection involved in-person interviews at baseline in the participant’s home, daily in-hospital delirium assessment by trained research staff, and medical record review. Demographic variables were collected through baseline interviews, whereas baseline comorbidity was ascertained through medical record review. Baseline interviews occurred on average 2 weeks (with a mean of 13 ± 15 days) before the index surgery (Schmitt et al., 2015). Participant enrollment is confirmed on the day of surgery completion and represents zero-time (Schmitt et al., 2012).

Measurements

Paternal occupation

The independent variable of interest, paternal occupation, was assessed through a semistructured in-person interview. The goal of data classification was to capture paternal occupation, while reflecting the nature of the occupation referent to the relevant time period. Given the timing of participants’ childhood (1930s and 1940s), we relied on 1950 U.S. census data (the temporally closest classification system) to classify paternal occupation. We then categorized each of the 528 reported occupations according to the 11 major categories listed in the U.S. census: (1) professional and technical workers; (2) farmers; (3) managers; (4) clerical workers; (5) sales workers; (6) craftsmen; (7) operatives; (8) household workers; (9) service workers; (10) farm laborers; and (11) general laborers (see Supplementary Tables S2 and S3 for detailed descriptions; U.S. Census Bureau, 1950).

The 11 major occupation categories were collapsed into four categories: upper white-collar occupations (1 and 3), lower white-collar occupations (4 and 5), upper blue-collar occupations (6 and 7), and lower blue-collar occupations (2, 8, 9, 10, and 11; Supplementary Table S2). If the participant reported more than one occupation, we coded

the highest status occupation (i.e., upper instead of lower or white collar instead of blue collar). The rationale behind this categorization has been detailed in previous occupational mobility studies (Hauser & Warren, 1975). Following independent coding by two raters, we applied a consensus-building approach to achieve agreement on all four-category occupation codes. The four categories were then collapsed into two categories, white-collar paternal occupation and blue-collar paternal occupation, to represent our final exposure. The more complex coding process was conducted with substantial reliability, with 82% agreement for subcategory assignment and Cohen's kappa $\kappa = 0.74$ (95% confidence interval [CI] = 0.69 to 0.79). The simple coding process demonstrated strong reliability, with 91% agreement and $\kappa = 0.83$ (95% CI = 0.78 to 0.87; Landis & Koch, 1977). Given the complexity of our coding methodology, we opted to use the simple, two-category coding scheme to maximize statistical power and improve interpretability. Additional details of the full 11-category classification are provided in [Supplementary Material](#).

Delirium incidence and severity

Delirium and delirium severity was determined using the Confusion Assessment Method (CAM; Inouye et al., 1990) and CAM-Severity (CAM-S; Inouye et al., 2014), respectively. The CAM is a widely used standardized method for the identification of delirium, which has been demonstrated to have a sensitivity of 94% (95% CI = 91% to 97%), specificity of 89% (95% CI = 85% to 94%), and interrater reliability of 0.70–1.00 in studies involving over 1,070 patients (Wei et al., 2008). The CAM-S was scored from 0 to 19 (19 = most severe) points, and the peak CAM-S captured the highest value of delirium severity recorded during the hospital stay.

Participants were assessed by trained research personnel once daily during daytime hours each day of the index hospitalization using a brief cognitive screen (orientation, short-term recall, verbal fluency), digit span testing, and the Delirium Symptom Interview. Nurses and family members were interviewed regarding the presence of acute confusion. These data were used to inform the CAM and CAM-S. A validated chart review was also conducted (Saczynski et al., 2014) because delirium fluctuates and may be missed by the once-daily interviews. We defined participants as delirious if they met the CAM criteria or were delirious by chart review.

Covariates

Covariates were carefully considered to control for confounding, but to avoid overcontrolling for variables that might be on the causal pathway. Known risk factors for delirium, such as education, participation in mentally stimulating activities, vocabulary scores, IQ, previous surgeries, and physical activity, among others, were excluded from our model due to potential mediation effects. In other words, we did not adjust for delirium risk factors that

might be significantly associated with paternal occupation, and thus, might be on the pathway between childhood socioeconomic status and delirium. This approach was important to allow us to isolate and approximate the direct effect of paternal occupation on delirium risk. Demographic covariates included participant age at baseline, race, and gender. The Charlson Comorbidity Index (CCI), scored from 0 to 35 (35 = highest) points, was used to establish the burden of comorbid medical conditions at baseline (Charlson et al., 1987).

