Delirium, neurofilament light chain, and progressive cognitive impairment: analysis of a prospective Norwegian population-based cohort

Maria Krogseth, Daniel Davis, Thomas Andrew Jackson, Henrik Zetterberg, Leiv Otto Watne, Morten Lindberg, Petronella Chitalu, Alex Tsui, Geir Selbæk, Torgeir Bruun Wyller

Summary

Background Previous population-based, longitudinal studies have shown that delirium is associated with an increased risk of dementia and cognitive decline. However, the underlying biological mechanisms are largely unknown. We aimed to assess the effects of delirium on both cognitive trajectories and any neuronal injury, measured via neurofilament light chain (NfL).

Methods In this analysis of a prospective, 2-year follow-up, cohort study of participants aged 65 years or older living in Sandefjord municipality, Norway, we included cohort participants who were receiving domiciliary care services at least once per week between May 12, 2015, and July 8, 2016. Individuals with a life expectancy of less than 1 week, with Lewy body dementia, with psychiatric illness (except dementia), or for whom substance misuse was the principal indication for domiciliary services were excluded. Participants had a comprehensive assessment at 6-month intervals for 2 years, which included the Montreal Cognitive Assessment (MoCA) and a blood sample for NfL to measure neuronal injury. All information on clinical diagnoses and medications were cross-referenced with medical records. During any acute change in mental status or hospitalisation (ie, admission to hospital), participants were assessed once per day for delirium with Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria. We also measured NfL from blood samples taken from participants who were acutely hospitalised.

Findings Between May 12, 2015, and July 8, 2016, 210 participants were eligible for inclusion and assessed at baseline (138 [66%] of whom were female and 72 [34%] of whom were male), 203 completed cognitive assessment, and 141 were followed up for 2 years. 160 (76%) of 210 had moderate or severe frailty and 112 (53%) were living with dementia. During the 2-year follow-up, 89 (42%) of 210 participants were diagnosed with one or more episodes of delirium. Incident delirium was independently associated with a decrease in MoCA score at the next 6-month follow-up, even after adjustment for age, sex, education, previous MoCA score, and frailty (adjusted mean difference –1·5, 95% CI –2·9 to –0·1). We found an interaction between previous MoCA score and delirium (β –0.254, 95% CI –0·441 to –0·066, p=0·010.), with the largest decline being observed in people with better baseline cognition. Participants with delirium and good previous cognitive function and participants with a high peak concentration of NfL during any hospitalisation had increased NfL at the next 6-month follow-up. Mediation analyses showed independent pathways from previous MoCA score to follow-up MoCA score with contributions from incident delirium (–1·7, 95% CI –2·8 to –0·6) and from previous NfL to follow-up MoCA score with contributions from acute NfL concentrations (–1·8, –2·5 to –1·1). Delirium was directly linked with a predicted value of 1·2 pg/mL (95% CI 1·02 to 1·40, p=0·029) increase in NfL.

Interpretation In people aged 65 years or older, an episode of delirium was associated with a decline in MoCA score. Greater neuronal injury during acute illness and delirium, measured by NfL, was associated with greater cognitive decline. For clinicians, our finding of delirium associated with both signs of acute neuronal injury, measured via NfL, and cognitive decline is important regarding the risk of long-term cognitive deterioration and to acknowledge that delirium is harmful for the brain.

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Introduction

The population determinants of dementia and chronic cognitive impairment are well established.[1] However, delirium—characterised by altered arousal, inattention, and global cognitive impairment arising from acute illness—is emerging as a further determinant of cognitive impairment.[2,3] Only two population-based studies have prospectively measured cognitive function

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Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway (M Krogseth PhD, Prof L O Watne MD, Prof G Selbæk MD, Prof T B Wyller MD); **Old Age Psychiatry Research Network, Telemark Hospital Trust and Vestfold Hospital Trust and Department of Internal Medicine, Telemark Hospital Trust, Skien, Norway** (M Krogseth); **Department of Medical Biochemistry** (M Lindberg PhD) **and Norwegian National Centre for Ageing and Health** (Prof G Selbæk), **Vestfold Hospital Trust, Tønsberg, Norway; Department of Nursing and Health Science, Faculty of Health and Social Sciences, University of South-Eastern Norway, Drammen, Norway** (M Krogseth); **Medical Research Council Unit for Lifelong Health and Ageing at UCL, UCL Institute of Cardiovascular Science** (Prof D Davis MRCP, P Chitalu MSc, A Tsui MRCP), **Department of Neurodegenerative Disease, UCL Institute of Neurology** (Prof H Zetterberg MD), **UK Dementia Research Institute at UCL** (Prof H Zetterberg), **University College London, London, UK; Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK** (T A Jackson PhD); **Department of Psychiatry and**

Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden (Prof H Zetterberg)**; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden** (Prof H Zetterberg)**; Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong Special Administrative Region, China** (Prof H Zetterberg)**; Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA** (Prof H Zetterberg)**; Department of Geriatric Medicine, Akershus University Hospital, Lørenskog, Norway** (Prof L O Watne)**; Institute of Clinical Medicine, University of Oslo, Oslo, Norway** (Prof L O Watne, Prof G Selbæk, Prof T B Wyller);

Correspondence to: Dr Maria Krogseth, Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo 0424, Norway
mkrogs@ous-hf.no

