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Extremes of baseline cognitive function determine the severity of delirium: a population study

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Abstract

Though delirium is a significant clinical and public health problem, little is understood about how specific vulnerabilities underlie the severity of its presentation. Our objective was to quantify the relationship between baseline cognition and subsequent delirium severity.

We prospectively investigated a population-representative sample of 1510 individuals aged ≥70 years, of whom 209 (13.6%) were hospitalised across 371 episodes (1,999 person-days assessment). Baseline cognitive function was assessed using the modified Telephone Interview for Cognitive Status, supplemented by verbal fluency measures. We estimated the relationship between baseline cognition and delirium severity (Memorial Delirium Assessment Scale, MDAS) and abnormal arousal (Observational Scale for Level of Arousal), adjusted by age, sex, frailty and illness severity. We conducted further analyses examining presentations to specific hospital settings and common precipitating aetiologies.

The median time from baseline cognitive assessment to admission was 289 days (interquartile range 130 to 47 days). In admitted patients, delirium was present on at least one day in 45% of admission episodes. The average number of days with delirium (consecutively positive assessments) was 3.9 days. Elective admissions accounted for 88 bed-days (4.4%). In emergency (but not elective) admissions, we found a non-linear U-shaped relationship between baseline global cognition and delirium severity using restricted cubic splines. Participants with baseline cognition two standard deviations (SD) below average (z-score = -2) had a mean MDAS score of 14 points (95% CI 10 to 19). Similarly, those with baseline cognition z-score = +2 had a mean MDAS score of 7.9 points (95% CI 4.9 to 11). Individuals with average baseline cognition had the lowest MDAS

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scores. The association between baseline cognition and abnormal arousal followed a comparable pattern. C-reactive protein ≥20 mg/L and serum sodium <125 mM/L were associated with more severe delirium.

Baseline cognition is a critical determinant of the severity of delirium and associated changes in arousal. Emergency admissions with lowest and highest baseline cognition who develop delirium should receive enhanced clinical attention.

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Abbreviations: DELPHIC Delirium and Population Health Informatics Cohort; DSM Diagnostic and Statistical Manual of Mental Disorders; MDAS Memorial Delirium Assessment Scale; OSLA Observational Scale of Level of Arousal; NEWS National Early Warning Score; TICS-m Telephone Interview for Cognitive Status (modified)

Introduction

Delirium is a severe neuropsychiatric syndrome characterised by acute changes in arousal, inattention, and other mental status changes. Its clinical importance is well-established: it affects 1 in 4 older inpatients, and in multiple settings, delirium is associated with adverse outcomes such as mortality, inpatient falls, delayed discharges, and significant patient and carer distress.[1–5] Delirium is also associated with future cognitive impairment and incident dementia.[6,7] There is wide variability in the natural history of delirium.[8] Though we know that older age, prior cognitive impairment, and frailty are delirium risk factors,[9,10] the combination of baseline cognition and acute illness could result in different degrees of delirium symptomatology. The influence of baseline cognition on subsequent delirium phenomenology has not been considered comprehensively. Yet, an empirical understanding of this relationship could affect delirium detection, assessment and management because the clinical significance of delirium symptoms might have different implications if framed in the context of a known baseline cognitive state.

Existing studies linking baseline cognitive function to delirium severity have used the methodological advantage of prospective follow-up in elective surgical populations.[11–13] However, most delirium in secondary care presents in unselected unscheduled medical admissions with a much greater range of pre-existing cognitive impairment and frailty.[14] Previous work in acute medical patients has assessed baseline cognition in two ways. First, by

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establishing a binary dementia diagnosis, or second by using cognitive testing on admission only in patients initially without delirium.[15,16] This is a crucial issue because around two-thirds of delirium is present on admission. [15,17] Very few reports in medical patients have assessed delirium severity in relation to baseline cognition.[18–20] More broadly, we do not fully understand the overlap between delirium severity and arousal changes.[21] Abnormal arousal may be a key driver to mortality after delirium, though its detailed quantification is under-represented in many delirium severity scales.[22] Finally, we know little about the specific aetiological precipitants that might be associated with more severe delirium in general hospital settings.

To understand the influence of baseline cognition on delirium phenomenology (including abnormal arousal) across the whole spectrum of hospital presentations, we needed to characterise cognitive function in a stable community sample and then at each subsequent acute hospitalisation systematically: (1) assess the severity of delirium on each day; (2) relate this to baseline cognitive function; (3) understand the relationship between hospital setting, aetiological factors and delirium risk. We hypothesised that lower baseline cognition would lead to greater severity of delirium symptoms in the event of acute hospitalisation.

