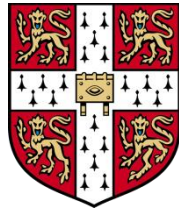Department of Public Health and Primary Care

The impact of delirium on cognitive outcomes

in population-based studies

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This dissertation is submitted for the degree of Doctor of Philosophy

October 2013

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Summary

Acute hospitals have seen unprecedented demographic changes, where older age, frailty and cognitive impairment now characterise the majority of health service users. Delirium is very common in this setting, and adverse outcomes are well described. However, studies investigating cognitive outcomes after delirium in unselected samples have been lacking. This thesis had four objectives: (1) To estimate the prevalence of delirium in the general population (2) To assess the association of delirium with cognitive outcomes (3) To investigate how these associations relate to underlying dementia pathology (4) To develop novel methods for retrospectively ascertaining delirium.

Methods:
Data from three population-based neuropathology cohort studies were used: Vantaa 85+; Cambridge City over-75s Cohort (CC75C); MRC Cognitive Function and Ageing Study (CFAS).
(1) To ascertain the prevalence of delirium in the general population, a measure of delirium was developed using data recorded in standardised interview schedules, with criterion validity evaluated through the association with mortality and dementia risk.
(2) The association with cognitive outcomes was tested in a series of logistic regression models, where delirium was the exposure and dementia (or worsening dementia severity) was the outcome. In addition, the association with change in Mini-Mental Status Examination (MMSE) score was assessed using random-effects linear regression.
(3) In brain donors from all three cohorts, the independent effects of delirium, dementia pathology, and their interaction, were investigated using the same approach.
(4) A chart-based method for deriving a retrospective diagnosis for delirium was developed, validated against bedside psychiatrist diagnosis. Vignettes from the medical record were abstracted and delirium status decided by expert consensus panel.

Results:
(1) Age-specific prevalence in CFAS increased with age from 1.8% in the 65-69 year age group to 13.5% in the ≥90 age group (p<0.01 for trend).
(2) Delirium was consistently associated with adverse cognitive outcomes: new dementia (OR 8.7, 95% CI 2.1 to 35); worsening dementia severity (OR 3.1, 95% CI 1.5 to 6.3); faster change in Mini-Mental Status Examination (MMSE) score (1.0 additional points/year, p<0.01)
(3) In the neuropathology analyses, decline attributable to delirium was -0.37 MMSE points/year (p<0.01). Decline attributable to dementia pathology was -0.39 MMSE points/year (p<0.01). However, the combination of delirium and dementia pathology resulted in the greatest decline, where the interaction contributed a further -0.16 MMSE points/year (p=0.01), suggesting that delirium worsened cognitive trajectories in dementia, but through distinct pathophysiological pathways not accounted for by Alzheimer's, vascular or Lewy body pathology.
(4) The chart abstraction method yielded a sensitivity of 0.88 and specificity 0.75 for 'possible delirium', with lower sensitivity (0.58) and higher specificity (0.93) for 'probable delirium' (AUC 0.86, 95% CI 0.82 to 0.89).

This thesis adds to the small body of work on delirium in prospective studies, with the first ever analyses conducted in whole populations. The findings suggest new possibilities regarding the pathology of cognitive impairment, positioning delirium and/or its precipitants as a critically inter-related mechanism.

Declaration

This dissertation is submitted for the degree of Doctor of Philosophy at the University of Cambridge. This research was conducted under the supervision of Professor Carol Brayne at the University of Cambridge and Professor Alasdair MacLullich at the University of Edinburgh.

I declare that this dissertation is substantially the result of my own work. Although I was not involved in any primary data collection (apart from that described in Chapter 7), I undertook all the literature reviews, analyses, interpretation of results, and compiled them for presentation.

Any additional work by colleagues and co-authors has been explicitly acknowledged where relevant. Most chapters have been published or are to be published as papers, and were reviewed and commented on by all authors. Reproduction of any figures from other publications have been referenced and permission sought from the publishers where necessary.

No part of this dissertation is substantially the same as any that has been, or is currently being submitted for any other degree, diploma, or other qualification at any other University.

The dissertation does not exceed 60,000 word limit (excluding appendices, figures, references and tables) set by the degree committee for Clinical Medicine and Clinical Veterinary Medicine.

This work submitted is identical to that which was examined, excepting corrections as required by the examiners.

Acknowledgments

Papers

Papers arising directly from work presented in this thesis

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Abbreviations

ACT   Adult Changes in Thought study

ADRDA   Alzheimer's Disease and Related Disorders Association

ADL   Activities of daily living

AGECAT   Automated Geriatric Examination for Computer Assisted Taxonomy

APACHE   Acute Physiology and Chronic Health Evaluation

ApoE   Apolipoprotein E

CAM   Confusion Assessment Method

CAMDEX   Cambridge Mental Disorders of the Elderly Examination

CAM-ICU   Confusion Assessment Method for Intensive Care Unit

CC75C   Cambridge City over-75 Cohort

CDR   Clinical Dementia Rating Scale

CFAS   Medical Research Council Cognitive Function and Ageing Study

CCI   Charlson Co-morbidities Index

CNS   Central nervous system

CI   Confidence interval

CSF   Cerebrospinal fluid

CSHA   Canadian Study of Health and Ageing

DIS   Diagnostic Interview Schedule

DSM   Diagnostic and Statistical Manual

EClipSE   Epidemiological Clinico-pathological Studies in Europe

EWS   Early Warning Scores

FHSA   Family Health Services Authority

GERDA	GErontological Regional DAtabase
GMS	Geriatric Mental State
GP	General Practitioner
HAS	History and Aetiology Schedule
HPA	Hypothalamus-pituitary-adrenal
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive Care Unit
LOCF	Last observation carried forward
MAR	Missing at random
MCAR	Missing completely at random
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MOOSE	Meta-analysis of observational studies in epidemiology
MPI	Multidimensional Prognostic Index
MRI	Magnetic resonance imaging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NIMH	National Institutes of Mental Health
OBS	Organic Brain Syndrome scale
OR	Odds ratio
OXVASC	Oxford Vascular Study
PSE	Present State Examination
RInI	Retrospective Informant Interview

SAPS	Simplified Acute Physiology Score
SPE	Standardised Psychiatric Examination
TIA	Transient Ischaemic Attack
ViEWS	VitalPAC Early Warning Score

1   Introduction: what is delirium?

Delirium is a serious acute neuropsychiatric syndrome which affects around 20% of hospitalised older adults (Inouye 2006; Siddiqi et al. 2006; Young et al. 2007; MacLullich et al. 2011; Ryan et al. 2013). It is characterised by inattention and fluctuating cognitive and/or perceptual deficits in the context of acute illness. The syndrome arises due to a wide range of aetiological precipitants, commonly: infections, hypoxia, or medications. The size of the insult necessary to precipitate delirium is inversely proportional to the vulnerability of the individual (Inouye et al. 1996). In this way, delirium is a sensitive – but not specific – sign of illness in older persons. Delirium can also be conceptualised as a consequence of cognitive decompensation under conditions of physiological stress.

This introductory chapter will outline some of the theoretical issues concerning delirium as a clinical entity, illustrating them with a case study. Following this is a more detailed description of delirium phenomenology, in the context of the standard psychiatric classification systems (particularly the American Psychiatric Association's Diagnostic and Statistical Manual, DSM). Lastly, research into delirium pathophysiology will be reviewed, examining the literature from experimental animal models and clinical studies.

Chapter outline

- Overview of concepts
- Case study
- Delirium phenomenology
- Delirium pathophysiology

1.1 Overview of concepts

A central feature of delirium is its development as a result of interacting predisposing and precipitating factors (Figure 1-1). In persons with high vulnerability e.g. older adults or children; prior cognitive impairment, a relatively minor illness can precipitate delirium, e.g. urinary tract infection. Conversely, in younger adults, delirium usually only results from severe illness, e.g. traumatic brain injury, meningitis. Commonly recognised risk factors for delirium are given in Table 1-1.
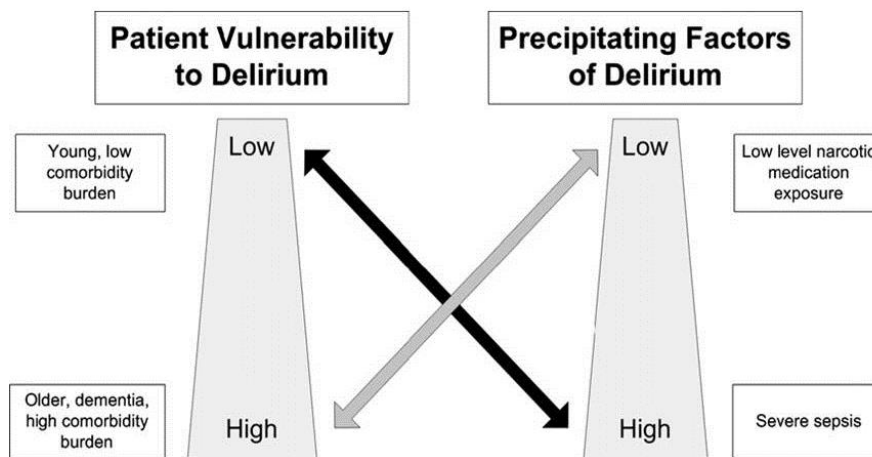
Figure 1-1 Multifactorial model of delirium (Inouye et al. 1996))

Table 1-1 Common risk factors for delirium.