Mediation analysis variables

To account for the potential indirect effects of adulthood SES and medical comorbidities on the association between paternal occupation and delirium risk, we ran three separate mediation models assessing participant ADI, income, and CCI for both delirium incidence and severity, totaling six mediation models. We measured adulthood SES with two variables readily available from our study that best capture SES at enrollment—ADI and household income level for each participant. The ADI is a well-cited measure of neighborhood-level socioeconomic disadvantage incorporating census indicators of poverty, education, employment, and housing quality into a single weighted measure. In the SAGES study sample, participant home address was linked to ADI national percentile, ranging from 1 to 100. Higher ADI percentile, indicating greater disadvantage, has been associated with poor health outcomes in previous studies, including multimorbidity (Chamberlain et al., 2020), rehospitalization, and mortality in cardiac patients (Johnson et al., 2021). Previous studies have used federal poverty guidelines to characterize family income level. Poverty for family households is measured by an annual household income at or below 150% of the federal poverty level. Echoing this approach and using the 2020 federal poverty level of \$12,760 dollars a year (“2020 Poverty Guidelines,” 2020), we classified household income below \$20,000 a year as low income (Arias et al., 2020). In mediation models, CCI was assessed as a mediator rather than a covariate to determine the indirect effects of adulthood comorbidities. Mediation analyses estimate the proportion of the association between paternal occupation and delirium risk that is mediated by ADI, income, and CCI by separating the total effect into the direct effect and indirect effect (Supplementary Figure S2).

Statistical Analysis

To estimate the association between paternal occupation and delirium incidence and severity, we conducted bivariate and multivariate regression models. Blue-collar paternal occupation was treated as the exposure group in all models. We first investigated the association between paternal occupation group and delirium incidence through logistic regression and then tested whether the association remained robust after adjusting for age, race, gender, and CCI. Next,

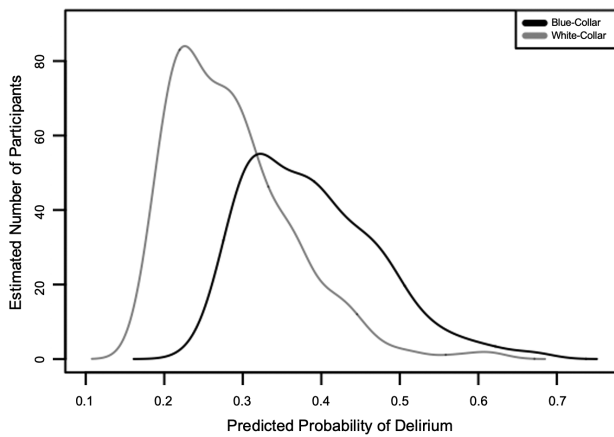


Figure 1. Paternal occupation and delirium incidence ($N = 528$). Analyses were completed using logistic regression lines and 95% confidence intervals were calculated using a standard formula ($\text{mean} \pm 1.96 \times SE$). See text for details.

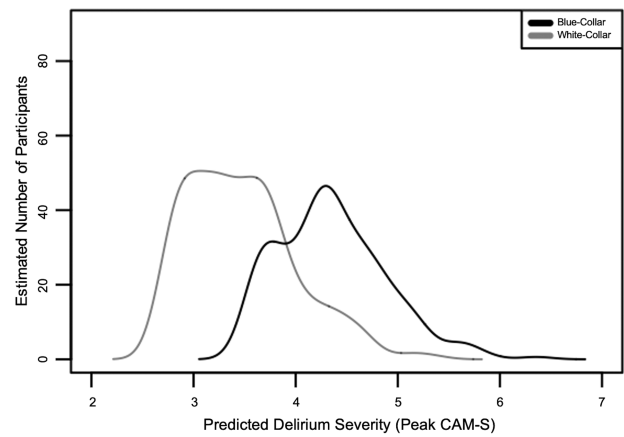


Figure 2. Paternal occupation and delirium severity (CAM-S Peak; $N = 528$). CAM-S = The Confusion Assessment Method Severity Score; CAM-S Peak = The highest single CAM-S rating during hospitalization. Analyses were completed using linear regression lines, and 95% confidence intervals were calculated using a standard formula ($\text{mean} \pm 1.96 \times SE$). See text for details.

we investigated the association between paternal occupation group and delirium severity through linear regression, both with and without adjustment for the same covariates. Linear regression techniques were used to obtain adjusted and unadjusted mean differences in Peak CAM-S scores. Nagelkerke R^2 and adjusted R^2 were used to assess logistic and linear model fit, respectively (Nagelkerke, 1991). Logistic regression results are presented as odds ratios for delirium incidence, and linear regression results are presented as mean differences in Peak CAM-S scores (blue collar – white collar) in Tables 3 and 4. Figures 1 and 2 were generated based on logistic and linear regression models, respectively. The figures display the distribution of predicted delirium incidence and severity values for every unique set of participant covariates. Histogram overlaying and smoothing techniques were used to depict continuous (smoothed) distributions of predicted values according to paternal occupation group (Irizarry & Love, n.d.). To estimate potential indirect effects due to adulthood SES factors, we tested the mediating effects of participant ADI and income level on the primary associations using the product-of-coefficients method (Rijnhart et al., 2021). We used point-biserial correlation to measure the collinearity of the two adulthood SES factors. All analyses were performed using R, version 1.2.5033 (R Core Team, 2013, n.d.). The two-tailed alpha level for all tests of statistical significance was prespecified at .05.