Materials and methods

Population

The Delirium and Population Health Informatics Cohort (DELPHIC) is a prospective longitudinal population-representative sample of older adults aged ≥70 years in the London Borough of Camden, a central city region with a population of 260,000 residents (Figure 1).[7,23] The National Health Service in England provides >95% of healthcare, and Camden is served by a single primary care system (the Camden Clinical Commissioning Group representing 39 general practices) and two acute hospitals (University College Hospital, Royal Free Hospital). This report is a planned analysis of the participants recruited between January 2017 and December 2018. Our overall pre-specified power calculations were for a separate outcome: two-year change in cognition at follow-up in the whole cohort. We anticipated that a minimum of

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11% of the cohort would need to be admitted to provide meaningful estimates describing the relationship between baseline cognition and incident delirium.[23]

Eligible participants were aged ≥70 years and registered with a Camden-based general practitioner. Based on coded problems in the primary care record, we did not approach those with severe hearing impairment, aphasia, or who could not speak English sufficiently to undertake any basic cognitive assessment or were in the terminal phase of illness. In addition to the primary care lists, we over-sampled from memory clinics and patients recently discharged from secondary care in an 8:1:1 ratio. Invitations were sent by letter. All individuals, or their nominated proxies, gave consent to participate. The direct sampling from memory clinics facilitated the inclusion of participants with pre-existing cognitive impairments and dementia.

Baseline assessments

Most participants were assessed through telephone interviews. However, we enabled eligible participants with previously unidentified yet significant hearing impairment to be assessed at a home visit. Cognitive function was the primary measure, assessed using the modified Telephone Interview for Cognitive Status (TICS-m), which covers orientation, attention, naming, praxis, calculation, and immediate and delayed recall of a 10-item non-semantically related word list.[24] We supplemented this with the two verbal fluency tasks (generating words beginning with the same letter, number of animals) from the Addenbrooke's Cognitive Examination to improve the measurement of executive function in the battery.[24,25] Through interview and real-time access to all health and social care records through the Camden Integrated Digital Record, we assessed the following domains: socio-demographic factors, index of multiple deprivation, general health, co-morbidities, medications, health behaviours, hearing, vision, quality of life, dental health, continence, falls, depression, personal and instrumental activities of daily living. Frailty was quantified using a Frailty Index, representing the proportion of accumulated health deficits (0 to 1). This was derived using 28 items drawn from the baseline assessment and calculated in line with standard procedures.[26] However, we did not include cognitive items to avoid collinearity with the primary cognitive measure. Further details for ascertaining baseline covariates have previously been published.[23] For these analyses, we also checked to assess the extent to which inclusion or exclusion of specific frailty index items might have affected the fundamental

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relationships between frailty and delirium and found the index to be robust (Supplementary Table 1)

Hospital assessments

All participants admitted to either of the acute hospitals were automatically flagged through daily electronic alerts and reviewed in person each day (Monday to Friday) from the day of admission by a researcher. We did not assess participants presenting to the emergency department who were discharged from there. At each assessment, we evaluated participants for changes in cognitive or physical function using the Memorial Delirium Assessment Scale (MDAS), Observational Scale of Level of Arousal (OSLA), and the Hierarchical Assessment of Balance and Mobility (although this last measure does not form part of this analysis). [21,27,28] We recorded additional information on acute aetiology, medications, illness severity (NEWS) and laboratory findings. The NEWS integrates clinically abnormal physiological indices: heart rate, blood pressure, respiratory rate, oxygen saturations, supplemental oxygen requirements, alertness) giving a score from 0 to 20.[29,30] Higher scores indicate risk of immediate deterioration, with scores above 4 indicating need for clinical review for escalation of care. Although NEWS2, which includes a measure of confusion, was introduced over the course of the study, this component had not been reliably implemented in routine care.[30]

Ascertainment of delirium

We used the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria as the case ascertainment for the primary outcome because it is the most widely used definition and allows comparative estimates with other studies. Delirium was ascertained for every day of hospital admission using all available information. Complete interview questions are available in supplementary material. On each day, we determined delirium to be present if individuals met Criteria A (*disturbance of consciousness*), B (*change in cognition and/or perception*) and C (*acute and fluctuates*). By virtue of their inpatient admission, all participants were deemed to fulfil Criterion D (*physiological consequence of a general medical condition*).

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Statistical analyses

Outcome measures

Delirium severity: MDAS assesses 10 domains of delirium symptoms (awareness, orientation, short-term memory, digit span, attention capacity, disorganised thinking, perceptual disturbance, delusions, psychomotor activity, sleep–wake cycle, each scored out of 3) to give a 30-point measure of delirium severity. *Abnormal arousal*: The Observational Scale for Level of Arousal was designed to quantify grades of arousal changes in delirium, specifically quantifying eye opening, eye contact, posture and movement. [21] It has 15 points, with higher scores representing deviations in arousal level in either direction, i.e., hyperactive and hypoactive.

Exposures

Baseline cognition: Composite cognitive score (TICS-m was scored out of 53 points, verbal fluency scored out of 14 points, summed to 67 points and standardised as a z-score (score-mean)/standard deviation). *Hospital setting*: We separately examined elective and emergency admissions, as well as those presenting to surgical and internal medicine services. *Aetiology*: We explored possible effects of broad aetiological categories based on laboratory results: C-reactive protein (≥20 mg/L); white cell count (<4x10^9 cells/L; 4-11x10^9 cells/L; ≥11x10^9 cells/L); acute kidney injury (defined by the NHS England patient safety alert algorithm[31]); anaemia (haemoglobin <100 g/L); hyponatraemia (<125 mM/L; 125-135 mM/L; 135-145 mM/L; ≥145 mM/L).