Predisposing factors	Precipitating factors
Age	Infections
Cognitive impairment	Medications
Depression	Hypoxia
Frailty and functional dependency	Metabolic disturbance
Co-morbidity score	Physical restraints
Nutritional state	Urinary catheterisation
Sensory impairment	

This interacting, multifactorial model of delirium is supported by empirical data, first demonstrated almost two decades ago (Inouye et al. 1996). In two tandem hospitalised cohorts, baseline risk factors for incident delirium were determined and validated (Inouye et al. 1993). The multiplicative effect of precipitants on baseline risk of delirium was then established in a different cohort of patients (Inouye et al. 1996). These data are reproduced in Figure 1-2.
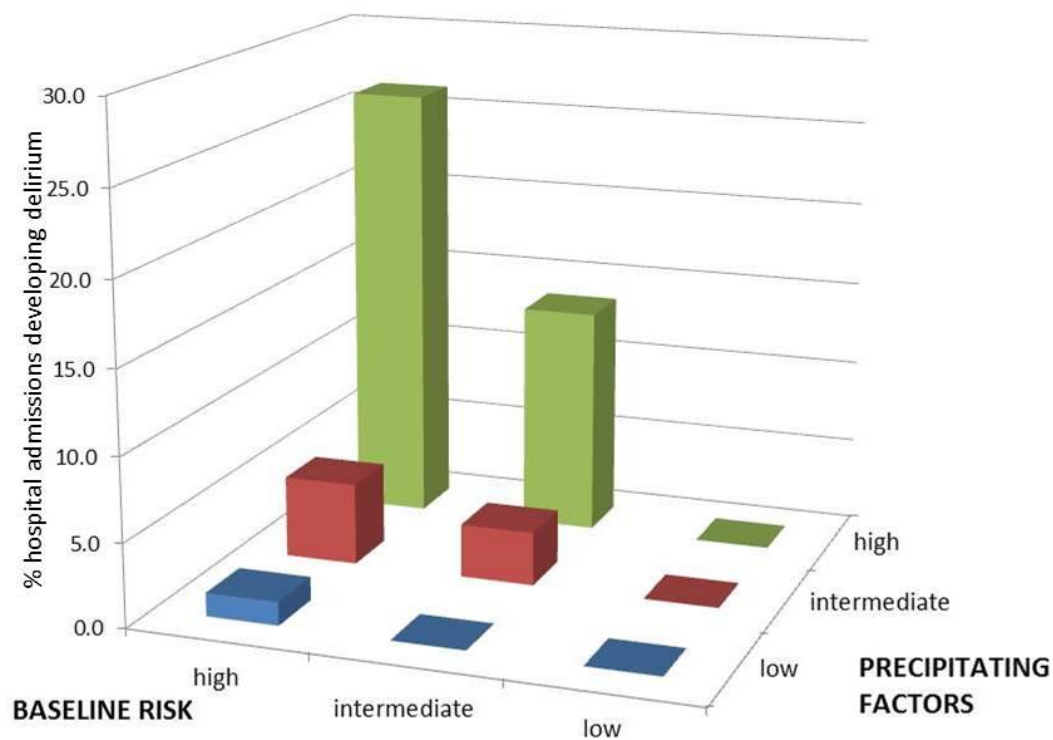
Figure 1-2. Data from Inouye et al. 1996 showing that precipitating and baseline factors are usually insufficient to produce delirium on their own. Proportion of individuals who developed delirium over the course of admission is shown on the y-axis.

1.1.1 Scope of thesis

This thesis is concerned with understanding the relationship between delirium and cognitive decline. To investigate this, an epidemiological approach has been adopted, that is, an

exploration of delirium in the context of population-based cohort studies of ageing and dementia. In this respect, there are a number of aspects of delirium that are outside the scope of this discussion, as outlined below.

Delirium is common in children as well as older adults. Vulnerabilities in brains undergoing maturation and development may be similar to those undergoing decline and degeneration. Compared to older adults, paediatric delirium has attracted much less research attention. Phenomenologically, the syndrome is thought to be broadly similar to that seen in adults, though it may develop more acutely and perceptual and psychotic disturbance may be more common (Leentjens et al. 2008).

Delirium tremens refers to a specific syndrome that arises through acute alcohol withdrawal. It has different phenomenological characteristics, treatments and prognoses and so will not be considered further in this thesis.

There is an important body of research into post-operative delirium and post-operative cognitive impairment. The phenomenon is observed after a range of different procedures and the risk profile is unlikely to be uniform across surgical and anaesthetic interventions (cardiac versus non-cardiac, elective versus emergency, general versus regional anaesthesia). This thesis will only refer to post-operative delirium if directly relevant to epidemiological studies.

There is growing interest in prodromal and subsyndromal delirium. Increasingly, it is apparent that these borderline cases also carry prognostic significance (Cole et al. 2011). This will only be addressed where relevant to discussing case-ascertainment and delirium nosology.

Finally, there are a number of pharmacological and non-pharmacological interventions that have been trialled for both delirium treatment and prevention. However, interventions for delirium are not a central focus for this thesis so will not be discussed in detail.

1.1.2 Clinical importance

This section provides some justifications as to why delirium is worthy of study. There follows a case study (Section 1.2) and then a detailed description of delirium phenomenology (Section 1.3).

1.1.2.1 Delirium is common

Delirium is extremely common among hospitalised older adults. A systematic review describing the epidemiology of delirium in medical inpatients reported delirium at admission (prevalent delirium)[2] ranging from 10% to 31% (Siddiqi et al. 2006). Delirium developing over the course of an admission (incident delirium) was between 3% and 29%. To put these figures in context, UK 2011/2012 Hospital Episode Statistics (HES) reported 5.7% emergency admissions were coded as being due to "ischaemic heart disease" and "other forms of heart disease" (www.hscic.gov.uk).

In settings where illness severity is greater, e.g. intensive care unit (ICU), prevalence is correspondingly higher. However, the wide range of reported prevalence estimates (20-80%) probably reflect differences in use of detection tools, illness severity and case-mix varying across hospitals and local practices with regard to use of sedation (Vasilevskis et al. 2012). The prevalence is similarly high in institutional care (range 7% to 58%), and the variation is also likely to be influenced by the same methodological issues (Siddiqi et al. 2009). In palliative care, expected prevalence of delirium on admission to specialist care is between 13% and 42% but rises to 59% to 89% in the last weeks before death (Hosie et al. 2013).

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[2] The literature on delirium in acute hospital settings uses the terms 'prevalence' and 'incidence' in a specific way that contrasts with the standard definitions in descriptive epidemiology. Using the point of admission as a reference, 'prevalent delirium' indicates delirium present at admission. 'Incident delirium' indicates delirium that develops over the course of a hospital admission. The distinction may reflect different aetiological precipitants, management options, and in some cases, outcomes (see McCusker et al. 2003).

1.1.2.2 Delirium is serious

Delirium is associated with a number of adverse outcomes, over the short and long term (Siddiqi et al. 2006; Witlox et al. 2010). A wide range is reported for in-hospital mortality after delirium (6% to 62%) (Siddiqi et al. 2006). In 5 studies comparing delirium cases with controls, and adjusting for illness severity and co-morbidities, the results were less clear: 2 showing increased mortality, 3 showing no significant difference (Siddiqi et al. 2006). Length of stay may be longer in persons with delirium (3 studies showing increases, 7 reporting no difference). For institutionalisation at discharge, studies showed either increased rates (3 studies) or no difference (1 study). Overall, comparison is markedly hampered by differences in study design, adjusted covariates, outcome measures and degree of reporting.

There is substantial evidence that delirium results in poor outcomes in older persons admitted to hospital over the longer-term (follow-up at least three months after delirium) (Witlox et al. 2010). This systematic review only included studies that investigated an independent effect of delirium (i.e., after adjusting for other associations with poor outcomes, for example co-morbidity or illness severity). In older persons admitted to hospital, pooled estimates found positive associations with mortality (HR 2.0 (95% CI 1.5 to 2.5), I^2 = 44%; 7 studies) and institutionalisation (OR 2.4 (1.8 to 3.3), I^2 = 0%; 7 studies).

1.1.2.3 Delirium is a marker for dementia

The association between delirium and dementia is complex, and is the main focus for this thesis. The literature will be reviewed more fully in Chapter 2. Here, it is worth highlighting the findings from the systematic review of long-term outcomes after delirium (Witlox et al. 2010, above). Two studies were included that reported an association with dementia (OR 13 (95% CI 1.9 to 84)). The first followed 200 elective hip surgery patients, and the dementia outcome was defined as MMSE <23 at 38 months (Bickel et al. 2008). The second study was performed in the acute

hip fracture setting where 78 patients were followed after perioperative assessment for delirium by a psychiatrist (Lundstrom et al. 2003). Dementia outcomes were decided at consensus meetings. There are two major difficulties with these studies. Firstly, the dementia assessments were probably not blinded to prior delirium status. Secondly, it is difficult to be certain how valid this estimate is because the population admitted to hospital includes persons with undiagnosed dementia (i.e. the dementia was present before the delirium, rather than caused by it). Indeed, because of the high proportion of persons with undiagnosed dementia in the hospital setting (Sampson et al. 2009), it could be argued that persons presenting with delirium is precisely the population that should be screened for dementia (MacLullich et al. 2011). This inferential limitation to follow-up of hospitalised persons is a major justification for the epidemiological work in population-based studies.

In addition to regarding dementia as a dichotomous state, there are advantages to modelling trajectories of cognitive decline as this regards both intra-individual and inter-individual differences in cognitive function as being on a continuum. The terminal cognitive decline hypothesis was proposed several decades ago, positing that cognitive decline might accelerate before death (Riegel et al. 1972), typically appreciable over the last three to eight years (Muniz-Terrera et al. 2011). The central implication of this observation is that some of the variation in cognitive aging could be better approached by considering distance to death, rather than chronological age (Piccinin et al. 2011). How delirium may relate to this process has not previously been considered, and is a major element of this thesis (Chapter 6).

1.1.2.4   Delirium is distressing

Delirium is undoubtedly a frightening experience. Patients can be troubled by agitation and hyperarousal, but psychotic symptoms may be equally distressing. Moreover, hallucinations and delusions are more likely to go unnoticed in patients with hypoactive delirium, though delirium

subtype does not appear to be directly associated with distress (Partridge et al. 2013). Even though a degree of amnesia due to reduction in new-memory formation may be a feature of delirium, increasing evidence indicates significant distress in those with recollection for the episode (Partridge et al. 2013).

After critical illness, the estimated prevalence of delusions or dream-like recollections ranges from 20% to 75% (Kiekkas et al. 2010). This wide variation is partly attributable to differences in illness severity, levels of sedation and other clinical variables, though some may also be due to under-reporting of symptoms. Symptoms of post-traumatic stress disorder (PTSD) in this population have been reported in 19% to 26% of patients after critical illness (Davydow et al. 2008; Jackson et al. 2011). An illustrative example:

> "On Sunday, I was on the ICU, where a horror ceremony like in a concentration camp was going on. Four patients were executed. Laying in their beds, they received a death pill. I was one of them. … The hangman gave us the pill, with a blank face… waiting to carry away our dead bodies. … The torturers watched us all the time, they asked us: "Do you feel anything yet? How does your foot feel? How does your arm feel?" The scene went on like a horror film. The children of Satan were in command. They were dressed in green coats and had scary faces. They were waiting for our death. … Worst was, that I did not try to resist. How can a man throw away his life like that? Why me? Did they do a mistake during the surgery and try to cover it up by killing all of us? … The pills did not work. I did not die. So they tried it again with gas, pressing a mask on my face. …"

ICU Delirium website[3] (used with permission)

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[3] www.mc.vanderbilt.edu/icudelirium/outcomes.html#post

Family are also likely to be affected by the experience of delirium in a patient, particularly in hospice settings (Breitbart et al. 2008). Distress in professional staff is also well-documented, though still probably receives less attention than is warranted (Breitbart et al. 2002).

1.1.2.5 Delirium is costly

It is clear that associations with longer hospital admissions, short and long-term clinical complications and higher rates of institutionalisation result in higher costs. In the USA, extrapolating from the annual health care expenditure of participants in a large delirium prevention study, inflation-adjusted costs were calculated from insurance reimbursements and hospital charges. This estimates the cost of a patient admission with delirium at between $16,000 and $64,000, suggesting the national burden of delirium may range from $38 billion to $150 billion per year (2008 estimate) (Leslie et al. 2008). Even this is likely to be an underestimate, as it may not adequately account for delirium that is unrecognised, but nonetheless incurs greater resource utilisation.