Research in context

Evidence before this study

We searched PudMed using the terms "Delirium" [title] and ("cognitive decline" or "dementia" or "epidemiology" or "prevalence" or "incidence" or "neurofilament light") [title and abstract]. We first conducted the search when planning the study in Sept 15, 2014, initially only using "Delirium" [title] and ("cognitive decline" or "dementia") [title and abstract]. The search was regularly repeated and most recently conducted on Jan 31, 2023, for papers published between database inception and Jan 1, 2023. We only included prospective population-based studies with direct delirium ascertainment; there were no language restrictions. We identified two such studies: the Delirium and Cognitive Impact in Dementia (DECIDE) study and the Delirium and Population Health Informatics Cohort (DELPHIC), both of which found delirium to be associated with cognitive decline and increased risk of dementia. However, no previous work has included biomarker measures of neuronal injury.

Added value of this study

Our data support previous results from the DECIDE and DELPHIC studies. We have replicated the finding that delirium is more closely associated with cognitive decline than with baseline cognitive function. Similar to DELPHIC, we found that the largest cognitive decline occurred in individuals with better baseline cognitive function. However, to our knowledge, we are the first to show this finding in a cohort with moderate or severe frailty. Showing evidence of neuronal damage mediated by increased neurofilament light chain (NfL) in participants and its association with cognitive decline is novel.

Implications of all the available evidence

Increased NfL as a marker of neuronal injury implicates delirium as harmful for the brain. For clinicians, this finding emphasises the importance of delirium prevention and might add prognostic information. Still, studies on whether delirium prevention could have an effect on long-term cognitive outcomes are needed, which has public health implications for dementia. Furthermore, whether there is a potential for cognitive rehabilitation after delirium should be investigated.

before, during, and after incident delirium. This longitudinal design has the advantage of quantifying the baseline cognitive state before acute delirium episodes. The Delirium and Cognitive Impact in Dementia (DECIDE) study[4] showed more episodes of delirium in hospital were associated with new dementia at 12-month follow-up after most recent hospital discharge, independent of the general effects of hospitalisation (ie, admission to hospital).[5] However, the study did not ascertain community delirium (ie, any episode of delirium identified outside of hospital). The Delirium and Population Health Informatics Cohort (DELPHIC) had findings consistent with DECIDE.[6] Furthermore, they showed that the largest cognitive decline occurred in people with high baseline cognition.[6] In DELPHIC, however, cognitive follow-ups were conducted via telephone interviews rather than in person, which was done in DECIDE.

The pathophysiological mechanisms underpinning the delirium–dementia relationship are unclear. Biomarkers of neuronal injury, such as neurofilament light chain (NfL), could be relevant for understanding the contribution of delirium to underlying neurodegenerative processes. NfL, a marker of axonal damage, is a measure of neurodegeneration and cognitive decline that can be assayed in peripheral blood.[7–9] Increased concentration of NfL is a risk factor for delirium, which might reflect concomitant neurodegeneration.[9] However, as NfL has been observed to increase during delirium in patients who have undergone surgery[10–12] and has emerged as a promising prognostic marker, this increase in NfL in relation to delirium is hypothesised to reflect a direct neurotoxic effect.[13] Increased NfL also predicts progression of Alzheimer's disease and brain atrophy.[14–16] However, no studies on delirium have serially measured NfL during both stable states and acute illness in prospective population-based cohorts.

We aimed to quantify the effects of directly ascertained delirium on cognition, considering both in-hospital and out-of-hospital delirium. Simultaneously, we investigated interactions between NfL, cognitive change, and any mediating pathways. In this cohort, we ascertained delirium during every acute illness, irrespective of hospitalisation. We hypothesised that delirium would be independently associated with worse cognitive outcomes and that increased NfL during acute illness and delirium would mediate worse cognition at follow-up.

Methods

Study design and participants

The Capturing Acute and Social Care in Dependent Elders (CASCADE) cohort was a prospective, 2-year follow-up, cohort study of participants aged 65 years or older living in Sandefjord municipality, Norway.[17] Eligible participants were receiving some degree of domiciliary care services (ie, at least once per week) between May 12, 2015, and July 8, 2016. Individuals with a life expectancy of less than 1 week, with Lewy body dementia, with psychiatric illness (except dementia), or for whom substance misuse was the principal indication for domiciliary services were excluded. Any potential

participants living with Lewy body dementia were excluded because the main clinical features of this disorder include fluctuating cognition, attention, and arousal. These symptoms overlap with delirium and make the diagnosis of delirium superimposed on dementia with Lewy bodies more challenging.[18] The manager of each domiciliary care team used the inclusion and exclusion criteria to identify eligible participants in consecutive alphabetical order by surname, then the nurse or health-care worker in the home-care nursing service who went to the next home visit of the participant asked them in their own home for oral consent to participate. Within 1 week after oral consent was obtained, participants were contacted by telephone and a date for the first home visit was made. Individuals who consented were then assessed by the research doctor (MK) or one of two research nurses trained in geriatrics.

Participants gave written informed consent at the first home visit before collecting of data began, unless their capacity to do so was impaired. In these circumstances, proxies for participants gave consent on their behalf. The CASCADE study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2014/1972).