Frailty was quantified using a Frailty Index, as described above. Education was categorised as: up to primary (6 years of school; up to secondary (12 years school); and degree level or above. We also adjusted for time from baseline assessment to first admission to account for any possible interval change in cognition.

Missing data

Whole assessments that were missing due to falling on a weekend or public holiday (missing at random) were forward-filled (Friday carried to Saturday) and backwards-filled (Sunday carried from Monday) in 24-hour intervals for up to 4 days. Imputation is primarily a statistical

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technique. However, for backwards filling, this approach has the advantage of automatically carrying over information from the next working day's chart review. Otherwise, data were assumed to be missing at random.

Models

In exploratory analyses, we examined the distribution of MDAS and OSLA scores by tertiles of baseline cognition (Supplementary Figure 1), which suggested the underlying relationships might be non-linear. We investigated this by fitting restricted cubic splines with three knots. We used the default knot positioning from the Stata *mkspline* function, which operationalises Harrell's recommended percentiles with the additional restriction that the first and last knots are bound by the fifth-smallest and fifth-largest values of baseline cognition, respectively.[32] We found equivalent results using fractional polynomials, a complementary technique for describing non-linear relationships (Supplementary Table 2, Supplementary Figure 2)

Models were estimated for each admission in each individual using mixed-effects linear regression, where each day's MDAS or OSLA scores were the dependent variable, adjusted by age, sex, baseline cognition (standardised as (score-mean)/standard deviation), frailty index, NEWS and time from baseline assessment to first admission. In separate models, we used standardised *z*-scores for executive function and memory domains as the explanatory variable.

Sensitivity analysis: Because MDAS items 2 (disorientation) and 3 (short-term memory impairment) may be higher because of prior cognitive impairment (i.e., worse baseline cognitive scores), we performed a sensitivity analysis, replicating the principal models with these items removed (modified outcome score /24 points).

After estimating each model, we checked assumptions using plots of the standardised residuals. We performed all analyses using Stata version 17.0 (StataCorp, Texas).

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Data availability

Complete de-identified participant data, along with study protocols, consent forms and case report forms, are available through the Dementias Platform UK Data Portal: https://portal.dementiasplatform.uk.

Results

Of 1510 participants recruited, median age was 77 (interquartile range 73 to 82), and 57% were women (Table 1). We undertook home assessments in n=32 participants because hearing impairment precluded telephone interview. Over the study period (follow-up to July 2021), 209 participants (13.6%) were hospitalised across 371 episodes, with 1566 days of data collection, totalling 1,999 person-days of assessment following imputation to account for weekends and bank holidays (Figure 1). Elective admissions accounted for 6% episodes (22/371) and 88 bed.days (4.4%). In emergency admissions, hospitalised individuals had lower baseline TICS-m cognitive scores (mean 35.5 versus 38.8 points, p<0.01), and more frailty (frailty index 0.25 versus 0.15, p<0.01) than those not hospitalised. Individuals admitted once accounted for 114 (55%) hospital episodes; the rest were admitted multiple times (median number recurrent admissions 2, IQR 2 to 4). The median time from baseline cognitive assessment to admission was 289 days (IQR 130 to 447 days).

The commonest presenting symptoms were general malaise and fever (15%), respiratory (dyspnoea, cough, 9%) and neurological complaints (confusion, 9%) (Table 1). Patients with delirium were less likely to have a respiratory presentation. There were some small statistically significant absolute differences in initial laboratory values (sodium, potassium, creatinine) for delirium patients, but these were unlikely to be clinically relevant (Table 1).

Delirium status

On any given day (point prevalence), 29% of all hospitalised participants fulfilled DSM-IV criteria for delirium. At any assessment, participants met DSM-IV criteria A, B and C 69%, 68%, and 41% of the time (Table 2). Over the course of an admission, delirium was ascertained in

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45% of inpatients (prevalent delirium at admission in 35%, incident delirium developing after admission in 10%). The average number of days with delirium (consecutively positive assessments) was 3.9 days.

Measures contributing to Criterion A included abnormal OSLA scores (31%) and inability to perform *months of the year* backward (13%). In those able to undertake serial subtractions of 7 from 100 at baseline, 16% could not do so on hospitalisation. Digit span was impaired in 10% of individuals.

Components of Criterion B included short-term memory impairment in 31% of cases and 32% could not answer at least 5/10 orientation questions correctly. Disorganised thinking was apparent in 15% of individuals. There was evidence of perceptual disturbance in 13%.

There was fluctuation (Criterion C) in OSLA or MDAS scores (differing from the previous assessment by ≥1 SD) 5% of the time. Informants (ward staff and/or visitors) described fluctuations in arousal or motor function in 22%. New severe sleep-wake cycle disturbance was present in 17%.