In the UK, a detailed analysis of the cost-effectiveness of a delirium prevention intervention was undertaken as part of the NICE guidelines on delirium (Akunne et al. 2012). The probabilistic analysis – accounting for baseline risk of delirium, adverse outcomes including new institutionalisation and dementia, falls, pressure ulcers and mortality – estimated the mean additional cost per admission as £13,200. Remarkably, the incremental cost of the intervention was actually less than usual for usual care: -£520, showing the substantial cost-effectiveness of delirium prevention.

1.2 Case study

AB[4] is a 78 year old man who fell and fractured his neck of femur while receiving inpatient psychiatric care for an episode of major depression. Prior to admission, he was functioning well in his own home. He was able to manage his personal care, though his daughter did his weekly shopping and assisted with more physically demanding tasks such as laundry and changing bed linen. He had some mild forgetfulness which had not changed in the previous two years and he was able to manage his own financial affairs. AB had a past medical history of stable angina, hypertension, mild chronic renal failure, benign prostatic hypertrophy, osteoarthritis of both knees and recurrent depression. There was no family history of note, and he was a lifelong teetotaller and non-smoker with a university education.

The current episode of major depression was precipitated by the unexpected death of his son. His affective state worsened despite a six-week period of community treatment with antidepressants and grief counselling. He was admitted to psychiatric care with psychotic depression and weight loss, for consideration of electro-convulsive therapy. At the time of his fall, he was on the following medications: venlafaxine 225mg od; trazadone 50mg od; quetiapine 25mg bd; amlodipine 5mg od; ramipril 10mg od; bisoprolol 2.5mg od; simvastatin 40mg od; finasteride 5mg od.

On admission to the orthopaedic ward, AB was drowsy and though responsive to voice, he was not able to give an account of recent events. Temperature was 36^{0}C, heart rate 100 regularly regular, blood pressure 105/55 and oxygen saturation was 97% on room air. Cardiovascular, respiratory and abdominal examinations were unremarkable. AB was only briefly able to engage with assessment and did not report any perceptual abnormalities. He was not aware how long

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[4] This is a fictionalised, but typical case.

he'd been in hospital and disorientated to time and place. On being asked to count backwards from 20, he gave the following answer: "20… 19… 18… 17… 16… 17… 16… 15… 13… 12… 11." There was psychomotor retardation and generalised depression of deep tendon reflexes.

1.2.1   Interpretation

AB has delirium. Despite the diagnosis of depression, symptoms of which may complicate the assessment of delirium, his fluctuating difficulty in engaging with assessment and inattention on a relatively simple cognitive task is fairly specific to delirium. This case illustrates the multifactorial nature of the causes of delirium. Prior to his fall (at which point he may have already been delirious), the major predisposing risk factors were his age, mild forgetfulness, depression, and being on three psychotropic medications.

His precipitating factors will now include further medications (specifically opioid analgesia), pain, surgical fixation of his hip under anaesthesia, and possible post-operative ICU admission. Hypotension and/or dehydration may also contribute to delirium if his fluid balance is not addressed. Constipation from opioids and reduced mobility may be a perpetuating factor if not pre-empted. He is also at risk of urinary retention and may require a catheter. Laboratory indices may already be abnormal, with possible hyponatraemia and acute on chronic renal impairment.

Continued delirium is very likely to complicate this patient's post-operative course. The duration of the delirium will be determined by how promptly the underlying medical problems can be optimised, and whether any new problems arise. In the meantime, efforts to improve and maintain his mobility will be hampered by continued drowsiness and inattention. He will be at risk of deconditioning, pressure ulcers and further falls. While each of his medical and psychiatric conditions is potentially reversible, return home is a reasonable goal for care. However, this is contingent on intensive multicomponent, multiprofessional intervention.

1.3 Delirium phenomenology

The term 'delirium' has many formal and informal synonyms (box), but 'delirium' has the most precise and historical meaning. In addition, the term is used in the two chief nosological systems for classification of psychiatric disorders, viz.: DSM and the International Classification of Diseases (ICD). Table 1-1 details the diagnostic criteria for the most recent iterations of these definitions, namely DSM-IV[5] and ICD-10. The DSM description has fewer required features than the ICD construct, and this more inclusive definition results in higher estimates of point-prevalence when the criteria are compared directly (at least in a geriatric medicine ward setting) (Laurila et al. 2003). These differences in ascertainment may not, however, actually affect prognosis for mortality at one year (Laurila et al. 2004a).

Terms suggestive of delirium

Formal terms
- acute confusional state
- acute confusion
- confusion
- agitation
- toxic psychosis
- ICU psychosis
- post-operative psychosis
- metabolic encephalopathy
- acute brain failure
- organic brain syndrome
- cerebral insufficiency
- subacute befuddlement

Informal terms
- non-compliant with examination
- a bit muddled
- not themselves today
- a bit knocked off
- vague
- poor historian

Courtesy of Alasdair MacLullich, University of Edinburgh

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[5] DSM-5 has recently been published. Though it differs from DSM-IV, the new edition does not have any direct relevance to the analyses presented in this thesis.

Table 1-2 Definitions of delirium

DSM-IV	ICD-10
A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.	A. Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.	B. Disturbance of cognition, manifest by both: 1. impairment of immediate recall and recent memory, with relatively intact remote memory; 2. disorientation in time, place or person. C. At least one of the following psychomotor disturbances: 1. rapid, unpredictable shifts from hypo-activity to hyper-activity; 2. increased reaction time; 3. increased or decreased flow of speech; 4. enhanced startle reaction. D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following: 1. insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle; 2. nocturnal worsening of symptoms; 3. disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day	E. Rapid onset and fluctuations of the symptoms over the course of the day.
D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.	F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D. Comments: Emotional disturbances such as depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity, disturbances of perception (illusions or hallucinations, often visual) and transient delusions are typical but are not specific indications for the diagnosis.

It is worth examining the foundations of the DSM-IV description, exploring the difficulty with using the definition for standardising case-ascertainment in research. Though successive revisions were based on epidemiological field testing, only two studies were ever conducted for DSM-IV, both in tertiary hospital samples (total n=560) (Johnson et al. 1990; Liptzin et al. 1991).

1.3.1.1   Criterion A

Deficits in attention have been recognised as a core diagnostic feature since DSM-III-R (Criterion A) (Table 1-2).

It supplanted the previous description 'clouding of consciousness' as the latter term was regarded as being too imprecise (Lipowski 1983). However, it is not clear what should constitute a minimum threshold for attentional deficits in the diagnosis of delirium (Lowery et al. 2010). Moreover, patients who present with reduced level of consciousness in an acute setting are often not included in delirium studies if the severity of their impairments means that they cannot undergo cognitive testing. These two unresolved but crucial issues reflect the general paucity of research on the neuropsychology of delirium (MacLullich et al. 2011).

1.3.1.2   Criterion B

DSM-IV also requires a change in cognition or perceptual disturbance (Criterion B). The extent to which delirium may have a differential effect on domains of cognition or perception is complex and not specified. Neuropsychiatric symptoms such as motor (Meagher et al. 2011) or sleep-wake (Jabbar et al. 2011) disturbance are frequently present but not specific for delirium. Affective symptoms, thought disorder and perceptual disturbances are also recognised as part of Criterion B, and assessment including these features would serve to maximise sensitivity of detection.

1.3.1.3   Criterion C

Criterion C states that symptoms should be acute (hours to days) and fluctuate over the course of the day. These features are highly specific to delirium, but may vary by subtype. However, by their nature, they make ascertainment more difficult, because a test score may vary over periods of hours or even minutes. Multiple assessments per day could increase detection of deficits as well as eliciting fluctuation, but are likely to be impractical. Currently best practice is to use tools which attempt to capture relevant information (e.g. informant history, clinical case notes) in the period preceding the assessment.

1.3.1.4   Criterion D

Specifying that delirium is due to an underlying medical disorder fulfils Criterion D. However, it is unclear what should actually constitute 'evidence' for cause and effect. For the vast majority of cases, acute medical and surgical events (e.g. urinary tract infection) and delirium are temporarily linked. However, as the pathophysiology of delirium remains elusive (MacLullich et al. 2008), the level of evidence required for aetiological links remains very unclear. Also, often multiple aetiologies are demonstrable over the course (Laurila et al. 2008), but may be unidentifiable in around 10% (Meagher et al. 2008). It is not known if the precipitant influences the phenomenological presentation (Meagher et al. 2008).

1.3.2   Delirium as a disturbance of consciousness

From the time that delirium was framed as an organic brain syndrome, its hallmark has always been considered a disturbance of consciousness. This was initially described as 'clouding of consciousness', but as mentioned above, this was regarded too difficult to operationalise. Two

approaches to understanding this construct have emerged, which could be described as 'constructivist' and 'reductionist'.

Broadly, the constructivist approach regards delirium as a failure of a high-order function (Rockwood 2004). For organisms with complex physiology, high-order functions include: maintenance of consciousness and upright bipedal ambulation. When complex systems fail, these functions are most vulnerable to disruption (Rockwood et al. 2004b). This view places delirium in the context of frailty – that is, not a specific neuropsychiatric problem as much a failure of the whole organism. Frailty arises from loss of redundancy in physiological systems, and this lack of robustness is key. From this perspective, delirium is a manifestation of frailty and should be understood principally through this characterisation of predisposing factors (Rockwood et al. 2004a).

1.3.3   Phenomenology as an empirical construct

A reductionist view seeks to separate the phenomenon of 'clouded consciousness' into component parts. This includes the full range of neuropsychiatric domains: cognition, thought, language, sleep-wake cycle, perception, affect, and motor behaviour, and recent work has examined the stability of these constructs in different countries and clinical settings (Franco et al. 2009; Meagher et al. 2012; Trzepacz et al. 2012; Franco et al. 2013). A principal idea in phenomenological studies is that syndromes have high-frequency 'core' symptoms, and less-frequent 'associated' symptoms. Evidence from exploratory and confirmatory factor analyses proposes that delirium phenomenology can be understood in three core domains, each of which contribute to consciousness as a distributed brain function: 'cognitive', which includes attention deficits; 'higher level thought', including executive symptoms, impairments in language; and 'circadian disturbance', including altered motor behaviour (Franco et al. 2009; Meagher et al.