Procedures

All participants had assessments at 6-month intervals for 2 years in their usual residence. Each assessment was conducted by the research doctor or one of the two study nurses. Sociodemographic data, years in education, years in work, and alcohol history were recorded. All information on clinical diagnoses and medications was cross-referenced with medical records. The height and weight of each participant were measured to calculate BMI. Sex data were self-reported; the options provided were male or female.

The primary cognitive measure was serial Montreal Cognitive Assessments (MoCA), with a score of up to 31 points. MoCA scores can be up to 30 points, but an additional point is given if 12 years or fewer were spent in education. Higher scores indicated better cognitive function.[19] The MoCA scores are generally normally distributed with fewer ceiling effects than similar cognitive tests, such as the Mini-Mental State Examination.[20] Depression symptoms were recorded with the Cornell Scale for Depression in Dementia[21] and neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory based on a caregiver interview.[22]

Caregivers also completed the short form of the Informant Questionnaire on Cognitive Decline in the Elderly[23] to establish dementia status. Based on all available baseline data, a diagnosis of dementia according to the International Classification of Diseases, tenth revision criteria[24] was made independently by a junior doctor (MK) specialising in geriatrics and a psychiatrist (GS) specialising in old age psychiatry. Disagreements were discussed by MK and GS until a consensus was reached.

Once per week, the domiciliary care team were asked the Single Question in Delirium on the basis of their routine contact with each participant.[25] If a participant showed any signs of delirium at home or was hospitalised for any reason, the project doctor (MK) was alerted within 24 h, either directly by the domiciliary care team or via an automated message sent as a standard notification by the community hospital. Participants were then assessed once per day, including weekends, in the community and in hospital, until either incident delirium or the participant was considered stable. All delirium assessments were conducted by one of four research team members (ie, the project leader [MK], one of the two study nurses, or a neurologist trained in delirium diagnosis). During any acute change in mental status or hospitalisation, Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria for delirium[26] were applied once per day after a test of attention (ie, months of the year backwards, days of the week backwards, digit span backwards, and a vigilance test by indicating hearing the letter A when S-A-V-E-A-H-A-A-R-T was read out; these tests were varied on consecutive days to minimise learning effects), a test of orientation with the Abbreviated Mental Test 4 (ie, age, date of birth, current location, and current year), and a test of level of arousal with the Richmond Agitation-Sedation Scale[27] and the Observational Scale for Level of Arousal were conducted.[28] Every delirium assessment was discussed with the research team member that had conducted the most recent home visit and MoCA to compare the acute presentation with the known baseline state. The main reason for hospitalisation was obtained from the hospital discharge summary.

On the basis of both participant and proxy information, physical function was measured with the Barthel Index, which assesses independence in activities in daily living.[29] It has a maximum score of 20; higher scores indicate more independence. Baseline frailty was quantified with a 34-item Frailty Index, as previously described.[17]

At each home visit, a blood sample was taken with BD Vacutainer SST II Advance Tubes 8·5 mL (Becton Dickinson, Plymouth, UK), stored at room temperature for 30–120 min, and then centrifuged for 15 min in a fixed angle at 3500 revolutions per min. The supernatant (serum) was aliquoted in 1 mL volumes in cryotubes stored at –32°C before transportation to long-term storage at –82°C. For participants admitted to hospital, we used the serum left over from any clinical samples after laboratory analyses on a convenience basis. Serum NfL was measured by Simoa NF-Light Advantage assay (Quanterix, Billerica, MA, USA) on an HD-1 Analyser, according to the manufacturer's instructions. The analyses of serum samples were conducted in Gothenburg, Sweden. Briefly, serum samples were thawed at 21°C, vortexed, and centrifuged at

10 000 relative centrifugal force for 5 min at 21°C. Onboard the HD-1 Analyser, samples were diluted (1:4) with sample diluent and bound to paramagnetic beads coated with a capture antibody specific for human NfL. Antibody-coated beads were incubated with a biotinylated anti-NfL detection antibody that was labelled with a streptavidin-β-galactosidase complex. After the addition of the β-galactosidase substrate resorufin β-d-galactopyranoside, a fluorescent signal proportional to the concentration of NfL present in the sample was generated in the antigen-containing microwells of the Simoa plates.

Sample concentrations were extrapolated from a standard curve, fitted with a four-parameter logistic algorithm. The lower limit of quantification for neurofilament light is 0·174 pg/mL; no samples from