Baseline cognition and delirium severity

Overall, there was a non-linear relationship between baseline cognition and delirium severity (Table 3, Figure 2). MDAS scores were higher when baseline cognition was both low and high. The negative relationship between baseline cognition and delirium severity for the first spline and positive relationship with the second spline led to MDAS scores of 14 (95% CI 10 to 19) points at *z*-score = -2 and MDAS of score 7.9, 95% CI 4.9 to 11 at *z*-score = +2) (Figure 3). The lowest MDAS severity scores were seen in those at the midpoint of baseline cognition (*z*-score = 0).

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Sensitivity analyses with *disorientation* and *short-term memory* items removed from the MDAS showed similar a similar bimodal distribution of scores (Supplementary Table 3 and Supplementary Figure 3).

Baseline cognition and abnormal arousal

The relationship between baseline cognition and abnormal arousal followed a comparable pattern. At the extremes of baseline cognition, OSLA scores were higher (OSLA 6.2, 95% CI 4.8 to 7.6 points at *z*-score = -2; OSLA 5.2, 95% CI 3.7 to 6.6 at *z*-score = +2) (Figure 3). Again, the lowest OSLA scores were recorded in those with baseline cognition *z*-scores of 0.

Hospital setting and delirium severity

Elective admissions were associated with lower MDAS scores (Table 3). There was an interaction between higher baseline cognition (second spline) and elective status. This effect countered the positive base coefficient (β=4.3, 95% CI 1.7 to 7.0) with negatively sloping estimates (elective β=-3.0, 95% CI -5.9 to -0.34; interaction β=-2.1, 95% CI -3.9 to -0.27) (Table 3). Together, this meant the relationship between baseline cognition and delirium severity was *linear* in elective, but not emergency settings (Figure 2). Surgical admissions (regardless of elective or emergency status) were also associated with lower MDAS scores (-3.4 points, 95%CI -6.2 to -0.5, p=0.02) (Supplementary Table 5). However, on further adjustment by elective or emergency setting, this association was no longer significant.

Aetiology and delirium severity

In all cases, adjusting for possible aetiological precipitants derived from laboratory results contemporaneous with delirium assessments did not alter the underlying relationship between baseline cognition and MDAS scores (Table 3). In mutually adjusted models, CRP above ≥20 mg/L and severe hyponatraemia (Na <125 mM/L) were associated with increased delirium severity. Lower and higher total white cell counts (outside the range 4-11 $x10^9$ cells/L) were associated with lower MDAS scores. Concurrent acute kidney injury or anaemia was not related to delirium severity (Table 3).

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Discussion

For the first time in a sample of unscheduled admissions, we showed that baseline cognition had a bimodal relationship with delirium severity and abnormal arousal, even after accounting for conventional physiological measures of illness severity, laboratory indicators of aetiologies and frailty. That is, emergency patients with both low and higher baseline cognition had a higher severity of delirium. This was not the case for the small number of elective admissions, where the more established linear relationship between baseline cognition and delirium severity was evident. Higher delirium severity scores in those with poorer baseline cognition were not confounded by pre-existing cognitive impairment. Delirium severity and abnormal arousal were closely related at all levels of cognition. Our results suggest that when acute illness is sufficient to lead to delirium, different factors may be at play across the range of baseline cognitive function. In the context of higher baseline cognition, the presence of delirium could be an important indicator of acute illness in older people, over and above physiological indices such as NEWS (insofar as NEWS may be specific in older people but not be sensitive), because delirium severity likely predicts worse outcomes.[33]

Our data should be interpreted in the context of some limitations. Despite comprehensive methods to identify hospitalised participants, there is inevitably a degree of selection bias that would have missed cases who developed delirium but remained in the community, and a small number of hospitalisations may have occurred in acute hospitals outside a participant's usual residence. Although we had the advantage of frequent clinical assessments, we made assumptions about missing data on delirium status over weekends and public holidays. Our exploration of possible differences attributable to underlying aetiology was limited to major categories that could be readily operationalised from laboratory abnormalities. A more comprehensive approach is an area of ongoing analysis, which includes possible effects related to medication use and a more detailed assessment of the temporal relationships between each factor and their interactions. In common with other observational studies, residual confounding may affect some of the estimates. Nonetheless, the prospective capture of brain symptoms before and during acute illness allows for the most systematic mapping of baseline cognition, hospitalisation and delirium in a population-representative sample to date.

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In respect to other studies, in a cohort admitted to ICU, the IQCODE, a retrospective estimate of pre-morbid cognitive impairment, was linked to different delirium trajectories in critical illness: baseline cognitive impairment was associated with worsening delirium severity.[34] As with elective surgical patients, however, the spectrum of pre-existing cognitive impairment was narrower compared with our data. In a study of general medical hospitalisations, a retrospective chart-based diagnosis of dementia was associated with a higher peak delirium severity score.[19] The only other study to prospectively ascertain delirium in unselected hospitalisations, the Delirium and Cognitive Impact in Dementia study, found that lower baseline MMSE scores were associated with binary delirium risk; the relationship with severity was not assessed.[20] There have not been previous reports linking high baseline cognition with more severe delirium or greater arousal abnormalities.[33,34]Our findings in respect of aetiology are also broadly consistent with other studies examining the relative contributions of delirium precipitants on outcomes.[35,36] Though all of the associations in our current study adjusted for acute illness severity, NEWS may be an insufficient measure in older people, at both the lowest and highest ends of the baseline cognitive spectrum. The idea that changes in behaviour and cognition, such as delirium itself, could be the sole or at least the predominant feature of acute illness has been observed in COVID-19, leading to the proposal that it be incorporated into the case definition for older adults.[37] Work on clinical outcomes after delirium in people with different levels of baseline cognition will investigate the degree to which delirium is a better marker of acute illness compared with standard physiological metrics.