2012; Franco et al. 2013) (Figure 1-3). Accordingly, attention (which has fronto-parietal 'top-down' and reticular activating system 'bottom-up' substrates); complex organisation of thinking (executive, semantic, abstraction); and fragmentation of circadian patterns of arousal, can all be considered characteristic components of disrupted consciousness in delirium.
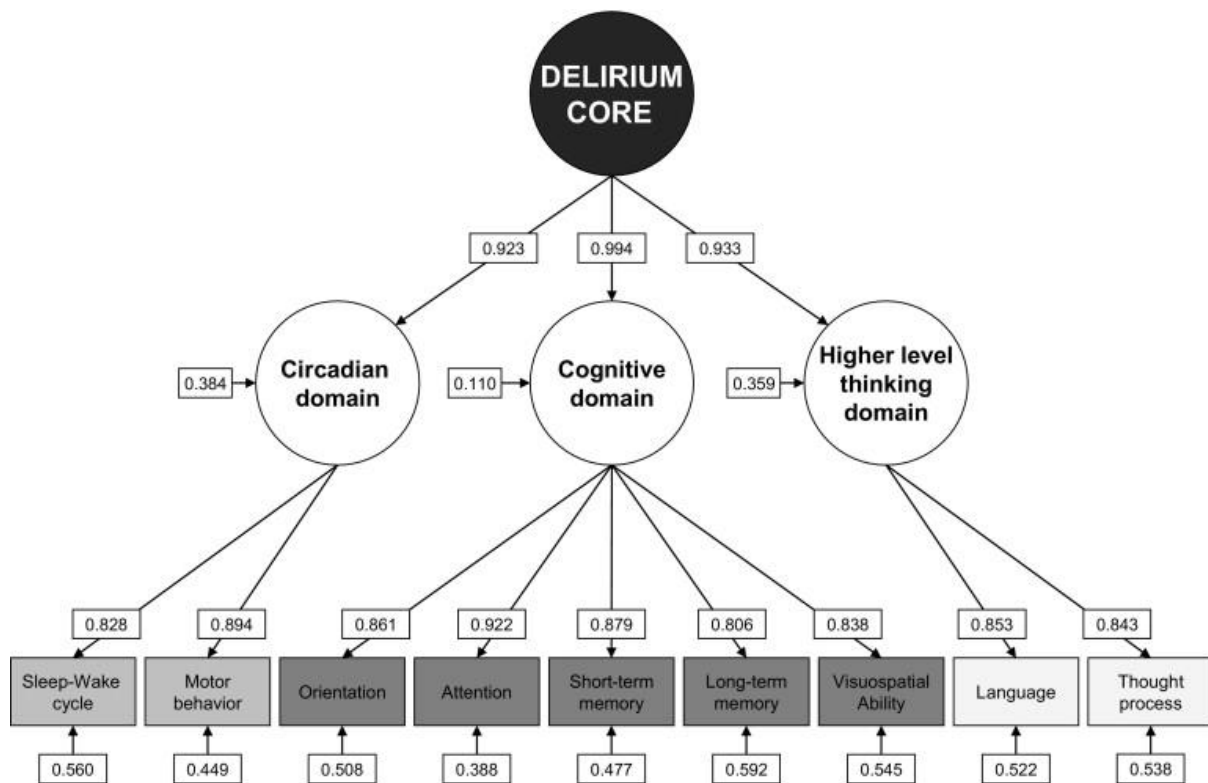
Figure 1-3. Domains of delirium phenomenology, as described through factor analysis (Franco et al. 2013).

1.3.3.1 Inattention and cognition

Inattention is the cardinal symptom and is required for the diagnosis of delirium. It may be apparent on observation that the patient is distractible, with an inability to shift, focus or sustain attention. As above, the assessment of attention is complicated by states of low arousal, and it is debatable if these can be phenomenologically separated in these circumstances (Meagher et al. 2008). Formal testing can involve 'days of the week backwards', 'serial sevens' or digit span tests.

However, it is not clear how well these tests truly discriminate between delirium and dementia (MacLullich et al. 2011; Morandi et al. 2012a). More broadly, there is a need to acknowledge that patients with a reduced level of alertness or agitation of a severity such that the presence or absence of inattention cannot be demonstrated should be classified presumptively as having delirium (Hall et al. 2012). However, studies that use criterion validity to establish the clinical significance of major disturbances of arousal – that is, to what extent it is associated with mortality, institutionalisation and other outcomes – are still urgently required, and some data on this topic are presented in Chapter 4.

Disorientation and short-term memory impairment are usually accompanying features of the inattention, so persons are often amnesic (though, as described in Section 1.1.2.4, patients may find fragments of residual memory to be highly distressing). Equally, long-term memories are relatively preserved. Visuospatial and constructional impairments can be observed or assessed by copying actions or figures (e.g. clock drawing test).

1.3.3.2   *Higher-order cognitive deficits*

A wide range of executive dysfunctions may be apparent, including difficulty with: abstract thinking, initiation/perseveration, switching mental sets, working memory, temporal sequencing and organisation, insight and judgment. Disorganised thinking includes tangentiality and loose associations (Hart et al. 1996; Trzepacz et al. 2001; Laurila et al. 2004b). Language disturbances in delirium include dysnomia, paraphasias, impaired comprehension, dysgraphia, and word-finding difficulties (Trzepacz et al. 2002).

1.3.3.3   *Circadian disturbance and motor activity*

Disruption of sleep-wake cycle is very frequently present in delirium, over 90% in some case-series (Rockwood 1993; Meagher et al. 2007). It may take the form of sleep fragmentation or even complete reversal of sleep-wake cycle, reflecting disordered circadian rhythms. Circadian

disturbance may be the basis of the fluctuating clinical course in delirium, but this is not fully understood (Rooij et al. 2013).

Changes in patterns of motor activity are very common in delirium, and are the basis for classifying clinical subtypes: hyperactive, hypoactive and mixed. Although hypoactive delirium is more common than hyperactive presentations, it tends to be under-detected by its very nature (Yang et al. 2009). Accordingly, it is difficult to be certain if motor activity is differentially associated with phenomenological profiles, pathophysiology, treatment or prognoses (Meagher 2009). The cognitive deficits are probably comparable (Leonard et al. 2011).

Though psychotic symptoms may be the most recognisable element of delirium, these features only occur in up to 50% of patients with delirium. Hallucinations are usually visual, though may be auditory. Disorders of thought content may range from overvalued ideas to frank delusions. Delusions are typically poorly-formed and may relate to persecutory ideas (Meagher et al. 2013).

1.4   Pathophysiology

Though there is increasing interest in the biological underpinnings of delirium, understanding of the fundamental pathophysiology is incomplete. Compared to the number of clinical studies in the last three decades, relatively less work has been done using animal models. As outlined above, any attempt to explain the pathophysiological substrates of delirium must account for the reciprocal interaction between predisposing and precipitating factors. Finding meaningful cognitive and behavioural animal models to explore possible hypotheses has not been straightforward.

It is convenient to consider two mechanisms for brain injury in the context of acute illness: direct and indirect (MacLullich et al. 2008). Direct brain insults may include hypoxaemia, stroke, trauma or medications. In such conditions, brain dysfunction evidently arises as a direct consequence of the pathological process.

Indirect insults can be used to explain how acute pathology (precipitating factors) may interact with chronic disease (predisposing factors). Usually, acute pathology arises in the periphery (e.g. infection/inflammation, pain). A unifying idea is that aberrant stress responses have an impact on brain and brain function (MacLullich et al. 2008; Cunningham et al. 2013). There are a number of routes through which systemic processes in the periphery can have an effect on the brain. Inflammatory mediators can interact directly with neurons in areas where the blood-brain barrier is deficient; there are neurohumoral connections that communicate directly through the vagus nerve; endothelial glial cells can transmit cytokine signals into the brain parenchyma (Figure 1-4).
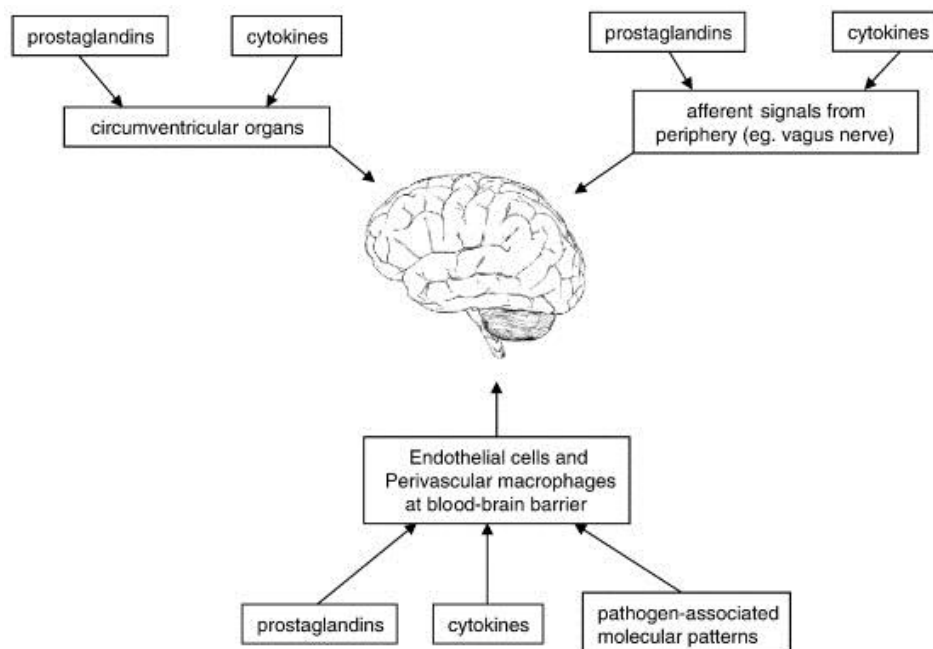
Figure 1-4. Routes of communication from periphery to central nervous system (MacLullich et al. 2008).

Neuroendocrine axes that are responsible for managing the normal stress response may become pathologically disrupted such that delirium is precipitated and/or sustained. For example, glucocorticoid regulation through the hypothalamus-pituitary-adrenal (HPA) axis is vital, because sustained high levels may lead to chronic activation of low affinity receptors and this in itself, is cytotoxic (e.g. Cushing's disease). Reciprocally, it is known that chronic neurodegeneration in the limbic system leads to dysregulation of the HPA axis so the higher order control of the cortisol response can become exaggerated. Together, these situate neuroinflammatory and neuroendocrine mechanisms as 'aberrant stress mediators'.

1.4.1   Experimental models

Relevant animal models in this field have been carefully grounded in the reciprocal predisposing / precipitating conceptualisation of delirium. The most developed construct has recreated predisposing cognitive impairment (e.g. prion disease, selective lesioning of the cholinergic system) and superimposed an acute event (e.g. bacterial or viral inflammation) (Cunningham et al. 2013).

At a cellular level, it is understood that neurodegenerative conditions such as Alzheimer's disease can initiate responses from microglia (Wyss-Coray 2006). Microglia are the resident monocyte/macrophage system in central nervous system (CNS). Morphologically activated microglia can adopt a wide number of functional phenotypes, determined by a range conditions. Crucially, microglial responses to neurodegeneration are on a spectrum from M1 (classical macrophage activity) to M2 (growth-repair functions). Thus, these immunological phenotypes may be deleterious (enhancing neurodegeneration) or beneficial (clearing amyloid deposits). In animal models, microglia have been shown to migrate to new amyloid plaques (Meyer-Luehmann et al. 2008). In vitro, microglial receptors (e.g. Toll-like receptor 4) can contribute to innate immunity through clearing amyloid plaques (Liu et al. 2005). Although the regulatory

mechanisms are not well understood, it appears that the predominant response to amyloid is not overly aggressive, and indeed may be anti-inflammatory in part. Taken together, this results in microglial priming. Microglial priming is a key concept, and represents a state whereby glia are morphologically activated, but not pro-inflammatory. However, this primed state can result in phenotypic switching in response to an inflammatory challenge.

