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Association of Delirium with Cognitive Decline in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies. 

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IMPORTANCE Delirium is associated with accelerated cognitive decline. The pathologic substrates of this association are not yet known, that is, whether they are the same as those associated with dementia, are independent, or are interrelated.

OBJECTIVE To examine whether the accelerated cognitive decline observed after delirium is independent of the pathologic processes of classic dementia.

DESIGN, SETTING, AND PARTICIPANTS Harmonized data from 987 individual brain donors from 3 observational cohort studies with population-based sampling (Vantaa 85+, Cambridge City Over-75s Cohort, Cognitive Function and Ageing Study) performed from January 1, 1985, through December 31, 2011, with a median follow-up of 5.2 years until death, were used in this study. Neuropathologic assessments were performed with investigators masked to clinical data. Data analysis was performed from January 1, 2012, through December 31, 2013. Clinical characteristics of brain donors were not different from the rest of the cohort. Outcome ascertainment was complete given that the participants were brain donors.

EXPOSURES Delirium (never vs ever) and pathologic burden of neurofibrillary tangles, amyloid plaques, vascular lesions, and Lewy bodies. Effects modeled using random-effects linear regression and interactions between delirium and pathologic burden were assessed.

OUTCOMES Change in Mini-Mental State Examination (MMSE) scores during the 6 years before death.

RESULTS There were 987 participants (290 from Vantaa 85+, 241 from the Cambridge City Over-75s Cohort, and 456 from the Cognitive Function and Ageing Study) with neuropathologic data; mean (SD) age at death was 90 (6.4) years, including 682 women (69%). The mean MMSE score 6 years before death was 24.7 points. The 279 individuals with delirium (75% women) had worse initial scores (−2.8 points; 95% CI, −4.5 to −1.0; P < .001). Cognitive decline attributable to delirium was −0.37 MMSE points per year (95% CI, −0.60 to −0.13; P < .001). Decline attributable to the pathologic processes of dementia was −0.39 MMSE points per year (95% CI, −0.57 to −0.22; P < .001). However, the combination of delirium and the pathologic processes of dementia resulted in the greatest decline, in which the interaction contributed an additional −0.16 MMSE points per year (95% CI, −0.29 to −0.03; P = .01). The multiplicative nature of these variables resulted in individuals with delirium and the pathologic processes of dementia declining 0.72 MMSE points per year faster than age-, sex-, and educational level–matched controls.

CONCLUSIONS AND RELEVANCE Delirium in the presence of the pathologic processes of dementia is associated with accelerated cognitive decline beyond that expected for delirium or the pathologic process itself. These findings suggest that additional unmeasured pathologic processes specifically relate to delirium. Age-related cognitive decline has many contributors, and these findings at the population level support a role for delirium acting independently and multiplicatively to the pathologic processes of classic dementia.

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Understanding the pathologic basis of cognitive impairment in whole populations is a prerequisite to mitigating the increasing public health burden of dementia.\textsuperscript{1} Many strands of investigation presuppose that Alzheimer, vascular, and Lewy body pathologic features are the predominant causes of dementia. This paradigm has directed the search for biomarkers, treatments, and potential prevention strategies. However, evidence indicates that these classic pathologic processes do not fully account for the clinical syndrome,\textsuperscript{2} especially in unselected populations of the oldest-old.\textsuperscript{3,4} For example, older people may have a large burden of the pathologic processes of classic dementia but no associated clinical dementia and vice versa.

Delirium is a syndrome of acute brain dysfunction characterized by inattention and other mental status impairments. It is a major public health problem that affects at least 20\% of older inpatients and has well-documented adverse associations.\textsuperscript{5} An emerging literature reveals that delirium is a strong predictor of new-onset dementia and acceleration of existing cognitive decline.\textsuperscript{5-10} These results are consistent across several different settings: after hospitalization,\textsuperscript{11} in those with dementia,\textsuperscript{6,12} in postoperative patients,\textsuperscript{13} and in a community population.\textsuperscript{8} In multiple animal models of neurodegeneration, triggers of acute cognitive dysfunction, such as systemic inflammation, also exacerbate the pathologic processes\textsuperscript{14,15} and accelerate functional decline during longer periods.\textsuperscript{16,17} This finding implies that delirium and/or its causes can contribute to the overall burden of dementia. Moreover, research indicates that 3 of 10 cases are preventable,\textsuperscript{18} which in turn suggests that delirium interventions might reduce at least some cognitive decline and dementia.