Overall, these data have several potential implications for clinical care. In people with delirium, early assessment of pre-delirium cognitive function, such as with IQCODE, could assist in identifying those at risk of severe delirium. This is important because severe delirium involves a higher risk of distress and future post-traumatic stress symptoms.[38] In those with higher baseline cognition, recall of distressing delirium symptoms may be more likely, warranting consideration of follow-up. The novel observation that patients with higher baseline cognition tended to have more severe delirium could also prompt enhanced management given the relatively worse long-term cognitive outcomes for these patients.[7] Abnormal arousal, commonly present in severe

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delirium, may also lead to more patient safety issues: longer length of stay, greater rehabilitation needs, reduced bulbar function and aspiration pneumonia and inpatient falls. For those with lower baseline cognition, family and carer education may mitigate this through better recognition of the specific links between abnormal arousal and delirium. For example, this could be a focus for patients recently diagnosed with dementia in the memory clinic, or where particular deficits in executive function have been identified. Such patients have a 50% risk of being admitted acutely in the next 12 months and public understanding of delirium is suboptimal.[39,40 41]

In conclusion, worse baseline cognition increases the risk of delirium. In patients who develop delirium, low and high baseline cognition are linked with a higher severity of delirium. The relationship between baseline cognition and delirium severity advocates for assessment of baseline cognition in patients with delirium, even if this must be retrospectively obtained using informant tools. Additionally, in patients with risk of severe delirium enhanced evaluation of causes and delirium symptoms such as distress may be warranted.

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Competing interests

Kenneth Rockwood is President and Co-founder of Ardea Outcomes, which in the last three years(as DGI Clinical) has contracts with pharma and device manufacturers (Shire, Hollister, Nutricia, Roche, Otsuka) on individualised outcome measurement. Otherwise any personal fees are for invited guest lectures and academic symposia, received directly from event organisers,

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chiefly for presentations on frailty. He is Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, and with additional funding from the Alzheimer Society of Canada and several other charities. He receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support from the Canadian Institutes of Health Research, The Canadian Frailty Network, the QEII Health Science Centre Foundation, the Nova Scotia Health Research Fund and the Fountain Family Innovation Fund of the QEII Health Science Centre Foundation. NC is remunerated for her membership of a data safety and monitoring committee of a trial sponsored by AstraZeneca. The remaining authors declare no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Participant flow diagramme. Cohort structure showing sample and schedule of assessments.

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Figure 2 Variation in delirium severity and abnormal arousal and baseline cognition. *Left*: delirium severity measured by MDAS scores; *Right*: abnormal arousal severity measured by OSLA scores. Restricted cubic splines fitted across the range of baseline cognition, defined by the modified Telephone Interview for Cognitive Status and augmented by two verbal fluency tasks. MDAS = Memorial Delirium Assessment Scale. OSLA = Observational Scale for Level of Arousal.

Figure 3 Delirium severity and abnormal arousal in relation to baseline verbal fluency and memory. (a) verbal fluency and MDAS scores; (b) verbal fluency and OSLA scores; (c) memory) and MDAS scores; (d) memory and OSLA scores. Restricted cubic splines fitted across the range of baseline executive function and memory, defined by verbal fluency episodic and semantic memory tests from the modified Telephone Interview for Cognitive Status, respectively.

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Table 1 Characteristics of the cohort in relation to hospitalisation and delirium status