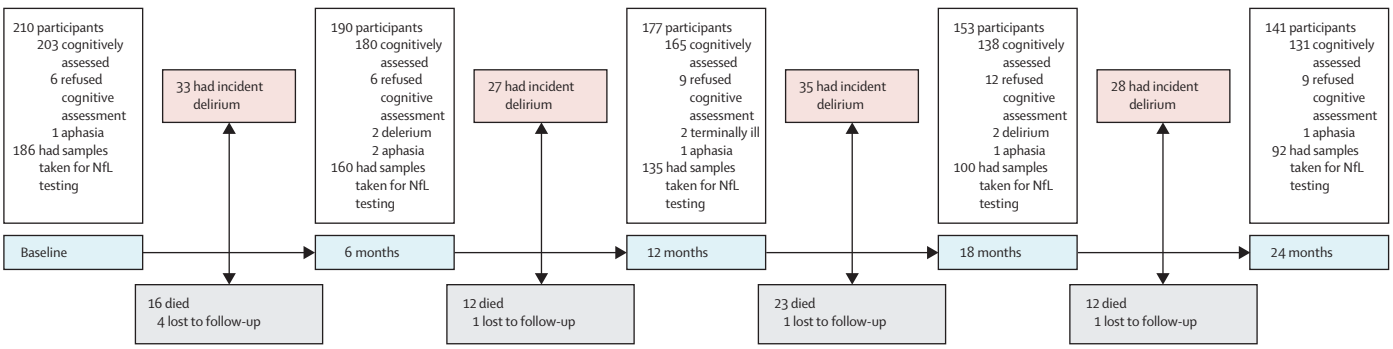

Figure 1: **Flow diagram**
One participant was not assessed at 18 months but remained in the study for the 24-month home visit. NfL=neurofilament light chain.

	Total (n=210)	Participants with missing data	No dementia at inclusion (n=98)		Dementia at inclusion (n=112)	
			No delirium (n=69)	Delirium (n=29)	No delirium (n=52)	Delirium (n=60)
Age, years	84·5 (8·3)	0	83·8 (9·3)	83·8 (8·0)	83·4 (7·8)	86·4 (7·3)
Sex						
Female	138 (66%)	0	45 (65%)	22 (76%)	33 (64%)	38 (63%)
Male	72 (34%)	0	24 (35%)	7 (24%)	19 (37%)	22 (37%)
Housing status						
Living alone	151 (72%)	0	57 (83%)	20 (69%)	34 (65%)	40 (67%)
Living with someone	59 (28%)	0	12 (17%)	9 (31%)	18 (35%)	20 (33%)
Years in education	9·8 (3·4)	0	9·6 (3·1)	10·0 (2·7)	9·6 (3·9)	10·0 (3·3)
Years in work	30·4 (16·8)	11	30·4 (16·5)	29·4 (16·4)	32·8 (16·4)	29·0 (17·9)
Charlson Comorbidity Index	2·6 (2·0)	0	2·3 (2·2)	2·8 (1·7)	2·4 (1·3)	3·1 (2·3)
Number of regular medications	7·3 (4·0)	0	8·0 (4·2)	8·6 (3·6)	6·8 (3·5)	8·1 (4·4)
MoCA score at inclusion	17·8 (6·4)	7	22·3 (4·2)	23·3 (3·7)	13·9 (4·8)	13·5 (5·4)
Barthel score at baseline	15·8 (3·7)	0	16·6 (3·0)	16·2 (3·2)	15·5 (4·0)	15·0 (4·2)
Home care per week, h	4·7 (4·9)	0	3·4 (4·1)	3·8 (5·9)	4·4 (4·0)	6·8 (5·3)
Visits from home care per week	16·6 (11·9)	0	12·6 (10·9)	12·3 (10·4)	17·1 (11·9)	22·7 (11·3)
Frailty according to the Frailty Index						
No frailty or prefrailty*	9 (4%)	0	3 (4%)	3 (10%)	2 (4%)	1 (2%)
Mild frailty†	41 (20%)	0	23 (33%)	4 (14%)	9 (17%)	5 (8%)
Moderate frailty‡	70 (33%)	0	29 (42%)	8 (28%)	14 (27%)	19 (32%)
Severe frailty§	90 (43%)	0	14 (20%)	14 (48%)	27 (52%)	35 (58%)
NfL at baseline, pg/mL	43·3 (30·9–64·7)	24	37·7 (28·1–52·3)¶	40·4 (31·8–66·4)‖	43·7 (31·7–64·3)**	53·9 (35·3–74·2)††
BMI	25·2 (4·8)	14	26·5 (4·9)	24·9 (4·8)	25·1 (5·0)	24·0 (4·2)

Data are mean (SD), n, n (%), or median (IQR). MoCA=Montreal Cognitive Assessment. NfL=neurofilament light chain. *Cutoff value ≤0·19. †Cutoff value 0·20–0·29. ‡Cutoff value 0·30–0·39. §Cutoff value ≥0·40. ¶Seven participants with missing data. ‖Four participants with missing data. **Eight participants with missing data. ††Five participants with missing data.

Table 1: **Demographic characteristics of the CASCADE cohort**

any control or acute hospitalisation were under the detection limit. For quality controls with concentration 9·3 pg/mL, the intra-coefficient of variability (CV) at each plate was 4·6% and inter-CV was 6·4%. For quality controls with concentration 102·8 pg/mL, intra-CV at each plate was 4·9% and inter-CV was 5·8%.

Statistical analysis

For cognition, both previous (ie, exposure) and follow-up (ie, outcome) measure was MoCA score, up to 31 points.[19] For NfL, values were log-transformed to produce a normally distributed variable. We created an acute burden score for measures taken during acute illness by summing values throughout hospital admission, expressed as (pg÷mL)×days, reflecting both NfL concentrations and length of stay in hospital. We categorised individuals into four groups. Three were reflective of tertiles of burden score (ie, high acute burden, median acute burden, and low acute burden) and all other participants were classified as no known acute burden, acknowledging the in-hospital samples having been acquired on a convenience basis. This approach allowed for simpler interpretation and is more likely to be robust than treating NfL values as a continuous variable, although it has the disadvantage of not necessarily being applicable to other cohorts.