Although delirium is now established as a strong predictor of cognitive decline in older adults,\textsuperscript{6,8,12} whether it accounts for additional, interrelated, or unexplained pathologic injury that contributes to dementia has not previously been examined. It is possible that when dementia follows delirium it has a different pathologic profile compared with dementia that develops without delirium. Therefore, understanding how delirium affects the evolution of dementia in the context of a particular burden of pathologic findings may offer new insights into independent mechanisms that explain cognitive decline after delirium.

In this study, the challenge was to examine a key hypothesis: that faster cognitive decline associated with delirium would act independently of the cognitive decline associated with the pathologic processes of classic dementia. Accordingly, we investigated the extent to which delirium and the pathologic processes of classic dementia contributed to associated cognitive decline in 3 unselected, population-based cohort studies with neuropathologic autopsy data: the Medical Research Council Cognitive Function and Ageing Study (CFAS), the Cambridge City Over-75s Cohort (CC75C), and the Vantaa 85+ study. These studies represent the entirety of such studies conducted in Europe and provide a unique opportunity to increase the understanding of the clinical significance of delirium and its interrelation with the pathologic processes of dementia in the general population.

**Key Points**

**Question** What is the association among delirium, the pathologic processes of dementia, and cognitive decline in older persons?

**Findings** In this cohort of 987 autopsied brains from 3 population-based cohort studies, delirium and the pathologic processes of dementia were associated with cognitive decline; however, the combination of delirium and the pathologic processes of dementia interacted to give the fastest trajectory of cognitive decline.

**Meaning** During cognitive decline in the oldest-old, delirium appears to act independently and multiplicatively to the neuropathologic processes of classic dementia.

**Methods**

The individual studies have previously been described in detail,\textsuperscript{19-21} and participant-level data have been harmonized as the Epidemiological Clinicopathological Studies in Europe (EClipSE) collaboration.\textsuperscript{22} Briefly, participants were sampled from general practitioners’ registers (CFAS [1991-2011] and CC75C [1985-2011] in the United Kingdom) and the Population Register Centre (Vantaa 85+ in Finland [1991-2001]) from January 1, 1985, through December 31, 2011. Data analysis was performed from January 1, 2012, through December 31, 2013. The CFAS recruited persons 65 years or older, the CC75C recruited persons 75 years or older, and Vantaa 85+ recruited persons 85 years or older. Individuals were assessed annually and in all 3 studies. Additional neuropsychological batteries were also performed, with some differences among the studies (eAppendix in the Supplement). Table 1 summarizes the characteristics of each cohort. Previous work found that participants in the brain donor programs had no systematic differences in clinical characteristics compared with other participants in the cohorts,\textsuperscript{24} although donors in the CFAS were selected by stratified random sampling, weighted to those who were older and cognitively impaired. Each study had local ethical approval (CFAS centers: Cambridge: North West Anglia Health Authority Local Research Ethics Committee [Peterborough]; Huntingdon Local Research Ethics Committee; Cambridge Local Research Ethics Committee; Gwynedd: Gwynedd Hospitals National Health Service Trust–North West Health Authority Research Ethics Committee (West); Liverpool: Liverpool Local Research Ethics Committee; Newcastle: Newcastle & North Tyneside Health Authority–Joint Ethics Committee; Northumberland and Tyne & Wear Health Authority–Local Research Ethics Committee; Nottingham: Queen’s Medical Centre National Health Service Trust Ethics Committee; Nottingham University Medical School Ethical Committee; City Hospital Ethics Committee; Oxford: Oxfordshire Health Authority: Central Oxford Research Ethics Committee; CC75C: Cambridge Research Ethics Committee; and Vantaa 85+: Ethics Committee of the City of Vantaa). Written informed consent was provided for each study, and all analyses were conducted with deidentified data.
Delirium Assessments
In the CFAS and CC75C, delirium symptoms were a feature of the standardized interview schedules administered by trained interviewers to participants and informants. These schedules assigned diagnostic groups based on validated, structured algorithms for psychiatric disorders, themselves based on DSM-III-R or related classifications. Questions included the following: “Were there brief episodes during the 24 hours when s/he seemed much worse and then times when quite clear?” “Were there marked fluctuations in his/her level of attention or alertness?” “Could a physical illness...”