	Whole Cohort	Hospitalised		Delirium	
	n = 1511	n = 209	p	n = 115	p
Whole cohort					
Age	77.8 (6.2)	80.7(6.4)	<0.01	81.9 (6.6)	0.03
Female	57%	54%	0.56	55%	0.95
Education			<0.01		<0.01
Degree level	65%	50%		40%	
Up to secondary (12y schooling)	21%	26%		30%	
Up to primary (6y schooling)	14%	24%		30%	
White ethnicity	94%	92%	0.45	89%	0.56
Frailty Index (SD)	0.15 (0.13)	0.25 (0.16)	<0.01	0.30 (0.17)	<0.01
TICS-m (total, SD)	38.8 (5.9)	35.5 (8.3)	<0.01	33.8 (8.7)	<0.01
Fluency (words, SD)	15.6 (6.2)	13.0 (7.0)	<0.01	11.6 (6.8)	<0.01
Fluency (animals, SD)	19.0 (7.0)	15.0 (7.8)		13.3 (7.4)	
Self-rated health (poor/very poor)	18%	42%	<0.01	49%	0.62
Past medical history					
Myocardial infarction	21%	34%	<0.01	37%	0.86
Diabetes mellitus	12%	19%	<0.01	19%	0.22
Hypertension	50%	62%	<0.01	61%	0.35
Stroke	9%	14%	<0.01	16%	0.11
Cancer	24%	28%	0.09	25%	0.13
COPD	14%	25%	<0.01	28%	0.75
Any impaired PADL	9%	23%	<0.01	31%	<0.01
Toileting	4%	5%	<0.01	7%	0.31
Dressing	4%	9%	<0.01	12%	0.17
Bathing	4%	11%	<0.01	16%	0.12
Any impaired IADL	73%	84%	<0.01	90%	<0.01
Shopping	18%	41%	<0.01	52%	0.05
Walking outside	15%	34%	<0.01	43%	0.04
Length of stay (days, IQR)		2 (1–4)		4 (2–8)	<0.01
Hospitalisation					
Presenting complaint (top 5 systems)					
General (malaise, fever)		14%		15%	0.48
Respiratory (dyspnoea, cough)		14%		9%	0.03
Neurological (delirium, weakness)		5%		9%	0.02
CV (chest pain, palpitations)		6%		6%	0.99
GI (abdominal pain, diarrhoea)		7%		5%	0.32
Sodium		137 (5.3)		139 (4.1)	<0.01
Potassium		4.2 (0.6)		4.4 (0.6)	<0.01
Creatinine		93.6 (66.3)		92.7 (52.3)	0.04
Haematocrit		0.34 (0.05)		0.36 (0.05)	<0.01
White cell count		9.7 (7.6)		9.2 (4.5)	0.61

Hospitalisation = sample hospitalised at least once, p-values in hospitalised patients refers to comparison with whole cohort; p-values in patients with delirium refers to comparison with all hospitalised patients. Delirium = any occurrence of delirium during any admission, p values refer to comparisons with hospitalised sample. TICS-m = telephone interview of cognitive status-modified; COPD = chronic obstructive pulmonary disease.

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Table 2 Point prevalence of delirium features in hospitalised sample contributing to DSM-IV case ascertainment from 1999 inpatient assessments

Criterion A: disturbance of consciousness 69%		**Criterion B: change in cognition and/or perception 68%**		**Criterion C: acute and fluctuating change 41%**	
Item 1 ≥2: reduced level of consciousness	33%	Item 2 ≥2: disorientation (time/place questions 5/10 errors)	32%	Item 10 ≥3: sleep-wake cycle disturbance	17%
Item 4 ≥2: impaired digit span (5 forward or 3 backward errors)	10%	Item 3 ≥2: short-term memory impairment (≥2 errors on 3-item delayed recall)	31%	Observed fluctuations in arousal	6%
Item 5 ≥2: inattention	30%	Item 6 ≥2: disorganised thinking	15%	Observed motor fluctuations	5%
Inattention during interview	4%	Item 7 ≥2: perceptual disturbance	13%	Informant report of fluctuations	22%
Dozes off during interview	1%	Item 8 ≥2: delusions	25%	MDAS or OSLA score different from previous assessment by ≥1 SD	5%
Distracted by environmental stimuli	3%	Informant report *more confused*	7%		
OSLA total ≥2	31%	*Odd thoughts* described on direct questioning	2%		
MOTYB >5 mistakes	13%	Hallucinations described on direct questioning	3%		
Serial 7 score lower than baseline	16%	*Strange things* described on direct questioning	1%		
		Three sentences to complete (three-choice answer) (any error)	8%		
		Two sentences to complete (free choice answer) (either error)	7%		
		Two-stage sequencing command (either error)	7%		

Each MDAS item is rated 0, 1, 2 or 3. Criterion present if one or more symptom/sign positive. Note MDAS item 9 (decreased or increased psychomotor activity) is not used in the case definition. OSLA = Observational Scale for Level of Arousal; MOTYB = months of the year backwards; Informants = health care staff and/or family/carers.

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Table 3 Delirium severity, by setting and/or possible aetiology, before and after adjustment by baseline cognition