A murine model of delirium exists which demonstrates these features, based on an ME7 (prion) model of neurodegeneration. Here, ME7 mice are challenged with a peripheral inflammatory stimulus (e.g. lipopolysaccharide (LPS), mimicking bacterial infection; poly I:C, mimicking viral infection) (Cunningham et al. 2007; Murray et al. 2012a). For both cognitive and motor tasks, ME7 + peripheral challenge mice perform worse than age-matched controls injected with normal saline. Similarly, for non-ME7 mice injected with a peripheral challenge, cognitive and motor tasks were not affected by generalised sickness-behaviour induced by LPS.

The neuropathological findings of this model demonstrate that in ME7 + peripheral challenge mice, microglia exhibit an exaggerated pro-inflammatory response. CNS transcription of TNF-α, IL-1β and IFN-β were markedly elevated in ME7 mice compared to controls injected with LPS, even after adjusting for cytokine levels in periphery. Thus, the neuroinflammatory pathway elaborated by this model is as follows (Figure 1-5):

- ME7 induces neurodegeneration and synaptic loss.
- This results in microglial priming, which in itself is insufficient to produce cognitive deficits in early disease.
- A peripheral inflammatory challenge initiates a phenotypic switch to aggressive up-regulation of inflammatory cytokines.
- This is responsible for acute working memory and motor deficits, analogous to delirium.

- A key feature of this model is the predisposed brain (primed by a neurodegenerative process) is pushed over a functional threshold by a precipitating peripheral challenge.
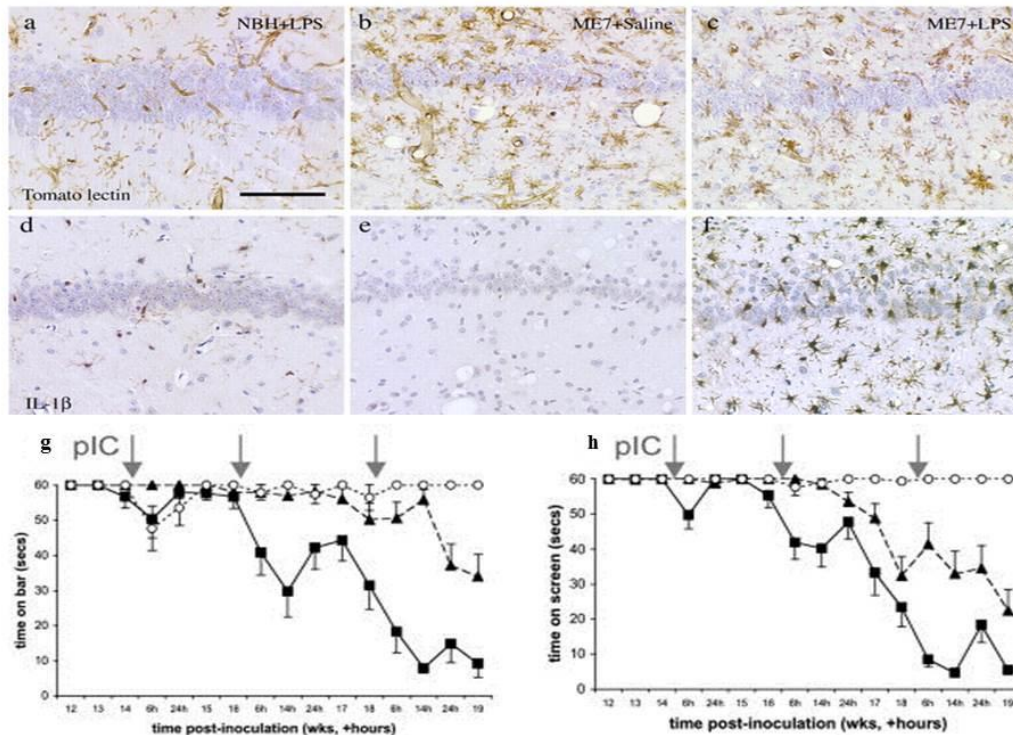
Figure 1-5. Pathological and inflammatory changes after LPS. a-c, Tomato lectin staining for microglial cells in brains from NBH+LPS (a), ME7+saline (b), and ME7+LPS (c) animals. d-f, IL-1β immunostaining in NBH+LPS (d), ME7+saline (e), and ME7+LPS (f) brains. (g and h) Weekly time point assessments to depict the course of neurological impairments when underlying disease and systemic challenge combine. Treatment with poly I:C is indicated by grey arrows.

Though microglial priming may be one important mediator in delirium pathophysiology, priming was not essential for the same cognitive deficits reproduced in cholinergically deficient mice, blocked by donepezil (Field et al. 2012). Therefore, the interplay between acetylcholine deficiency and microglial priming requires better definition. Nonetheless, these models have begun to explore pathophysiological pathways that may identify future targets for intervention. In the progressive neurodegeneration model, microglia express cyclo-oxygenase (COX) 1 and

synthesise prostaglandins. Inhibition of this using COX-1 selective inhibition or indeed ibuprofen is protective against systemic LPS or IL-1 induced cognitive deficits (Griffin 2013).

There is not yet direct evidence that the delirium *per se* and the concurrent neuronal death actually occur by the same mechanisms. However, it has been shown in other murine models that lipopolysaccharide in itself can result in generation of nitric oxide, inducing neuronal apoptosis and persistent cognitive deficits (Semmler et al. 2005; Weberpals et al. 2009).

1.4.2 Clinical studies of delirium pathophysiology

The following sections are based on systematic reviews of the literature, updated to February 2013, using the original search strings described in by the original systematic review (Medline only).

1.4.2.1 *Cerebrospinal fluid biomarkers*

Studies of cerebrospinal fluid (CSF) in delirium are difficult to perform. Apart from the general difficulty of recruiting participants who are often unable to give consent, the inherently invasive nature of CSF sampling makes such research particularly challenging. However, a few studies have exploited the opportunity to sample CSF from persons undergoing spinal anaesthesia for elective or emergency surgery. Indeed, spinal anaesthesia may in fact be the anaesthetic modality of choice for frail older patients, so these studies are often undertaken in highly relevant populations.

A recent systematic review identified 8 studies involving 235 patients (142 with delirium) (Hall et al. 2011). Overall, 17 different biomarkers were considered and each article identified in the review focused on a narrow range of biomarkers with no overlap between studies. Studies were

generally small, studying heterogeneous populations with different times of CSF sampling in relation to delirium, and no clear conclusions could be drawn. Age and concomitant dementia were likely to be major confounders, and this was not always adequately addressed. Broadly, delirium may be associated with: increased serotoninergic and dopamine signalling; reversible fall in somatostatin; increased cortisol; and increase in some inflammatory cytokines (IL-8), but not others (TNF-α, IL-1β).

In updating this systematic review, one additional study was identified (Witlox et al. 2011). Reporting a cohort of 76 individuals admitted for emergency hip fractures, this is comparable in size to the largest study described in the systematic review. Here, postoperative delirium was identified in 30 participants (40%) and this was strongly associated with premorbid cognitive decline (as assessed by IQCODE). However, CSF Aβ1-42, tau, and phosphorylated-tau levels were not associated with delirium status, nor did they correlate significantly with IQCODE score. The two main explanations for these findings are either: (1) the study was underpowered to detect mediating pathways between premorbid cognitive impairment, Alzheimer's pathology biomarkers and subsequent delirium; or (2) postoperative delirium arises through pathophysiological pathways that are distinct from Alzheimer disease.

Overall, CSF studies may be a valuable method for investigating pathophysiological correlates of delirium However, larger studies in relevant populations will be necessary.

1.4.2.2 Neuroimaging

The neuroimaging correlates of delirium are very difficult to establish. Many attempts to image people with concurrent delirium will be unsuccessful. In addition, there is a more general bias selecting younger and fitter participants amenable to scanning, especially if using intensive protocols such as MRI.

The literature has been summarised by a systematic review (Soiza et al. 2008). This found 12 articles for inclusion, most with small sample sizes (total number of cases 127). There was substantial heterogeneity in populations, study design, and imaging modalities such that no firm conclusions were made. Generally, structural imaging suggested that diffuse brain abnormalities such as atrophy and leukoaraiosis might be associated with delirium, though few studies could account for differences in key variables such as age, sex, education or underlying cognitive function. Two functional studies reported perfusion abnormalities in delirium.

In updating the systematic review, five further studies were identified. In addition, a single study reporting proton magnetic resonance spectroscopy findings in 14 persons undergoing bone marrow transplant for haematological malignancies (5 developing delirium, 9 not) and 10 age- and sex-matched controls (drawn from family and friends) was not considered further due to the very specific clinical circumstances under investigation (Yager et al. 2011).

The largest-scale report was VISIONS (Gunther et al. 2012; Morandi et al. 2012b). This was a prospective cohort study that examined neuroimaging correlates of delirium in 47 participants after critical illness. Following ICU admission, in which individuals were evaluated with CAM-ICU (33 with ≥1 day of delirium), diffusion tensor imaging (DTI) was performed at discharge and at 3 month follow-up (Morandi et al. 2012b). The principal DTI measure was fractional anisotropy, a marker of white matter integrity. Delirium duration was related to fractional anisotropy and this in turn was related to poorer cognitive outcomes at 3 and 12 months. In addition, brain volumes were also assessed and related to cognitive outcomes in the same manner (Gunther et al. 2012). Overall, the study found that longer duration of delirium was associated with smaller brain volume and more white matter disruption, and both these correlated with worse cognitive scores 12 months later.

Two studies examined delirium risk as a post-operative complication after elective cardiac surgery. The first showed that Fazekas score, a semi-quantitative measure of white-matter hyperintensities, was associated with post-operative delirium in the 18 cases developing in 130 Japanese patients (Hatano et al. 2013). Some caution should be applied to these findings as delirium was ascertained through (blinded) chart review. Though the study appeared to have ready access to liaison psychiatry input, the under-detection of delirium is likely. In a similar population, fractional anisotropy (in left frontal lobe and regions of interest in the deep white matter) was also predictive of post-operative delirium, even after adjusting for age (Shioiri et al. 2010). It should be noted when considering these findings that cardiac surgery, which requires a period of extracorporeal bypass, represents a specific route for peri-operative brain dysfunction that may not be generalisable to the rest of the population undergoing surgery.