Neuropathologic Analyses
Paraffin-embedded brain tissue samples were used to assess neuropathologic markers with investigators masked to clinical data. Each study reported Braak stage as a semiquantitative measure of neurofibrillary tangles and neocortical amyloid plaque burden from the Consortium to Establish a Registry for Alzheimer’s Disease protocol. The presence of infarcts (>10 mm), lacunes, and hemorrhage was histologically assessed using hematoxylin-eosin. Lewy bodies in the substantia nigra were assessed with hematoxylin-eosin but also included immunohistochemical staining against α-synuclein (or ubiquitin in some of the earlier CC75C specimens) (eAppendix in the Supplement).

Statistical Analysis
Consistent with previous approaches, delirium exposure was operationalized as never or ever. Change in MMSE score before death was modeled using a time-to-death random-effects (random slopes) model. We were interested in estimating the final trajectory toward death because this approach makes associations with pathologic data easier to define. The mean time from the start of the trajectory identified by the model to death was 5.2 years; therefore, the start point (intercept) for this trajectory was set (centered) at 6 years. This start point is not so near the point of death that rates of change (slopes) cannot be estimated yet not so far from death that the pathologic findings at autopsy might not plausibly be related to the estimated parameters. Six years before death is also comparable to start points from change-point models of the final trajectory of cognitive decline and in the range observed in other analyses (3-8 years). Models were adjusted for baseline MMSE score, age at death (centered at a mean age of 90 years), sex (0 for men, 1 for women), years of education (0-3, 4-7, 8-11, or ≥12), and study. Missing data were assumed to be missing at random given that outcome ascertainment was essentially complete in this brain donor cohort.

Results
There were 987 participants (290 from Vantaa 85+, 241 from the CC75C, and 456 from the CFAS) with neuropathologic data (mean [SD] age at death, 90 [6.4] years; 472 females [67%] without delirium and 210 [75%] with delirium). Table 2 describes the characteristics of the sample. Persons with delirium were slightly

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Table 1. Characteristics of Studies Comprising the EClipSE Database

<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Patients</th>
<th>Site</th>
<th>Age, y</th>
<th>Baseline Survey Year</th>
<th>Follow-up, y</th>
<th>No. of Surveys</th>
<th>Donors, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vantaa 85+</td>
<td>553</td>
<td>Vantaa, Finland</td>
<td>≥85</td>
<td>1991</td>
<td>10</td>
<td>5</td>
<td>290 (52.4)</td>
</tr>
<tr>
<td>CC75C</td>
<td>2166</td>
<td>Cambridge, England</td>
<td>≥75</td>
<td>1985</td>
<td>25</td>
<td>9</td>
<td>241 (11.1)</td>
</tr>
<tr>
<td>CFAS</td>
<td>18 226</td>
<td>UK multicenter &lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥65</td>
<td>1993</td>
<td>10</td>
<td>7</td>
<td>456 (2.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CC75C, Cambridge City Over-75s Cohort; CFAS, Cognitive Function and Ageing Study; EClipSE, Epidemiological Clinicopathological Studies in Europe.

<sup>a</sup> Number of surveys refers to the maximum number of times a participant could have been seen up to the most recent follow-up point.

