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Featured Article

Delirium symptoms are associated with decline in cognitive function between ages 53 and 69 years: Findings from a British birth cohort study

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Abstract

Introduction: Few population studies have investigated whether longitudinal decline after delirium in mid-to-late life might affect specific cognitive domains.

Methods: Participants from a birth cohort completing assessments of search speed, verbal memory, and the Addenbrooke's Cognitive Examination at age 69 were asked about delirium symptoms between ages 60 and 69 years. Linear regression models estimated associations between delirium symptoms and cognitive outcomes.

Results: Period prevalence of delirium between 60 and 69 years was 4% (95% confidence interval 3.2%–4.9%). Self-reported symptoms of delirium over the seventh decade were associated with worse scores in the Addenbrooke's Cognitive Examination (−1.7 points; 95% confidence interval −3.2, −0.1; $P = .04$). In association with delirium symptoms, verbal memory scores were initially lower, with subsequent decline in search speed by the age of 69 years. These effects were independent of other Alzheimer's risk factors.

Discussion: Delirium symptoms may be common even at relatively younger ages, and their presence may herald cognitive decline, particularly in search speed, over this time period.

Keywords: Delirium; Dementia; Cognitive decline; Life course

1. Introduction

Delirium is a neuropsychiatric syndrome characterized by acute cognitive dysfunction and attentional deficits precipitated by acute illness. Delirium is common, affecting around 25% of older inpatients [1,2], and is associated with increased length of hospital admission, risk of institutionalization, and mortality [3]. In a range of settings, delirium has been linked with subsequent cognitive decline and incident dementia [4–7]. The precise mechanisms underlying these relationships are unknown but may be independent of classical Alzheimer's pathologies such as amyloid beta, hyperphosphorylated tau, or *APOE* ε4 genotype [8–10].

Although delirium clearly has an impact on long-term cognition, current understanding is incomplete in a number of ways. First, delirium has mainly been investigated in hospital samples [11–13], and population studies are less common [14,15]. This is relevant because not all patients with delirium can be assumed to be admitted to hospital; those who are may have more severe or prolonged episodes [16]. Second, there is little knowledge of whether cognitive function after delirium declines in specific domains or whether the observed associations relate to cognition more generally. Third, there are few studies with prospective assessments of cognition, before and after delirium, which are necessary to quantify prior vulnerability to delirium and its subsequent effects [5,6,14,17]. None of these studies are exclusively in populations younger than age 70 years. It is likely that delirium and dementia have shared and interacting risk factors, although when these processes start in the life course is unclear.

The authors declare that they have no competing interests.

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Our aims were to investigate the association between reported delirium symptoms and change in two key domains of cognition—episodic memory and processing speed—between ages 53 and 69 years, using data from a British birth cohort study, accounting for the influences of prior cognitive function as well as early-life and midlife risk factors for Alzheimer's disease. We addressed three questions: (1) What is the 10-year period prevalence of reported delirium symptoms in a birth cohort aged 69 years? (2) Are delirium symptoms subsequently associated with deficits in any particular cognitive domains? (3) Are reported delirium symptoms associated with cognition at age 69, and cognitive decline since midlife independently of other factors known to be associated with Alzheimer's risk?

2. Methods

The MRC National Survey for Health and Development (NSHD) is a British birth cohort study, following a sample of 5362 participants born in March 1946. In 2015, when participants were aged 69 years, 2698 individuals living in England, Scotland, and Wales were invited to have a home visit by a research nurse as part of the 24th follow-up [18]. The other 2664 participants had either died (n = 995), permanently refused participation (n = 654), moved abroad (n = 583), or were lost and untraced (n = 432). Of the 2698 invited, 2148 (80%) completed a home visit and the maximum sample for this analysis is 2090 who responded to a question about delirium symptoms (97%).

2.1. Cognitive outcomes at age 69

Main outcome variables were verbal memory and visual search speed at age 69. All cognitive assessments were carried out by the research nurse according to the same standardized protocol as at earlier ages [19]. Verbal memory was assessed using a 15-item word-learning task, where each word was presented for 2 seconds. The score represents the total number of words correctly recalled over three identical trials (maximum 45). Visual search speed was assessed by crossing out the letters P and W, randomly embedded within a grid of other letters, as quickly and accurately as possible in 1 minute. The score represents the total number of letters searched (maximum 600). For the first time, participants were also administered the Addenbrooke's Cognitive Examination (version III) (ACE-III), which gives scores in five domains: attention & orientation (scored 0–18); verbal fluency (0–14); memory (0–26); language (0–26); and visuospatial function (0–16) (total score 100).

2.2. Delirium symptoms

At age 69, participants reported whether they had experienced an episode of delirium in the previous 10 years: "Please think to a time when you have been unwell, perhaps while in hospital. Sometimes a person's memory, thinking, and concentration can get worse over hours and days due to an illness, for example, infection, operation, or due to medications. This is delirium. Since 2006, have you experienced delirium symptoms?"

2.3. Covariates

We used previous scores of verbal memory and visual search speed at age 53 (in 1999) as a baseline measure predating any delirium from 2006 [19]. Other covariates were selected from the data collection at ages 60 to 64 years [20], based on factors previously demonstrated to be important in the primary prevention of Alzheimer's dementia. These were as follows: diabetes [21], smoking [22,23], hypertension [24], body mass index (BMI) [20], educational attainment [22,25,26], and level of physical exercise [23,27].

At ages 60 to 64 years, diabetes was defined as a diagnosis of type 1 or 2 diabetes mellitus by a doctor. Hypertension was defined as a physician-diagnosed hypertension, or regular prescription of an antihypertensive, or systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg taken from two measurements. To assess BMI, height and weight were measured by standardized protocols using stadiometers and scales. Smoking status was defined as current smoker, ex-smoker, or lifelong nonsmoker, corroborated with reports at earlier ages. Participants were asked how many times in the last 4 weeks they had taken part in sports or vigorous activities, classified as inactive (no episodes), less active (1–4 exercise episodes per month), and more active (five or more exercise episodes per month). Educational qualifications by the age of 26 years were categorized into no educational qualifications or less than ordinary "O" level; "O" levels; advanced "A" level and higher.

2.4. Statistical analysis

First, using the maximum samples, the cognitive test scores (verbal memory, search speed, ACE-III, and its subdomains) at age 69 and all covariates were assessed in respect to reported delirium symptoms using chi-squared tests and t-tests as appropriate. Second, for participants with complete data for visual search speed and verbal memory at 53 and 69 years, we used linear regression to estimate the associations between delirium symptoms and individual cognitive domain at age 69, adjusting only for sex and the corresponding cognitive measure at age 53. We then used all other covariates in a multivariable model. We tested for interactions between delirium and each covariate in the fully adjusted models. Finally, we tested the associations between delirium symptoms and ACE-III measures (total scores), to derive a comparable estimate of effect size on a clinically relevant scale. Residuals for all regression models were checked for heteroscedasticity. Stata 14.1 (StataCorp, Texas) was used for all analyses.

3. Results

Of 2090 participants responding to the delirium question, 83 reported symptoms between ages 60 and 69 years, thus a