A small number of individuals were lost to follow-up, so we conducted a complete-case analysis. This analysis assumes data to be missing completely at random.

For incident delirium and subsequent cognition, we used linear regression to estimate the standardised follow-up cognitive score adjusted by the lagged cognitive score from the previous assessment (eg, 6-month score adjusted by baseline score or 12-month score adjusted by 6-month score). Incident delirium, answered as either yes or no, was an independent variable. We estimated robust SEs clustered by participant to account for repeated assessments. We fitted a multiplicative interaction term to assess different associations between delirium and previous cognition. All analyses were adjusted by age (per year), sex (female participants compared with male participants), education (per year), and frailty (per SD).

For incident delirium, NfL, and subsequent cognition, we used a similar lagged model with robust SEs to estimate follow-up cognitive score, with incident delirium, adjusted by NfL concentration measured at the previous 6-month assessment. We included age, sex, previous cognition, education, frailty, and BMI.

For incident delirium, acute change, and follow-up NfL, we used random-effects models to quantify the relationship between acute change in NfL during illness and subsequent NfL when next assessed in the community. The outcome was follow-up log NfL concentration, adjusted by the acute burden measure (ie, none, low, medium, or high), delirium during the admission, age, sex, education, and frailty. Months since enrolment was the time metric.

In the mediation analysis, we estimated a generalised structural equation model to explore any pathways between delirium and follow-up MoCA score that could be mediated through NfL. We tested several variables,

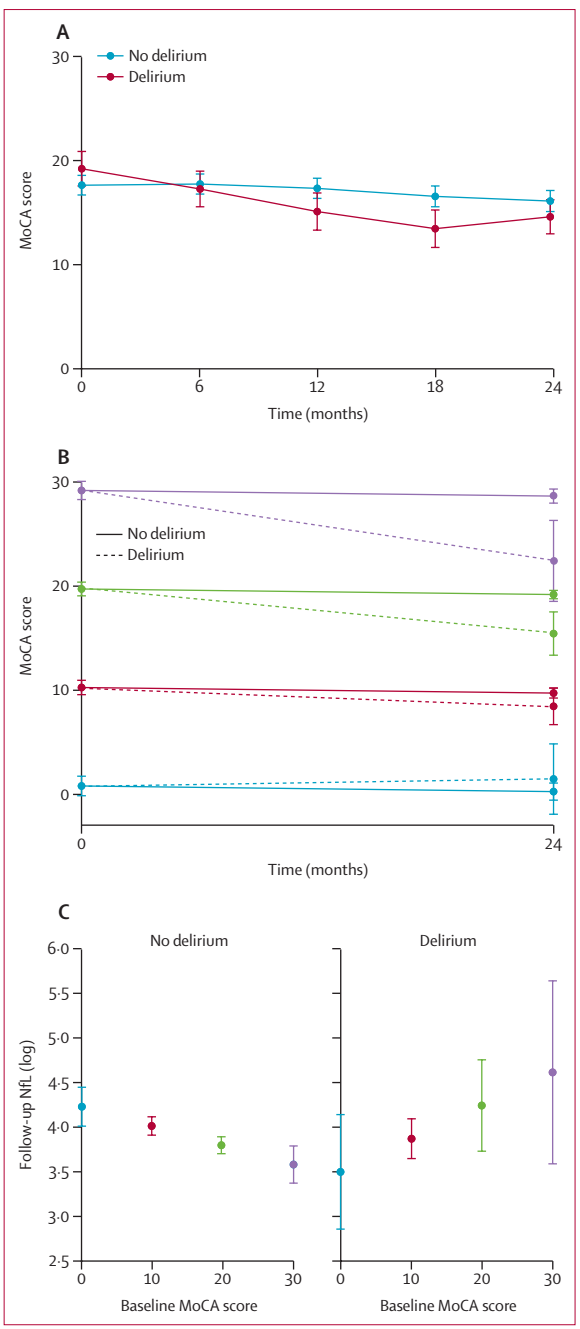

Figure 2: **Effects of delirium on MoCA and NfL**
(A) Trajectory of MoCA by delirium status at each 6-month interval, showing average effects for each group. A participant could be represented in either line depending on incident delirium during any 6-month period. (B) Predicted marginal effects for change in MoCA scores during the study period (ie, 24 months) by baseline MoCA score. (C) Follow-up NfL (log) by baseline MoCA score and any episode of delirium (appendix 2 p 4). MoCA=Montreal Cognitive Assessment. NfL=neurofilament light chain.

including education and frailty, but did not include them in the final model if they were not statistically significant. Therefore, the final selected variables to test constituent pathways to follow-up MoCA score were delirium (adjusted by previous MoCA score, age, and sex) and acute NfL (adjusted by previous NfL, age, sex, and BMI). We allowed an independent pathway between delirium and acute NfL.

All analyses were conducted with Stata version 17.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Data on acute hospitalisations have previously been reported; there were 307 acute hospital admissions representing 1235 hospital days.[17] Of these 307 admissions, the principal acute diagnoses were infections (102 [33%]), fractures (30 [10%]), renal failure or electrolyte atypicalities (22 [7%]), and heart failure (18 [6%]; appendix 2 p 2). The cumulative incidence of delirium was 89 (42%) of 210 participants. Of the 63 participants who died, 51 (81%) had one or more episodes of delirium, nine (14%) had delirium only as a part of the terminal phase, and three (5%) had no episodes.