Results

The demographic and clinical characteristics of our sample are displayed in Table 1.

The average age was 76.5 (5.2) (mean [SD]) years among the 528 participants in our sample. Three hundred and two (57%) participants were female, 37 (7%) identified as non-White, and 234 (44%) reported blue-collar paternal

occupation. The incidence of delirium in the entire sample was 33% ($n = 175$), with a mean CAM-S Peak score of 7.0 (3.2) among those with delirium, and a mean score of 2.3 (1.2) among those without delirium. We observed greater incidence and severity of delirium among excluded participants ($n = 32$) compared with included participants, with an incidence of 47% ($n = 15$) and a mean CAM-S Peak score of 5.4 (4.9), although neither of these differences were statistically significant. The only significant difference between the groups was the proportion of women participants (75% of the excluded group). Demographic and clinical characteristics of excluded participants are included in Supplementary Table S1.

Among participants who reported white-collar paternal occupation (294/528, 56%), the incidence of delirium was 29% and the mean CAM-S Peak score was 3.5 (2.8) points. Among participants who reported blue-collar paternal occupation (234/528, 44%), the incidence of delirium was 39% and the mean CAM-S Peak score was 4.4 (3.3) points (Table 2).

Blue-collar paternal occupation predicted a significantly higher incidence of delirium among participants (Table 3). Even after adjusting for participant age, race, gender, and CCI at baseline, blue-collar paternal occupation was associated with a significantly higher rate of incident delirium (adjusted OR = 1.60; 95% CI = 1.10 to 2.32; model $R^2 = .06$) compared with white-collar paternal occupation (Table 2). These results are reflected in Figure 1, which shows that participants in the blue-collar group had higher predicted probabilities of delirium at the peak of the distribution, as well as over the entire distribution of predicted values. Before conducting mediation analyses, we identified a weak correlation between the adulthood SES variables, participant ADI and income level ($r_{pb} = -.146$), that would not affect the interpretability of our results. Mediation

Table 1. Baseline Characteristics of the Sample and Paternal Occupation ($N = 528$)

Characteristic	Entire sample ($N = 528$)	Delirium ($n = 175$)	No delirium ($n = 353$)	p -Value
Age in years, mean (SD)	76.5 (5.2)	77.5 (5.3)	76.1 (5.0)	<.01*
Female, n (%)	302 (57%)	102 (58%)	200 (57%)	.72
Non-White, n (%)	37 (7%)	11 (6%)	26 (7%)	.65
CCI, mean (SD)	1.0 (1.3)	1.2 (1.3)	0.93 (1.2)	.01*
CCI ≥ 2 , n (%)	154 (29%)	67 (38%)	87 (25%)	<.01*
Blue-collar paternal occupation, n (%)	234 (44%)	91 (52%)	143 (41%)	.01*
Delirium incidence, n (%)	175 (33%)	—	—	—
CAM-S Peak, mean (SD)	3.9 (3.1)	7.0 (3.2)	2.3 (1.2)	<.01*

Notes: CCI = Charlson Comorbidity Index (scored 0–35, highest scores = increased comorbidity); CAM-S Peak = single highest Confusion Assessment Method Severity score rating during hospitalization (scored 0–19, highest scores = increased severity); * $p < 0.05$.

Table 2. White-Collar Versus Blue-Collar Paternal Occupation ($N = 528$)

Occupation category	Subgroup N	Delirium ($n = 175$)	No delirium ($n = 353$)	CAM-S peak mean (SD)
		n (%)	n (%)	n (%)
White-collar paternal occupation	294	84 (29)	210 (71)	3.5 (2.8)
Blue-collar paternal occupation	234	91 (39)	143 (61)	4.4 (3.3)

Notes: CAM-S Peak = single highest Confusion Assessment Method Severity score rating during hospitalization (scored 0–19, highest scores = increased severity).