<sup>b</sup> The CFAS sampled from 6 geographic areas: 4 urban (Newcastle, Nottingham, Liverpool, and Oxford) and 2 rural (Cambridgeshire, Gwynedd).
Results from the random-effects models that described delirium and cognitive decline are presented in Table 3. The median number of longitudinal observations for participants in the model was 2 (interquartile range, 1-4). In the fully adjusted model (including delirium and pathologic burden), the start point was estimated at 24.7 MMSE points. The start point should be interpreted as the estimated MMSE score 6 years before death in persons in whom all covariates are in the reference category (e.g., youngest age, no delirium). For the typical 90-year-old, the mean base rate of decline was 0.35 points per year (base rate indicates all covariates in the reference category, e.g., no delirium, lowest pathologic score). There was no significant influence of study source (Vantaa 85+, CC75C, or CFAS) on the model estimates (eAppendix in the Supplement).

Effect of Delirium on Start Point and Rate of Change
Delirium was associated with a mean 2.8-point lower MMSE score ($P < .001$) 6 years before death. For these persons, the rate of change was an additional 0.37 points per year ($P < .001$). These coefficients are additive. Therefore, for the typical individual aged 90 years at death with delirium, the estimated MMSE score is 24.7 points (baseline) with −2.8 points equaling 21.9 MMSE points, declining at 0.35 points (base rate) with −0.37 (attributable to delirium) equaling 0.72 points per year.

Effect of Pathologic Burden on Start Point and Rate of Change
An increasing pathologic burden score was associated with a lower MMSE score (−0.7 for 1 instance of high dementia pathologic marker, −2.2 point for 2 markers, and −4.4 for 3 or more markers; $P < .001$). Pathologic burden conferred an additional 0.39-point decline in MMSE score over and above the effect of age and delirium ($P < .001$).

Interaction Between Delirium and Pathologic Burden
A significant interaction between delirium and pathologic burden estimated an additional decline of 0.16 MMSE points per year ($P = .01$). Therefore, individuals with delirium and high dementia pathologic burden had estimated rates of decline of −0.35 points (base rate), −0.37 points (attributable to delirium), and −0.72 points (attributable to delirium and pathologic burden) per year.
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Discussion

This is the first report, to our knowledge, that people with delirium and higher levels of pathologic processes of classic dementia have the greatest cognitive decline. Delirium in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical (n = 877 Cases and 2570 Observations)</th>
<th>Clinical and Delirium (n = 877 Cases and 2570 Observations)</th>
<th>Clinical and Pathologic Burden (n = 872 Cases and 2558 Observations)</th>
<th>Clinical, Delirium, and Pathologic Burden (n = 872 Cases and 2558 Observations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P Value</td>
<td>β (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Intercept</td>
<td>21.73 (19.98 to 23.48)</td>
<td>&lt;.001</td>
<td>22.18 (20.51 to 23.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Slope</td>
<td>−0.86 (−0.93 to −0.78)</td>
<td>&lt;.001</td>
<td>−0.66 (−0.74 to −0.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>−0.27 (−0.33 to −0.20)</td>
<td>&lt;.001</td>
<td>−0.25 (−0.31 to −0.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>−2.08 (−2.81 to −1.34)</td>
<td>&lt;.001</td>
<td>−1.96 (−2.69 to −1.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EDUCATIONAL LEVEL, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4-7</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8-11</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12-15</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0-3</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4-7</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8-11</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12-15</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pathologic burden score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3 or 4</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
<td>−0.20 (−2.13 to 1.73)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 3. Quantifying Trajectories of Mini-Mental State Examination Change in Relation to Delirium and Dementia Pathologic Burden

The term dementia pathologic burden refers to classic dementia pathologic variables known to contribute to cognitive impairment (e.g., Braak stage, amyloid plaques, infarcts, and Lewy bodies). Observations refer to the total number of longitudinal outcomes in the model. Each of the 4 columns represents a model of cognitive trajectories adjusted by study source. The intercept and slope are given for each model. These variables indicate the estimated Mini-Mental State Examination scores 6 years before death (intercept) and the rate of decline per year (slope). The intercept from 6 years before death was chosen because the mean time before death was 5.2 years, and the model is centered just before the mean. The figures given in this row are for the baseline group, that is, where all other variables in the model are in the lowest category.