	Adjustment per aetiology/setting				Multivariable adjustment			
	β	95% CI		p	β	95% CI		p
Cognition (first spline)	−5.00	−7.11	−2.89	<0.01	−4.56	−6.53	−2.59	<0.01
Cognition (second spline)	4.81	2.11	7.52	<0.01	4.34	1.73	6.96	<0.01
Elective admission	−4.83	−6.85	−2.81	<0.01	−2.95	−5.91	−0.34	0.03
Elective x cognition (second spline)					−2.10	−3.92	−0.27	0.03
Cognition (first spline)	−4.97	−7.07	−2.87	<0.01				
Cognition (second spline)	4.94	2.21	7.67	<0.01				
CRP ≥20 mg/L	1.33	−0.01	2.68	0.05	2.28	0.75	3.81	<0.01
Cognition (first spline)	−4.99	−7.08	−2.89	<0.01				
Cognition (second spline)	4.92	2.18	7.66	<0.01				
White cell count								
< 4 x 10^9 cells/L	−3.10	−6.08	−0.12	0.04	−3.37	−6.74	−0.27	0.03
4-11 x 10^9 cells/L	[ref]				[ref]			
≥11 x 10^9 cells/L	−0.48	−1.36	0.41	0.29	−2.00	−4.00	−0.52	0.01
Cognition (first spline)	−4.87	−6.92	−2.82	<0.01				
Cognition (second spline)	4.77	2.08	7.45	<0.01				
Acute kidney injury	−1.35	−4.17	1.47	0.35	−1.89	−4.48	0.69	0.15
Cognition (first spline)	−4.88	−6.92	−2.85	<0.01				
Cognition (second spline)	4.73	2.01	7.45	<0.01				
Haemoglobin <100 g/L	0.61	−1.14	2.35	0.50	0.64	−1.38	2.66	0.53
Cognition (first spline)	−4.96	−6.94	−2.98	<0.01				
Cognition (second spline)	4.70	2.02	7.38	<0.01				
Sodium								
<125 mM/L	8.58	4.35	12.80	<0.01	8.72	4.48	13.0	<0.01
125–135 mM/L	1.31	−0.67	3.28	0.19	1.07	−0.84	2.97	0.27
135–145 mM/L	[ref]				[ref]			
≥145 mM/L	0.77	−0.14	1.68	0.10	1.49	0.03	2.95	0.05

Coefficients represent Memorial Delirium Assessment Scale points (out of 30). First spline = restricted cubic spline describing first slope for lower cognition towards an inflection midpoint (knot). Second spline = restricted cubic spline describing second slope for higher cognition after an inflection midpoint (knot). All multivariable estimates also adjusted by age, sex, frailty index and NEWS (coefficients not shown). Acute kidney injury derived by algorithm from NHS England https://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf. CRP = C-reactive protein.

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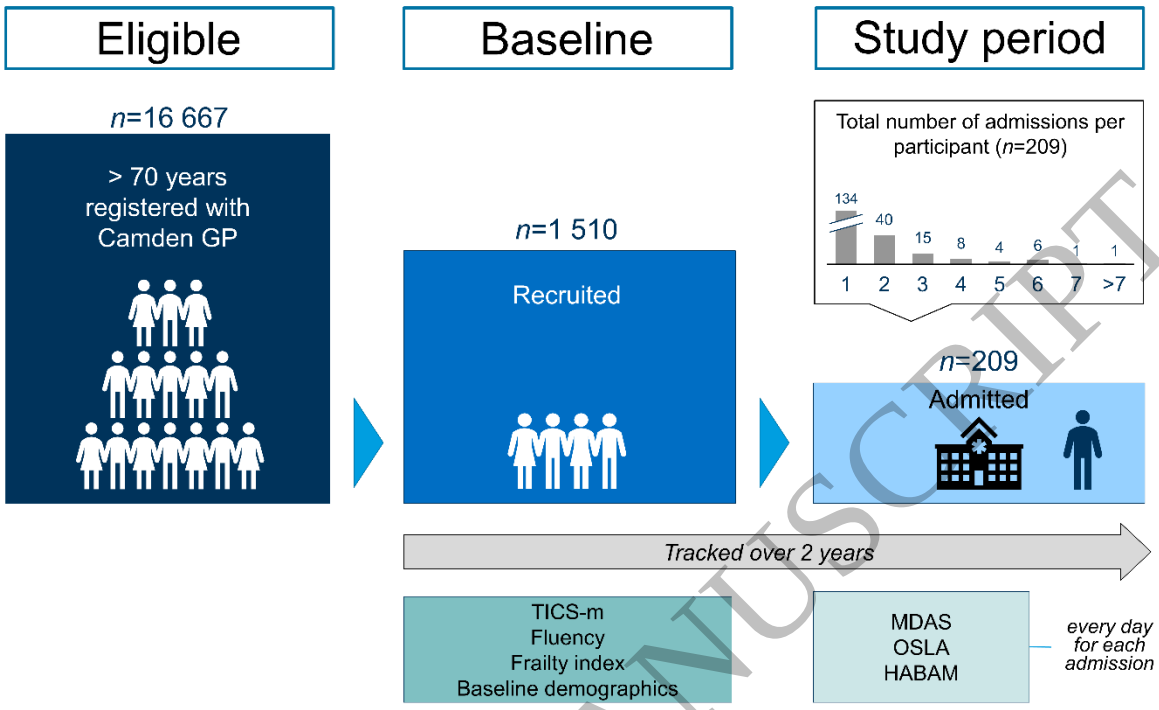