See Online for appendix 2

During enrolment, 588 people aged 67 years or older were living in and receiving domiciliary care services in Sandefjord municipality. In consecutive alphabetical order by surname, 271 people were selected. We had to stop inclusion after 210 included participants due to available resources. The 317 other people who received home-care nursing service in the municipality and possibly fulfilled the inclusion and exclusion criteria were never asked to participate. 210 were eligible for inclusion and consented to inclusion into the CASCADE cohort (138 [66%] of whom were female and 72 [34%] of whom were male), and 203 had baseline cognitive testing. Of the 210 included participants, 141 were followed up for 2 years (figure 1). Six participants (3%) were lost to follow-up, one participant (<1%) was not assessed at 18 months but remained in the study for the 24-month home visit, and 63 (30%) participants died. Mean age at inclusion was 84·5 years (SD 8·3) and mean years in education was 9·8 years (3·4, range 4–22; table 1). At inclusion of all 210 participants, 160 (76%) had moderate or severe frailty and 112 (53%) were living with dementia. Stratified by dementia status, baseline MoCA score was similar in participants with and without subsequent delirium (table 1; appendix 2 p 1).

We conducted 2066 delirium assessments (1193 during acute illness and 873 at routine follow-up at-home visits). During scheduled follow-up visits, six participants were found to have delirium, so we excluded these MoCA assessments from the cognitive analyses as the delirium would substantially affect their cognitive performance and potentially not reflect their typical cognitive performance. During the 2-year follow-up, 89 (42%) of 210 participants were diagnosed with one or more episodes of delirium. Incident delirium was associated with a decline in MoCA score (figure 2A; appendix 2 pp 1, 9), even after adjustment for age, sex, education, previous MoCA score, and frailty (table 2). There was an interaction between previous MoCA score and delirium. The association between delirium and follow-up MoCA score varied according to cognitive function at the previous 6-month assessment, with the largest cognitive decline observed in people with good cognition (table 2; figure 2B).

At baseline, median NfL was 43·3 pg/mL (IQR 30·9–64·7 pg/mL; table 1; appendix 2 p 3). During hospitalisation, incident delirium was associated with increased median NfL levels during admission (88·2 pg/mL [42·7–125·0] *vs* 54·0 pg/mL [38·4–81·7]; p=0·020). We found an interaction between previous cognition and incident delirium for NfL concentrations at all follow-ups, such that after an episode of delirium, individuals with increased MoCA score at the previous 6-month assessment had the highest concentrations of NfL at next follow-up (figure 2C; appendix 2 p 4).

NfL measured at scheduled home visits every 6 months increased over time (appendix 2 p 5), whereas

	Adjusted model without interaction term			Adjusted model with interaction term		
	β	95% CI	p value	β	95% CI	p value
Age per year	−0·021	−0·050 to 0·009	0·17	−0·030	−0·060 to 0·000	0·050
Sex (female *vs* male)	−0·578	−1·163 to 0·006	0·053	−0·242	−0·833 to 0·349	0·42
Educational attainment per year	0·040	−0·054 to 0·134	0·40	0·012	−0·064 to 0·088	0·76
Frailty index per SD	−1·364	−3·790 to 1·062	0·27	−0·774	−3·112 to 1·564	0·51
Delirium	−1·495	−2·857 to −0·133	0·032	2·137	−0·796 to 5·069	0·15
Previous MoCA per point	0·916	0·868 to 0·964	<0·0001	0·938	0·895 to 0·982	<0·0001
Interaction between delirium and previous MoCA	..	..	..	−0·254	−0·441 to −0·066	0·010

The delirium row shows incident delirium between home assessments. Previous MoCA refers to the value of this variable in the previous 6 months. MoCA=Montreal Cognitive Assessment.

***Table 2*: Factors associated with MoCA score at next 6-month follow-up**

MoCA scores decreased over time (appendix 2 pp 6–7). NfL was negatively correlated with MoCA score (Spearman's r=–0·27; p<0·0001; appendix 2 p 10). In the subgroup of participants in whom we assayed NfL during acute hospitalisation (136 samples from 62 individuals), peak concentration was associated with increased NfL at all follow-ups (figure 3; appendix 2 p 5).

Mediation analyses showed independent pathways from previous MoCA score to follow-up MoCA score, with a contribution from incident delirium (figure 4; appendix 2 p 8). Similarly, previous NfL had a significant association with increase in acute NfL and higher acute NfL had a significant negative association with MoCA. A direct pathway from delirium to acute NfL was evident; delirium was linked with a predicted value of 1·2 pg/mL median increase in NfL (95% CI 1·0 to 1·4; p=0·029; figure 4; appendix 2 p 8).