Table 3. Logistic Regression Model for Delirium Incidence ($N = 528$)

Delirium incidence	n (%)	Unadjusted		Adjusted	
		OR (95% CI)	p -Value	OR (95% CI)	p -Value
White-collar paternal occupation ($N = 294$)	84 (29)	Ref	—	Ref	—
Blue-collar paternal occupation ($N = 234$)	91 (39)	1.59 (1.11, 2.29)	0.01*	1.60 (1.10, 2.32)	0.01*
R^2		0.02*		0.06*	

Notes: CI = confidence interval; OR = odds ratio; * $p < 0.05$.

analyses demonstrated that adulthood SES variables and adulthood comorbidities do not significantly mediate the association between paternal occupation and delirium incidence. We found that 12.2% of the association between paternal occupation and delirium incidence is mediated by participant ADI (indirect effect estimate = 0.011; 95% CI = -0.005 to 0.029 , $p = .22$), and 5.1% of association is mediated by participant income level (indirect effect estimate = 0.005; 95% CI = -0.004 to 0.018 , $p = .41$). Through mediation analysis of medical comorbidities, we found that 6.0% of the association is mediated by participant CCI (indirect effect estimate = 0.006; 95% CI = -0.002 to 0.019 , $p = .23$; [Supplementary Figure S2](#)).

Similar findings were demonstrated between blue-collar paternal occupation and higher delirium severity scores ([Table 4](#)). The association persisted after controlling for covariates in our linear regression model, yielding a significantly higher average delirium severity score among participants who reported blue-collar paternal

occupation (adjusted mean difference = 0.86 units higher; 95% CI = 0.35 to 1.38; model $R^2 = .05$; [Table 4](#)). The frequency plots in [Figure 2](#) accordingly depict higher delirium severity scores in the blue-collar group at the peak of the distribution, as well as over the entire distribution of predicted values. Mediation analyses demonstrated that adulthood SES variables and adulthood comorbidities do not significantly mediate the association between paternal occupation and delirium severity score. We found that 7.1% of the association between paternal occupation and delirium severity is mediated by participant ADI (indirect effect estimate = 0.057; 95% CI = -0.047 to 0.175 , $p = .32$), and 10.1% of the association is mediated by participant income level (indirect effect estimate = 0.067; 95% CI = 0.001 to 0.167, $p = .12$). Through mediation analysis of medical comorbidities, we found that 5.6% of the association is mediated by participant CCI (indirect effect estimate = 0.048; 95% CI = -0.016 to 0.136 , $p = .22$; [Supplementary Figure S2](#)).

Table 4. Linear Regression Model for Delirium Severity (*N* = 528)

Delirium severity	CAM-S peak, mean (SD)	Unadjusted		Adjusted	
		Mean difference (95% CI)	<i>p</i> -Value	Mean difference (95% CI)	<i>p</i> -Value
White-collar paternal occupation (<i>N</i> = 294)	3.5 (2.8)	Ref	—	Ref	—
Blue-collar paternal occupation (<i>N</i> = 234)	4.4 (3.3)	0.89 (0.37, 1.41)	<0.01*	0.86 (0.35, 1.38)	<0.01*
<i>R</i> ²		0.02*		0.05*	

Notes: CAM-S Peak = single highest Confusion Assessment Method Severity score rating during hospitalization (scored 0–19, highest scores = increased severity); CI = confidence interval. Full model adjusted for participant age at baseline, race, gender, and Charlson Comorbidity Index. Multivariate and univariate logistic regression were used to describe the association between occupation category and delirium status with and without controlling for the covariates, respectively. Nagelkerke *R*² and adjusted *R*² were used to assess logistic and linear model fit, respectively. Linear regression techniques were used to obtain adjusted and unadjusted mean differences (blue collar – white collar) in CAM-S Peak scores, with and without controlling for the covariates, respectively; **p* < 0.05.

Discussion and Implications

In our study, the association between blue-collar paternal occupation and delirium risk was significant and reflected in both higher incidence of delirium and higher delirium severity. This association remained significant and of similar magnitude after adjusting for participant age at baseline, race, gender, and the presence of comorbid medical conditions. Our results support the hypothesis that childhood SES, as represented by blue-collar paternal occupation, may capture delirium risk not otherwise measured by proximate indicators. For example, we accounted for the mediating effects of ADI, income level, and CCI at the time of surgery, and the effect of paternal occupation remained significant. The indirect effect estimates for participant ADI, household income, and CCI were not statistically significant for both delirium incidence and severity. Thus, the association between paternal occupation and delirium risk was not explained by markers of adulthood SES in this cohort. It is possible that other markers of adulthood SES, such as long-term financial stability or access to health care, would explain a greater proportion of the association. CCI, a measure of disease burden in adulthood, did not explain the association between paternal occupation and delirium risk either. Our findings lend preliminary support for the significance of childhood as a sensitive period for the exposure of SES. However, additional measures of SES and disease burden both during middle and late life not captured by our data are important to explore in future work.