In a population of inpatients referred to a tertiary liaison psychiatry service, functional networks were assessed in 22 patients during delirium using fMRI (mean DRS-R-98 score 18 (SD 4.1)) (Choi et al. 2012). Follow-up was possible after resolution in 13 patients (median interval 5.8 days), and age- and sex-matched controls were drawn from a database of inpatients receiving the same imaging protocol for other indications. This study reported reversible reduction in subcortical connectivity between dorsolateral prefrontal cortex and posterior cingulate during delirium, as well as enhanced integration in posteromedial cortices after recovery. These findings identify brain areas localising with cognition and attention function, and the study is unique in reporting fMRI results during and after delirium. Though the study design is likely to be biased through selection of controls (and the spectrum of medical illness in these controls), it serves as a possible model for future research.

1.4.2.3 Neurophysiology

Electroencephalography (EEG) is an attractive mode of study in delirium as it is able to capture measures of global brain function. There are also opportunities to summarise temporal fluctuations as continuous recordings, compressed into power spectra (quantitative EEG, qEEG). Since the work of Engel and Romano in the 1950s, delirium has been known to be associated with a generalised slowing of background activity (Engel et al. 2004).

A systematic review identified 14 studies for inclusion, representing a range of different populations: 6 in older populations, 3 in ICU, sample sizes between 10 and 50) (Kooi et al. 2012). Four studies compared dementia with delirium and dementia to normal controls. In the main, a psychiatrist was used to ascertain delirium. For most studies, the outcome of interest was the relative power measures, in order: alpha, theta, delta frequencies. These power measures relate to the EEG wave bands, which in themselves reflect specific characteristics of brain function. The relative power of the theta frequency was consistently different between delirium and non-delirium patients, suggesting metabolic effects on arousal might be important. Similar findings were reported for alpha frequencies. In two studies, the relative power of all these bands was different within patients before and after delirium.

No other relevant studies were identified since publication of the systematic review.

1.4.2.4 Neuropathology

Only a handful of studies exist where there has been an attempt to correlate delirium with pathological findings at autopsy; no systematic review on the topic was identified. A case series has been reported on 7 patients who died during ICU admission (Janz et al. 2010). These patients had a mean age of 55 years (SD 8.4), with a median number of days with delirium of 7 (IQR 2 to 12). Each case was admitted with a range of primary pathologies, but all had acute respiratory distress syndrome and/or septic shock contributing to the delirium. 6/7 had evidence

of hypoperfusion and diffuse vascular injury, with consistent involvement of the hippocampus in 5/7.

A case-control study examined 9 delirium cases with 6 age-matched controls (Munster et al. 2011), investigating inflammatory cytokines and their role in delirium. Cases were drawn from patients who had their delirium diagnosed by a geriatrician and then died during the index admission. Controls were selected from other brain autopsies that had been performed for clinical reasons, and whose medical records documented no neuropsychiatric symptoms suggestive of delirium. Cases had higher scores for HLA-DR and CD68 (markers of microglial activation), IL-6 (cytokines pro-inflammatory and anti-inflammatory activities) and GFAP (marker of astrocyte activity). These results might suggest a neuroinflammatory substrate to delirium (or at least terminal delirium), but the conclusions are limited by biases from selection of controls.

Finally, a case series reporting dementia and delirium in 4 patients with an inherited spinocerebellar ataxia was not considered further given the highly specific nature of the pathological condition (Ishikawa et al. 2002).

1.5 Chapter summary

Delirium in the older population is common, serious and important. It arises through the interaction of predisposing and precipitating factors. As such, it should be taken as a sign of acute illness having an impact on arousal mental status. The syndrome is characterised by acute and fluctuating inattention accompanying new cognitive and/or perceptual change. Disruption of circadian rhythm is also common.

Table 1-3. Summary of clinical methods used to investigate delirium pathophysiology

	Biomarkers	**Imaging**	**Neurophysiology**	**Neuropathology**
Design	Cohort, case-control	Cohort, case-control	Case-control	Case-control, Case series
Measures	Plasma, CSF	CT, MRI, MRS, fMRI	Differences in power bands, quantitative EEG	Histopathology, immunohistochemistry
Outcomes	Delirium, delirium severity	Delirium, subsyndromal delirium	Delirium, delirium superimposed on dementia	Delirium
Conclusions	Possible role for cortisol, cytokines	Possible role for white matter integrity, cortical and subcortical pathology	Possible role as diagnostic tool	Possible role for microvascular and inflammatory pathology

The pathophysiological substrates of delirium are likely to involve a range of direct and indirect mechanisms of brain injury, though firm conclusions are still not established (Table 1-3). Neuroinflammatory and neuroendocrine pathways are implicated and these may or may not interact with the pathological processes that underlie dementia.

The next chapter will discuss the epidemiological possibilities in delirium research. By reviewing previous literature on delirium in community samples (including a systematic review of the descriptive epidemiology of delirium in population-based studies), gaps in the understanding of delirium can be identified. This then leads to the specification of questions to be addressed by this thesis.

2 Epidemiological research in delirium

The previous chapter detailed the clinical constructs that underlie delirium. The purpose of this next chapter is to place the study of delirium and its sequelae in an epidemiological context. This will start by examining the principles of epidemiology relevant to this thesis. Following this, two systematic reviews will be presented: (i) the descriptive epidemiology of delirium in population-based studies, assessing the quantity and quality of work done to date; and (ii) the association between delirium and/or systemic illness with trajectories of cognitive decline. This thesis addresses some of the gaps identified by these systematic reviews. Accordingly, the final section of this chapter specifies the aims of this thesis: the investigation of delirium and trajectories of cognitive decline in population-based studies.

Chapter outline

1. Principles of epidemiology
    - Population
    - Case-ascertainment
    - Attitrition
    - Residual confounding
2. Systematic review: population studies in delirium
3. Systematic review: delirium and trajectories of cognitive decline
4. Core questions and statement of aims

2.1 Principles of epidemiology

2.1.1 Population

In considering the importance of defining a population, the question being asked is: to what extent is the chosen population representative of the full spectrum of persons with delirium in that population? For example, if the incidence of post-operative delirium in patients aged ≥70 years with urinary tract infections is being studied, are the individuals in the study representative of everyone with delirium, or are there biases that arise because this is a relatively easy group to

identify and recruit? How does the approach to sampling enable a valid capture of the chosen population? These are critical questions as the provenance of the sample population has the potential to systematically bias findings both in magnitude and direction.

The majority of studies in delirium have been undertaken in specific hospital settings and often among patients with particular medical or surgical conditions (Siddiqi et al. 2006; Witlox et al. 2010). Together, these studies indicate that delirium is a common problem in inpatients and is associated with serious adverse outcomes, such as increased mortality, institutionalisation and dementia (Section 1.1.2). However, there are three limitations to the inferences that can be drawn about delirium as a whole in the existing literature. Firstly, it cannot be assumed that all persons with delirium from a given population will actually present to the particular hospital from which the respondents come. Secondly, once in hospital, there is only retrospective information on a person's cognitive and functional status. This lack of reliable data on pre-admission status makes it difficult to ascertain delirium (and pre-existing dementia) because the diagnosis requires determination of acute *change* in mental status (Section 1.3). Third, referral and selection bias inherent in hospital-based studies with particular subgroups of people with delirium leads to questionable generalisability and conflicting findings across studies.

2.1.1.1   *Example: populations in stroke epidemiology*

The importance of an unselected population has been shown through the findings of the Oxfordshire Community Stroke Project (OCSP) (Bamford et al. 1988; Bamford et al. 1990) and its successor, the Oxford Vascular Study (OXVASC) (Rothwell et al. 2004). A working definition for population-based study might be: 'a study where all subgroups of the population are sampled, regardless of disease or residential status' (Zaccai et al. 2006). These studies of stroke incidence made comprehensive efforts to ascertain all cases of transient ischemic attack (TIA) or stroke from a defined population registered on general practitioners' (GP) lists, where virtually all

primary care is delivered. Each participating surgery maintained close personal contact with the study, and collaborating GPs reported suspected cases to the study as soon as patients presented. If participants were not admitted to hospital directly, they were assessed on the day of referral in a dedicated research clinic or at the participant's own home. All computerised diagnostic codes were reviewed, strengthened by record linkage systems between primary and secondary care. Hospital and emergency department presentations were reviewed daily and all deaths out of hospital were identified via the Coroner's Office.

This strategy to include all cases from the general population resulted in major advances in understanding of the prognosis and outcomes from TIA and stroke, precisely because it included the full range of persons with acute neurovascular events. In a systematic review of studies reporting the risk of early stroke following TIA, it is clear that population-based studies had much higher estimates of early recurrence (within seven days) compared to those samples presenting solely to specialist stroke services (proportion recurring within seven-days in population-based studies 10.4% (95% CI 8.1 to 12.6%); proportion in specialist stroke services 0.9% (95% CI 0.0 to 1.9%)) (Giles et al. 2007). It is now clear that the relationship between TIA and early stroke can be predicted using a clinical risk score (Rothwell et al. 2005; Giles et al. 2010). These findings have had a major impact in the planning of stroke services and in improving patient outcomes (Rothwell et al. 2007).

2.1.1.2 Example: Populations in dementia epidemiology

There have been similar issues in respect of the descriptive epidemiology of dementia, where estimates vary according to setting. A systematic review of prospective studies of mild cognitive impairment (MCI), the current conceptualisation of a dementia prodrome, sought to determine the criterion validity of the construct, that is, the extent to which MCI correlated with outcomes already considered to be valid, e.g. conversion to dementia (Mitchell et al. 2009). The consistent

finding was that conversion rates in the general population are much lower than in clinic samples. It would be reasonable to expect this, as selection into a clinic setting represents more a more advanced disease (or at least referral) stage. However, this also demonstrates that studying selected populations may lead to falsely inflated effect sizes. So for conditions which evolve slowly, selected clinic populations tend to overestimate outcomes of interest. Conversely, where outcomes may occur over a short interval, selected samples may underestimate the association. It is clear that population-based studies are essential if we are to contextualise the limitations of clinic samples.

For delirium research, there is a need to consider how explicitly the population is defined. Ideally, one would start with a broad, unselected denominator (i.e. a true population-based study) followed-up with serial cognitive and functional assessments. This would represent a comprehensive range of symptoms and severities, but also identify what happens, to whom, and when. This would help to establish the determinants and effects of delirium most completely. Of course, ensuring that a study population is comprehensive in this way requires substantial effort, but there are gains of equal degree in terms of achieving results with external generalisability.

2.1.2   Case-ascertainment

In order to reliably track states of health in populations, looking for emerging patterns and trends, one must be able to define exposures and outcomes of interest in a standardised way. For psychiatric syndromes, the reference-standard definition is necessarily a set of clinically agreed descriptions of psychopathology, preferably collected in a standardised manner, rather than any objective measures. The possibility that biomarkers might eventually contribute to case-ascertainment is briefly reviewed below.