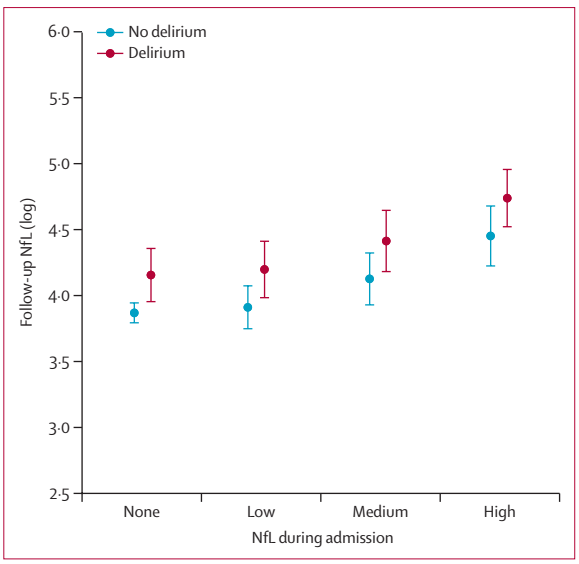

Figure 3: **Follow-up NfL (log) by peak concentration of NfL during hospitalisation and delirium**
For details, see appendix 2 (p 5). NfL=neurofilament light chain.

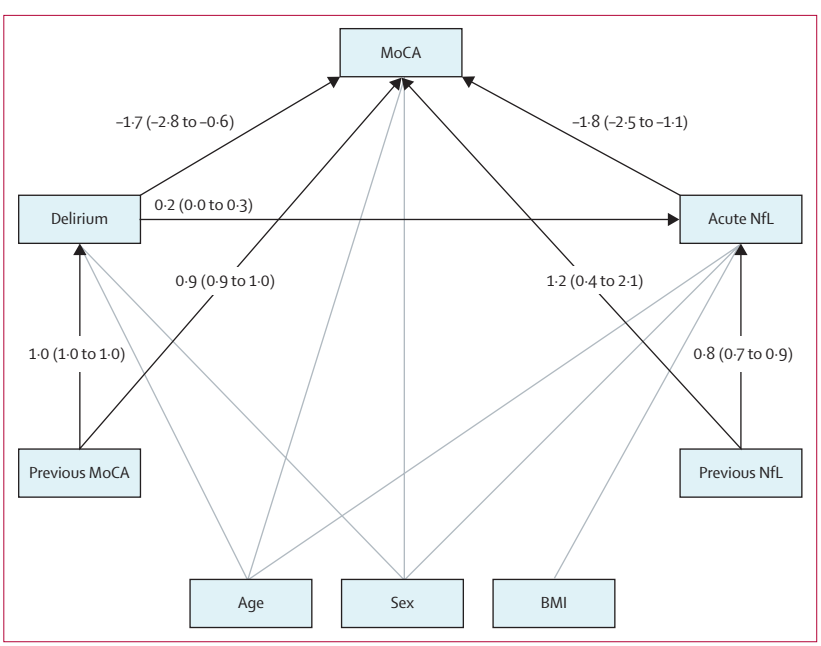

Figure 4: **Mediation analysis exploring any path between NfL and cognitive function at next scheduled follow-up via MoCA and between delirium and follow-up MoCA, including an independent pathway between incident delirium and follow-up MoCA through acute NfL**
Data are β (95% CI). Numbers on arrows are the standardised effects of one variable on another. Grey lines show variables that are adjusted for in the model (appendix 2 p 8). Previous NfL and previous MoCA refer to the value of these variables at the previous 6-month assessment. MoCA=Montreal Cognitive Assessment. NfL=neurofilament light chain.

Discussion

In a population-based cohort of people aged 65 years or older receiving domiciliary care in Norway, of whom 76% had moderate or severe frailty and 53% had dementia at inclusion, we found incident delirium to be associated with worse cognition at all follow-ups, with a larger effect in people with previously higher cognition. From data collected at scheduled home visits, the highest concentrations of NfL were found in participants with good cognitive function at the previous 6-month assessment and incident delirium. Acute rises in NfL during hospitalisation (ie, admission to hospital) also contributed to increased concentrations of NfL at all follow-ups. Therefore, changes in NfL during acute illness might be related to the mechanism by which delirium mediates worsening cognitive impairment.

The CASCADE study is the third population-based study to show cognitive decline after incident delirium via robust delirium assessment and to prospectively account for baseline cognition.[4,6] However, to our knowledge, it is the first cohort in which participants were assessed for delirium during acute events in every setting (eg, in hospital or at home), cognitive decline was associated with biomarker evidence of neuronal damage, and the effect of delirium on cognition in a population characterised by moderate or severe frailty was shown. These data support a previous finding from a prospective population-based study of the most significant reduction in cognitive scores occurring in people with previously better cognition.[6] There are five potential explanations. First, this finding might be due to any non-equivalence of points in the MoCA scale, although scores were normally distributed in our sample. Second, a more extreme neurotoxic stressor might be necessary to precipitate delirium in people who are cognitively robust, resulting in a worse prognosis. Third, the diagnosis of delirium is most challenging in people with pre-existing severe cognitive impairment; an increased number of people who are false delirium-positive might reduce the true attributable proportion of delirium on cognitive trajectories. Fourth, in participants with severe chronic cognitive impairment, an increased risk of death from any acute events precipitating delirium would be expected, which might lead to a survival effect. Finally, floor effects in MoCA prevent people scoring a very low

number of points (eg, close to zero) from attaining lower scores if they deteriorate further.