We fully acknowledge that this work is exploratory, providing preliminary proof-of-concept for the role of early-life exposures in later-life cognition. In addition, our findings are limited by the use of cross-sectional data. Longitudinal data on SES and other social determinants of health would strengthen our understanding of both sensitive periods and delirium risk over the life course. Regular collection of social determinants data will be critical for future exploration.

In addition to replicating and expanding on these findings, future studies are needed on the value of early-life proxy exposures in the context of delirium risk. The

application of life-course epidemiology to delirium risk is grounded in the cognitive reserve theory, but additional work is needed to better substantiate our hypotheses. We need agreed-upon measures of early-life SES that account for geographical, temporal, and cultural differences in income, occupation, and education. Such a measure may be valuable to clinicians, along with other measures of the social determinants of health, to target and treat those facing a greater risk of cognitive impairment.

This study has many strengths, including well-validated assessment methods for delirium incidence and severity, as well as a novel approach to conceptualizing sensitive periods for delirium risk over the life course. Our study is novel in the application of life-course methods to delirium and in providing empirical support for our proposed conceptual framework. Additionally, we implemented a rigorous coding process to classify our exposure of interest, paternal occupation. Despite the inherently subjective nature of coding open-ended data, we achieved a high level of interrater agreement. Our results encourage further exploration of early-life risk factors for delirium and other cognitive disturbances.

This study has several important limitations. Although the SAGES cohort reflects the ethnoracial diversity of the target population from which it is drawn and spans a wide range of demographic and clinical characteristics, our sample may not capture the ethnoracial diversity of all older adults across the country. For this reason, our findings may not be generalizable to the larger population of older adults in the U.S. In addition, individuals who undergo elective surgery may not be representative of the general population. Our results may be conservative, given the homogeneous sample of older surgical patients, and a stronger association may have been observed in a more heterogeneous sample with a greater diversity of health exposures. The SAGES study excluded individuals with dementia and conducted a comprehensive neuropsychological evaluation to identify patients at risk of cognitive decline. It is possible that patients with mild cognitive insufficiencies may have been enrolled in the study. Patients with mild cognitive impairment are

at increased risk of developing delirium. Elevated risk of delirium at baseline may have confounded the relationship between paternal occupation and delirium incidence and severity. Regarding our methodology, the binary characterization of occupation offers ready interpretability; however, this simplification may come at the expense of a more detailed evaluation of occupations and associated responsibilities. While our mediation analyses for ADI and income provide meaningful estimates of indirect effects, we are limited by the availability of data on adulthood SES factors. Regarding our exposure of interest, we acknowledge that socioeconomic status is a multidimensional exposure that we cannot thoroughly describe using a two-category approach. This point is emphasized by the small proportion of variance in delirium risk explained by paternal occupation group in our models. Thus, our findings only contribute a small component of a more complex life-course model that we have yet to establish, and which would include examination of the important longitudinal factors described above. Despite this limitation, our significant results provide preliminary proof-of-concept for the importance of paternal occupation for delirium risk even decades later.

Conclusions

This study breaks new ground in the application of life-course exposures to delirium risk among older adults. By applying emerging concepts in life-course epidemiology to defined clinical endpoints, we have demonstrated the power of this framework. We hope that an improved understanding of life-course mechanisms will allow clinicians to intervene on early-life risk factors and ultimately to mitigate patients' risk of developing delirium.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

None declared.

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Author Contributions

All authors made significant contributions to the final manuscript. H. M. Shiff led project conception, data coding, analysis, and interpretation, and manuscript preparation. F. Arias supported all aspects of the project including conception, data coding, analysis and interpretation, and manuscript preparation. A. B. Dufour supported the statistical analysis plan and interpretation of results. D. Carr was involved in project conception and manuscript preparation. F. Chen was involved in data analysis and data acquisition. Y. Gou was involved in data analysis and data acquisition. R. N. Jones was involved in project conception and design, as well as data analysis and interpretation. E. M. Schmitt was involved in data collection and data interpretation. T. G. Trivison was involved in project conception and data interpretation. Z. J. Kunicki was involved in project design, data analysis and interpretation, and manuscript preparation. O. I. Okereke was involved in project conception, data interpretation, and manuscript preparation. S. K. Inouye was involved in all aspects of the project, including conception, design, obtaining funding, data acquisition, analysis and interpretation, manuscript preparation, manuscript revision, and approval for final submission.

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