2.1.2.1   *From definition to operationalisation*

There are some differences between the ICD (World Health Organization) and the DSM (American Psychiatric Association) definitions of delirium, and these have an impact on case-ascertainment (Liptzin et al. 1991; Cole et al. 2003b; Laurila et al. 2004a) (Section 1.3). The definitions evolve with each revision and therefore are not stable over time. More problematic is that these clinical criteria have the potential to be interpreted differently by individual clinicians. For example, the threshold for impairment on cognitive testing in delirium may decrease with age, in line with a belief that some deficit is to a degree expected, and thus not abnormal, in older age (Brayne 1993). One way of mitigating this variability is to use an algorithmic approach to case-ascertainment (described in more detail in Section 2.1.2.3 and Chapter 5).

2.1.2.2   *Diagnosing delirium in the context of dementia*

Expanding on the issues around case-ascertainment introduced in Section 1.3, the boundaries for the delirium syndrome become more complex when considering co-morbid dementia. DSM separates the delirium and dementia definitions, but the problem of identifying one superimposed on the other remains. This is crucial because delirium can be missed, under an assumption that observed cognitive deficits are due to dementia. When delirium and dementia co-exist, the delirium symptoms (for example, prominent inattention with fluctuating deficits) are thought to dominate the presentation over the impairments seen in dementia, and this has been reviewed in detail (Meagher et al. 2008; Meagher et al. 2010; Blazer et al. 2012). However, if much of the delirium fieldwork explicitly excluded persons with dementia, the resultant conceptualisation may have over-emphasised features that are more likely to be reported in cognitively intact persons (e.g. psychotic symptoms). Conversely, delirium scales which include assessments of memory or other cognitive deficits known to be present in dementia (such as the Delirium Rating Scale – Revised – 98) (Trzepacz et al. 2001) may be confounded by the presence of dementia. Moreover, some delirium assessment instruments have been validated in separate

delirium and dementia groups, so that no assessment of the phenomenological overlap can be made. One consequence of this is that scores in memory subscales are worse due to dementia, regardless of if there is also delirium. Currently it is not known if delirium and dementia can be distinguished in a cross-sectional assessment on cognitive and phenomenological grounds alone, but some studies suggest that this might be possible (Brown et al. 2009; Brown et al. 2011; Chester et al. 2012).

A history (likely from an informant, even if dementia is not yet diagnosed) is required to establish the acuity of change from baseline. In hypoactive delirium, the fluctuating course may be less obvious and so may be more difficult to distinguish from co-existing dementia. There is considerable phenomenological overlap between hyperactive delirium and behavioural and psychological symptoms of dementia (BPSD) and the boundaries are not well-established. Pragmatically, symptoms should only be attributed to BPSD if an acute medical precipitant has been ruled out (Meagher et al. 2008).

The chief difficulty with operationalising delirium, then, is that the main constructs and their boundaries are not clearly defined. DSM does not specify duration, severity, minimum thresholds, or which symptoms should fluctuate over which time frames. However, empirical data suggest that each of these parameters may influence outcomes and so perhaps define prognostic groups (Table 2-1) (Meagher et al. 2008; Blazer et al. 2012). Further detailed population-based fieldwork involving increased use of standardised definitions and measurements with high reliability, preferably objective, is essential if case-definitions are to describe useful phenotypes. Despite these limitations, the aim is to operationalise these criteria so that case-ascertainment can be achieved in a consistent manner in the research setting. The next section considers in more detail approaches to operationalisation in epidemiological studies, using dementia as an exemplar.

Table 2-1 Clinical features in delirium not currently defined by DSM criteria with a theoretical influence on determining prognostic categories.

Clinical feature	Effect on prognosis	Comment	References
Motoric subtypes	Hypoactive delirium associated with higher mortality, especially where co-morbid dementia	Motoric assessment, including accelerometer-based measures have scope to inform prognostic categories	(O'Keeffe 1999; Meagher 2009; Yang et al. 2009)
Duration	Minimum and maximum duration unclear.	Delirium may evolve into dementia. Short term v persistent delirium proposed (though not adopted) in DSM-5 (threshold not specified)	
Temporal fluctuations	Specifying short fluctuations (hours) favours identification of hyperactive over hypoactive subtype	Hypoactive delirium has poorer prognosis, so any specification of temporal fluctuations should take this into account	
Severity	Clinical rating scales in existence (e.g. DRS-98, MDAS, Delirium Index). Higher scores associated with worse outcomes	Categories of severity might be incorporated into diagnostic criteria, but the issue of measurement is still difficult	(Adamis et al. 2006)
Subsyndromal delirium	Higher mortality and worse cognitive outcomes	Variably defined, represents a state between normality and full delirium syndrome. Current definition of delirium might perhaps be broadened to include milder deficits.	(Cole et al. 2003c; Meagher et al. 2012)

2.1.2.3   *Operationalisation in dementia epidemiology*

Dementia is clinically defined by identifying progressive deficits in two or more cognitive domains sufficient to impair function in activities of daily living. The three population-based studies that form the basis of this thesis can be used as examples to illustrate the different ways in which this definition has been operationalised in the context of research (each study is described more fully in Chapter 3. Vantaa 85+ defined dementia cases through the agreement of two neurologists at clinical examination (Polvikoski et al. 2006). While this was more reliable than assessment by a single clinician, more than one assessment introduces greater variability in the measures and how this is addressed can hamper cross-study comparisons. In the Cambridge

City over-75 Cohort (CC75C) brain donors (Fleming et al. 2007), as well as other studies in both Europe (Ott et al. 1995) and North America (Launer et al. 1995), the approach to case-ascertainment was addressed through the agreement of dementia diagnoses at multidisciplinary consensus meetings, held after all study information became available. This method of case-ascertainment is labour-intensive and so limits its practical use to some extent.

In parallel to the development of the multidisciplinary conference to standardise case-ascertainment, use of the Present State Examination (PSE) (Wing et al. 1977) led to the possibility of creating diagnostic categories through algorithms. The PSE – and the version validated in older persons, the Geriatric Mental State (GMS) (Copeland et al. 1976) – is a systematic operationalisation of the psychiatric mental state examination. It uses answers generated from the interview to group symptom clusters which can then be used to derive diagnostic groups. Once these categories have been validated against clinician-applied diagnoses, this algorithm approach can be automated and applied by trained lay interviewers. The MRC Cognitive Function and Ageing Study (MRC-CFAS) (Brayne 2006) used such an approach with the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) (Copeland et al. 1986). This allowed for much greater numbers of persons to be examined and MRC-CFAS remains one of the largest population-based studies of dementia incidence of its kind. The algorithm diagnosis has been considered again more recently by studies such as the Health and Retirement Study (Plassman et al. 2007), which includes attempts to reduce the cost of case-ascertainment (Weir et al. 2011). In addition, an algorithm approach has been applied to the consensus diagnosis itself, with the aim of making the process more time-efficient (Duara et al. 2010).

2.1.2.4 Biomarkers and psychiatric syndromes

Biomarkers have been widely considered in dementia in the hope that a greater understanding of dementia pathophysiology might be able to contribute to case-ascertainment, or even supplant the current clinical reference standard (Sunderland et al. 2006; Dubois et al. 2007; McKhann et al. 2011). There has been substantial progress in the field, identifying amongst other things, amyloid burden *in vivo* (Klunk et al. 2004) and putative markers of neurodegeneration (Blennow et al. 2003; Mosconi 2005). However, such work has only ever been generalisable to the selected populations able to tolerate procedures such as PET-MRI or lumbar puncture.

There is a real need for biomarker research to be validated within the context of a general population before they can be proposed as part of a new reference standard (Brayne et al. 2012). Most individuals with dementia in Western societies are aged over 80 years, but such persons have been under-represented in research. The consequences of selection bias in relation to putative biomarkers can be illustrated by autopsy work in MRC-CFAS, where two important findings have been reported (Matthews et al. 2009; Savva et al. 2009). Firstly, the relationship between recognised neuropathological markers of dementia (amyloid load and neurofibrillary tangles in both hippocampus and neocortex) had weaker relationships with clinical dementia in individuals in their late 80s and 90s (Savva et al. 2009). Secondly, it is clear that mixed (particularly vascular) pathologies all contributed to dementia in this unselected population and that many other people tolerate moderate to high levels of pathology without expressing clinical symptoms and signs (Matthews et al. 2009). These are serious challenges yet to be sufficiently addressed in biomarker validation studies.

There are lessons to be learned for clinical delirium research. Current plasma biomarker candidates, such as apolipoprotein E, insulin-like growth factor-1 and S-100β for predicting delirium risk, prognosis or severity have recently been reviewed (Khan et al. 2011). The CSF,

neuroimaging and neurophysiological correlates were reviewed in Section 1.4.2. It is clear that biomarkers in delirium are still in their infancy, but advances in our understanding of delirium pathophysiology may eventually help to refine case-ascertainment, provided that these are done in relevant populations.

In conclusion, the optimal operationalisation of DSM-IV for delirium would require (i) a reliable and valid test of inattention that operates well with or without co-existing dementia; (ii) reliable and valid assessments of cognition and neuropsychiatric symptoms (iii) temporal nature of acute change captured by regular observation, with or without a contribution from informants. Ultimately, validation studies of biomarkers could be undertaken in unselected populations, serving to improve delirium knowledge at the clinical and population levels.

2.1.3   Attrition

Loss to follow-up is common to all longitudinal studies of older persons. Reasons for loss of follow-up include drop-out and death between interviews (Chatfield et al. 2005). This is also known as censoring – where individuals contribute to the observed period of follow-up, but where loss to follow-up means that case-status cannot be ascertained. There is a clear effect on how accurately associations with outcomes can then be made. Elaborating how these biases can be addressed is relevant for all follow-up studies of delirium.

It is important to explore possible reasons why outcome data may be missing. This involves considering whether the fact that data are missing might be associated with any other variables known (and unknown) to the study. Three characterisations of missing data mechanisms have been proposed: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Table 2-2) (Little 2002).

Table 2-2 Theoretical mechanisms for missing data.

Mechanism (Little 2002)	Definition	Example	Implications for delirium research
MCAR	Does not depend on observed or unobserved data	Lost data due to technical error such as mis-calibration of MRI machine	Missing data is usually ignorable, but this is a rare situation
MAR	Depends on observed data	Unable to tolerate MRI sequences, predictable from knowledge of participant's cognition or ADL	Other parameters may explain the mechanism of missingess, but not fully enough to provide unbiased estimates in analyses.
MNAR	Depends on the value the outcome would have taken had it been observed	Attrition through death, driven by incident delirium or dementia that was not captured by the follow-up schedule	The most common mechanism of missing data in aging research. Requires specific and robust mechanisms for case-ascertainment, with statistical analyses to account for attrition.

MCAR missing completely at random; MAR missing at random; MNAR missing not at random; MRI magnetic resonance imaging; ADL activities of daily living

Several approaches are available to analyse incomplete data. The simplest method consists of excluding cases with missing observations. This method, known as complete case analysis, is a very inefficient way of analysing data, and does not make use of all available information. Because data in longitudinal studies of older persons are unlikely to be MCAR, such an approach will bias the analysis in favour of better performing participants. This illustrates why missing data cannot simply be ignored; the very fact that some data are missing is informative and an appropriate analysis must be adopted.