The Figure shows how the rate of cognitive decline varies by delirium and pathologic status. The slowest decline was seen in persons with no history of delirium and least dementia pathologic burden. The fastest decline was seen in persons with a history of delirium and most dementia pathologic burden. Intermediate rates of decline were observed in individuals with delirium but least dementia pathologic burden and in those with no delirium history but most dementia pathologic burden.

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Interaction between systemic or central nervous system inflammation and existing neurodegenerative pathologic processes, and acute exacerbation of inflammation clearly leads to neuronal death, synaptic changes, and accelerated decline. These changes occur independently of increased extracellular amyloid. However, we now need to know whether individuals with delirium superimposed on dementia have different patterns of inflammation, synaptic loss, axonal pathologic findings, and/or differential loss of key neuronal populations of the hippocampus and cortex and of cholinergic and noradrenergic projection areas.

Strengths and Limitations
This analysis has a number of strengths. It focuses on a major question arising from the prevalence of cognitive impairment and aging. In terms of study design, the 3 cohorts have high generalizability for the oldest-old populations, who are underrepresented in dementia research despite having the highest prevalence of dementia. This is also the first article, to our knowledge, to examine delirium and the pathologic correlates of cognitive decline at the end of life in the general population; the other analysis comes from a leading study in this area, the Religious Orders cohort study, which is, however, focused on specific populations. Modeling change in cognitive outcomes as continua rather than simply the presence or absence of dementia allows for an exploration of the effect of delirium across the whole spectrum of cognitive function (ie, from no baseline impairment through mild cognitive impairment to more severe dementia severity). The power to assess such effects as interactions between delirium and neuropathologic processes is unique.

A number of limitations should be taken into account. Delirium was retrospectively ascertained and by slightly different methods. In the Vantaa 85+ study, assessments for history of delirium occurred at each visit, using information from participants, informants, and medical records. Ascertained of data in the CFAS and CC75C relied on diagnostic interviews at each study visit, but these data are likely to underestimate delirium in the intervening period. The diagnostic classification criteria also varied, although the different diagnostic schedules for delirium have good agreement with DSM-III-R. Despite these differences, the results appear to be consistent across the cohorts. The implication, either way, is that core symptoms in delirium—acute fluctuating change in attention in association with acute illness—represent an adverse state for subsequent cognitive trajectories regardless of the exact methods for operationalizing the syndrome. As with other prospective cohort data, the possibility remains that residual confounding contributes to these observed associations. Another consideration is that only a limited range of pathologic markers and comorbidities could be examined in this harmonized data set. Finally, although recent research based on neuroimaging and neuropathologic examination suggests that insults in earlier life can also be malignant, this hypothesis could not be examined within this study.

Conclusions
Our results indicate that delirium interacts with underlying pathologic processes of classic dementia and so represents a potential independent but interrelated pathologic pathway to chronic cognitive impairment and dementia. If delirium prevention could lead to consequent prevention of dementia, it will be essential to understand whether certain dimensions of the delirium syndrome might have a greater effect on cogn-
nitive trajectories than others. For example, duration, severity, and/or cause (eg, medications vs acute illness, surgery vs sepsis) may be differently important. The degree of preexisting multimorbidity or frailty may have a significant bearing. Animal studies modeling different causes and severities have some scope to elucidate some of these questions, but greater clarity on these issues must also come from careful prospective studies in representative populations. Nonetheless, our findings indicate that clinicians need to be alert to older people’s cognitive changes during acute episodes and in follow-up across all settings and therefore support wider implementation of best practice in delirium prevention. 45

REFERENCE