Figure 1
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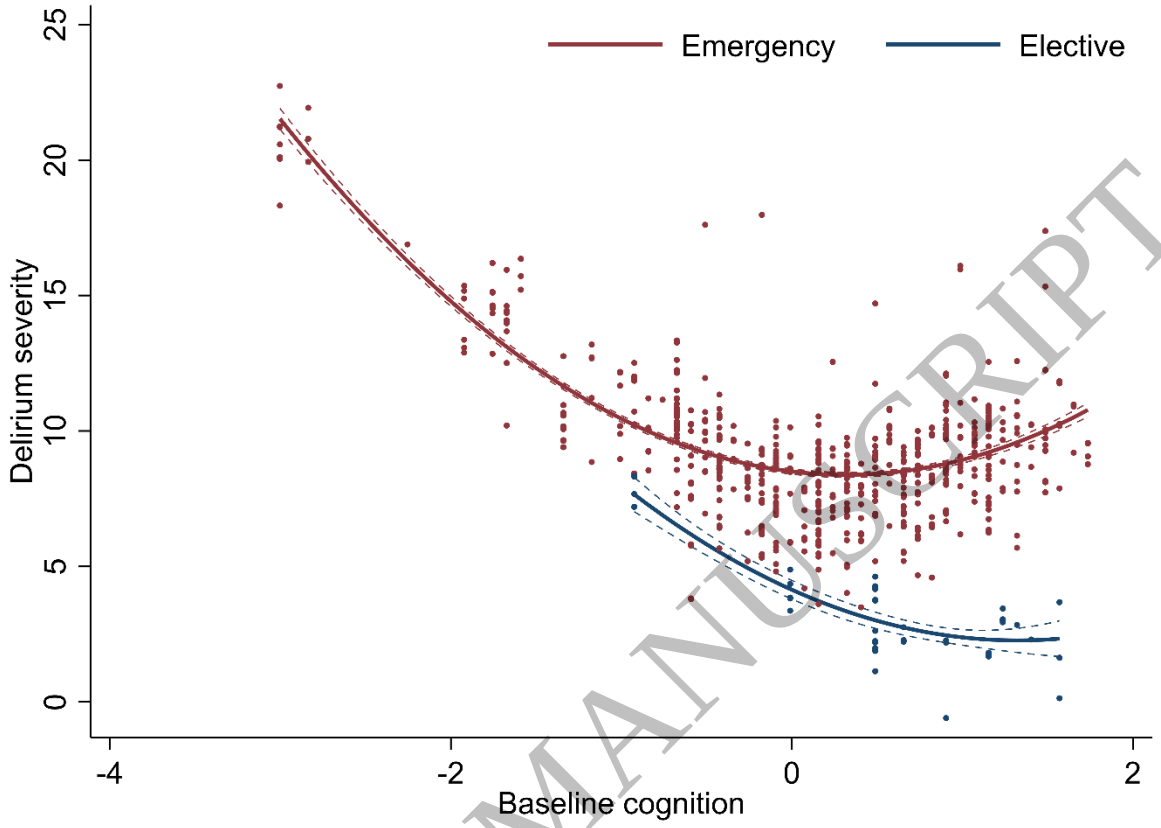

Figure 2
159x113 mm (x DPI)

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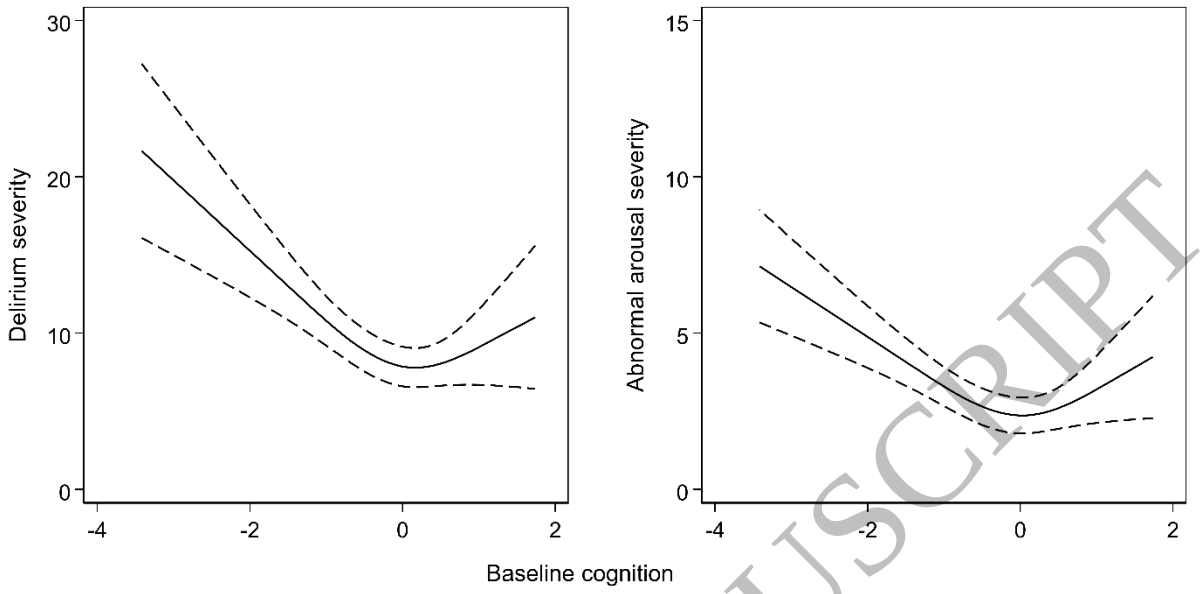

Figure 3
159x81 mm (x DPI)

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