Delirium has been proposed, to an extent, to reveal underlying (ie, subclinical) brain impairment.[30] However, when we stratified on baseline dementia status, MoCA scores at inclusion were similar in participants who did and participants who did not subsequently develop delirium. The largest decline in MoCA scores was evident in participants with good cognitive function. This finding might reflect the parallel observation in longitudinal population-based cohorts of increased terminal decline in individuals with higher education and presumed cognitive reserve.[31]

As NfL is a marker of neuronal damage, our finding that concentrations of NfL assessed at scheduled home visits were inversely related to cognitive function was expected.[32] However, we are the first to document increasing concentrations of NfL at follow-up in people with incident delirium and good cognitive function at the previous 6-month assessment, the same group with the largest decline in cognitive function. People with better cognitive function might have more function to lose, resulting in a larger reduction in cognitive test scores, more neurons susceptible to injury, and, therefore, higher NfL concentrations. Furthermore, as a more severe precipitating factor is necessary to precipitate delirium in people who are cognitively more robust, those with better cognitive function who are developing delirium might have had a more severe acute illness, which is known to be associated with increased concentrations of NfL, than those with worse cognitive function.[33] Nonetheless, DELPHIC showed that adjusting for measures of illness severity (ie, physiological and laboratory parameters) did not alter the underlying relationships between baseline cognition and incident delirium severity.[34] In our analysis, the increase in NfL during acute events was associated with higher concentrations of NfL at all follow-ups, suggesting that NfL can be persistently increased, perhaps as a marker of an ongoing neurodegenerative process triggered during delirium or acute illness.

The timeframe for delirium recovery is variable.[35] Despite screening participants for delirium at each home visit and omitting test results from participants with delirium at each follow-up, that some of the cognitive and functional decline associated with delirium in our analysis might be due to potentially reversible delirium symptoms persisting at the next follow-up is impossible to rule out. Future research should investigate the nature of persistent delirium and the potential for cognitive rehabilitation after an episode of delirium to mitigate risk of cognitive decline. Furthermore, whether delirium prevention has an effect on long-term cognitive outcomes should be further explored. As we found NfL to be highest after delirium in people with better cognitive function at the previous 6-month assessment, we suggest further research on whether structural measures (eg, brain volume) are related to NfL dynamics after neuronal injury.

42% of participants included in our analysis had one or more episodes of delirium during the 2-year follow-up, reflecting the high prevalence of the two most important risk factors for delirium in our sample: increased age and baseline dementia. Moreover, the numerous acute events show the high frequency of potential delirium precipitants. All participants were receiving home-care service, 76% had moderate or severe frailty, and 30% died during follow-up, emphasising that delirium is a substantial concern in later life.

Our data have several limitations. First, the observational study design cannot rule out residual confounding. Second, the increased degree of frailty and high prevalence of dementia among participants limits generalisability to other populations. Third, we did not measure the severity of any illness provoking any acute event, neither were severity or duration of delirium assessed. The most important strengths are the completeness of the data (only six participants were lost to follow-up); our inclusion of episodes of delirium that did not lead to hospitalisation; and our use of validated and well known tests for delirium, cognitive function, and frailty. Moreover, we provided a consensus diagnosis of dementia based on all available information (ie, cognitive and physical function, caregiver information, and validated screening for depression).

In people aged 65 years or older who were living at home, we found delirium to precipitate a decline in cognition and an increase in NfL, most evidently in people with better cognitive function at the previous 6-month assessment. A direct acute neurodegenerative process could partly mediate the effect of an episode of delirium on cognitive decline. This finding could extend our understanding of pathophysiological routes to dementia and lead to a broader strategy regarding the effects of delirium on dementia prevention.

Contributors

MK and TBW conceptualised the study. MK curated the data. MK, PC, AT, and DD conducted the analyses. MK, GS, and TBW acquired funding. MK and HZ did the investigation. MK, DD, TAJ, GS, LOW, and TBW developed the methods. MK and TBW administered the project. MK, HZ, and ML acquired resources. TBW supervised the study. MK and DD visualised the data. MK, DD, and TBW wrote the original draft. All authors reviewed and edited the manuscript. MK, DD, AT, and PC verified all data in the study. All authors were permitted full access to all the data in the study (if they wished) and had final responsibility for the decision to submit for publication.

Declaration of interests

HZ has been on scientific advisory boards for AbbVie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; been a consultant for Red Abbey Labs; and has given lectures in symposia sponsored by Fujirebio, Alzecure, Cellectricon, Biogen, and Roche. HZ is a co-founder of Brain Biomarker Solutions in Gothenburg, Sweden, part of the University of Gothenburg Ventures Incubator

Program. GS has participated in an advisory board for anti-dementia drugs for Roche and Biogen. All other authors declare no competing interests.

Data sharing

There are several legal restrictions to data sharing in Norway. The Norwegian Social Science Data service has not approved data delivery outside of Europe, consent for publication of raw data was not obtained from participants included in the study, and complete anonymisation is not possible as the data contain potentially identifying participant information that might be trackable. For these reasons, data are available only upon reasonable request to the corresponding author from date of publication until June 30, 2028. In the consent signed by each participant, we have consent to share de-identified participant data with collaborating research groups within the EU and European Economic Area. Each collaboration and the plan of any other project must individually be approved by the Norwegian Regional Committees for Medical and Health Research Ethics. The informed consent form is available elsewhere (https://www.sthf.no/helsefaglig/forskning-og-innovasjon/forskningsprosjekter/delirium-blant-hjemmeboende-eldre-med-hjemmesykepleie).

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