Other *ad hoc* methods are based on the idea of 'filling in' or imputing missing values to complete the data. Imputation has been proposed as a method of accounting for missing data on exposures (independent covariates) and outcomes (dependent variables). However, it should be noted that imputing *outcomes* is intrinsically problematic. This is because studies aim to determine a given outcome, and it would be unsatisfactory for this to be simulated in any way. Examples of

imputation methods include: 'last observation carried forward' (LOCF) imputation; regression mean imputation; and multiple imputation.

LOCF is an imputation method that consists of replacing every unobserved value by the last observed value. This is a reasonable approach, as mentioned above, because to some extent the last observation (of for example, low cognitive test score) is associated with a higher likelihood of drop-out. However, it makes a strong assumption of no change over the unobserved time, and this is very unlikely in delirium. Regression mean imputation imputes the missing value by the predicted value given the variables that are available. This predicted value is obtained from a regression analysis where the outcome is the variable being imputed and the observed variables as covariates. One disadvantage with this approach is that regression mean imputation will underestimate variances in the outcome and so in general, estimates of associations produced using this method will be biased. Multiple imputation is a much improved technique of imputing missing observations. It consists of creating several copies of completed datasets according to certain rules, and conducts the planned analysis on each of these completed datasets, combining the results obtained. Multiple imputation is a valid method of analysis when we are willing to assume that missing observations are MAR and produces appropriate measures of precision. Further, it is particularly useful when missing data occur in covariates.

If imputation for missing outcome data is to be avoided, other analytical techniques are recommended. If it is assumed that missing data are MAR, random-effects modelling is a statistical technique that produce robust estimates and use all available data. However, if a MNAR mechanism is a more reasonable assumption to make, then more sophisticated statistical techniques such as shared parameter models might be the most adequate method of analysis (Henderson et al. 2000). Shared parameter models consist of two sub-models: a longitudinal random-effects sub-model for the description of change over time, and one time-to-event sub-model to describe features of the survival process. To link both, some of the parameters of the

longitudinal model are included as covariates in the survival sub-model. Shared parameter models have been applied to longitudinal studies of aging (McArdle et al. 2005; Ghisletta et al. 2006; Muniz Terrera et al. 2011). In the presence of missing data due to death and dropout, the shared parameter model can be extended to account for the two reasons for dropout (i.e. death and dementia), modelling them using a competing risk approach. The use of these techniques is not widespread in the ageing literature, but if it is believed that a MAR assumption is not valid, these more refined analytical methods should be considered. While these techniques have been important in the dementia epidemiology, they have yet to be applied systematically to follow-up studies of delirium which almost certainly under-estimate the effect of drop-out (Adamis 2009; Deiner et al. 2009; Neufeld et al. 2011).

2.1.4 Residual confounding

Observational epidemiology seeks to identify associations between exposures (independent variables) and outcomes (dependent variables). Delirium can be considered in both contexts. For example, delirium might be modelled as an exposure with dementia as an outcome. Alternatively, sometimes delirium is considered the outcome, where for example, statin therapy is the exposure. These analyses should be undertaken with attention to the possibility of confounding.

Confounding occurs when an apparent relationship between an exposure and an outcome is actually being driven by a third variable. For example, in examining the association of dementia with mortality, if two groups are not balanced in respect of the distribution of ages, the group of older persons (who are more likely to have dementia) may show a higher mortality by virtue of their being older, rather than because of the dementia. In these analyses, regression models can be used to adjust for age (or any other variable simultaneously). This serves to isolate the effect of dementia on mortality after accounting for all other variables that might otherwise be

associated with risk of death. This is one of the reasons that observational studies cannot directly prove causative relationships, as one cannot be certain that all possible confounders have been identified (or measured). This is known as residual confounding.

As outlined in section 1.1, the psychiatric formulation identifies two dimensions that need to be accounted for when considering prospective associations in delirium studies: precipitating and predisposing factors. Precipitating factors include measures of illness severity (which may include measures of intensity of surgery) and predisposing factors include cognitive impairment and frailty.

Can the effects of predisposing and precipitating factors be accounted for, such that the independent associations with delirium can be assessed? In other words, is delirium directly responsible for the association in question, or is it a marker for some more fundamental, less-measurable mechanism? This problem was recognised in the systematic review of outcomes after delirium in hospitalised patients, where one of the inclusion criteria was that studies had to adjust for co-morbid illness or illness severity (Witlox et al. 2010) (Section 1.1.2.2). The review considered predisposing and precipitating factors together, and the individual studies operationalised these dimensions as follows:

Predisposing factors, for example: presence of dementia or cognitive and functional impairment on e.g. MMSE, IQCODE; Charlson co-morbidities index; functional measures such as activities of daily living.

Precipitating factors, for example: acute physiology and chronic health evaluation II (APACHE II) score (Acute Physiology scale); physiological or metabolic parameters: systolic blood pressure, C-reactive protein, urea, creatinine.

Scales combining assessments of both factors, for example: Burvill scale (a physician judgment-based scoring of several organ systems where severity of acute and chronic conditions and their contribution to disability are assessed).

All studies made an attempt to adjust for predisposing factors, suggesting that it is easier to operationalise this dimension. To account for illness severity, many studies used APACHE, which has not, as yet, been validated outside ICU or in older persons (Minne et al. 2011). The other approach to adjusting for illness severity was to use a marker of overall metabolic or physiological disturbance.

Another systematic review assessed prognostic models for mortality in those aged 50 years and over (Minne et al. 2011). In particular, the review evaluated the number of models that had been validated in other cohorts. Of 193 models identified, only 4 were found to have more than two external validation studies: Charlson co-morbidities Index (CCI) (Charlson et al. 1987); Deyo score (Deyo et al. 1992) (adapted from the CCI); Simplified Acute Physiology Score (SAPS) (Le Gall et al. 1993); Multidimensional Prognostic Index (MPI) (Pilotto et al. 2008).

The CCI is very well established, and provides a weighted score representing co-morbidities (and therefore chronic predisposing factors). One problem is that the weightings and the conditions were validated over 20 years ago and so secular trends limit its validity. For example, a diagnosis of acquired immunodeficiency syndrome scores the same as metastatic disease and peptic ulcer disease is weighted the same as congestive heart failure. The Deyo score is subject to the same limitations. SAPS-II is only relevant to the ICU population. The MPI operationalises the comprehensive geriatric assessment and also only reflects the predisposing factors, rather than any acute precipitant.

Overall, the question remains as to how to reliably detect and, where possible, quantify acute precipitating factors in delirium. Moreover, the possibilities of measuring particular factors (e.g. degree of invasiveness) will vary according to setting. Another approach from the acute internal medicine literature examines 'early warning scores' (EWS). The best performing tool to date is the VitalPAC early warning score (ViEWS) (Prytherch et al. 2010). This was devised to predict in-hospital mortality within 24-hours of acute admission and uses a weighted aggregate of seven parameters: pulse rate; respiratory rate; temperature; systolic blood pressure; oxygen saturation; inspired oxygen; level of consciousness. The model was validated on 35,585 patient episodes, and the median age was 68 years. This approach has not been considered before in delirium, but could be valuable. However, many of these indicators may not perform in the same way in older people (Metlay et al. 1997), and measures of level of consciousness overlap with many symptoms of delirium.

2.1.5   Section conclusions

The epidemiological study of delirium requires attention to population, case-ascertainment, attrition and residual confounding. With these principles in mind, the quantity and quality of epidemiological research in delirium can be assessed in the following two systematic reviews: (i) descriptive epidemiology of delirium in community settings, and (ii) delirium and/or acute illness in relation to trajectories of cognitive decline.

2.2 Systematic review: population-based studies of delirium

Question:

What is the descriptive epidemiology (prevalence and incidence) of delirium in the general population?

Review of the population-based studies ascertaining delirium gives an indication of the burden in community settings, as well as the strategies used to gather sufficient data to make cognitive diagnoses. Here, studies reporting the descriptive epidemiology of delirium in population-based studies were of primary interest. For the purposes of this review, 'population-based' was defined as studies sampling from a geographically-defined population, regardless of health or residential status.

2.2.1 Methods

The methods followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al. 2000).

2.2.1.1 Eligibility criteria

Cross-sectional (prevalence) or cohort (prevalence and incidence) studies reporting delirium measures were considered. Studies were required to define delirium according to a standardised classification system, be conducted in groups sampled from the whole population unrestricted by residential or health status, and could be in any language.

2.2.1.2 Search strategy and data extraction

A systematic search of Medline (from 1950) on Pubmed, Embase (from 1980) on embase.com and the Science Citation Index (from 1950) on Web of Science (all until 31st December 2012) was conducted. Conference abstracts indexed in the Science Citation Index were considered.

Bibliographies of included articles and other reviews were screened. In accordance with MOOSE recommendations, abstracts were screened and data extracted in duplicate. The second reader was Andrew Hall, University of Edinburgh and the findings were published as Davis 2013.

Comprehensive text word, Medical Subject Headings and Emtree terms were used to find relevant studies (search strategies given in Appendix, Section 10.1). Any estimates of prevalence or incidence (and their standard errors) were extracted, along with any relevant clinical variables, specifically: age, sex and education (where reported).

2.2.1.3   *Studies describing epidemiology in enriched sub-samples*

One important strategy in population epidemiology is the over-sampling of sub-groups of interest. For example, over-sampling groups more likely to have delirium (older, more pre-existing cognitive impairment) would identify more cases. Findings from such studies only remain externally generalisable if this enrichment process (of higher risk groups) is balanced by a random sub-sample of the rest of the denominator (lower risk groups). This approach was taken in CFAS (described in more detail in Section 3.3, expanded further in Chapter 4).

Analytically, this could be dealt with by two methods. Firstly, back-weighted estimates can be calculated to account for the sampling strategy, and it might be appropriate to use these estimates in quantitative synthesis. The second strategy, if only a narrative synthesis is warranted, is simply to report enriched estimates, but be clear about the provenance of the denominator.

2.2.1.4 *Data analysis*

Statistical analyses were performed in Stata version 12.1 (Statacorp, USA). Given the range of different populations identified in the studies, estimates were pooled using a DerSimonian and Laird random-effects model (DerSimonian et al. 1986). 95% confidence intervals were calculated and statistical heterogeneity was assessed using the τ^2 statistic.

2.2.2 Results

96 studies were identified (Figure 2-1), 10 of which retrieved for full text review. Three studies reported point-prevalence of delirium, and two reported period-prevalence. Vantaa 85+ (a constituent cohort of this thesis) was also identified as this applied a retrospective diagnosis of delirium in the context of a cohort study of dementia incidence (described more fully in Section 3.1). Characteristics of these studies are summarised in Table 2-3.

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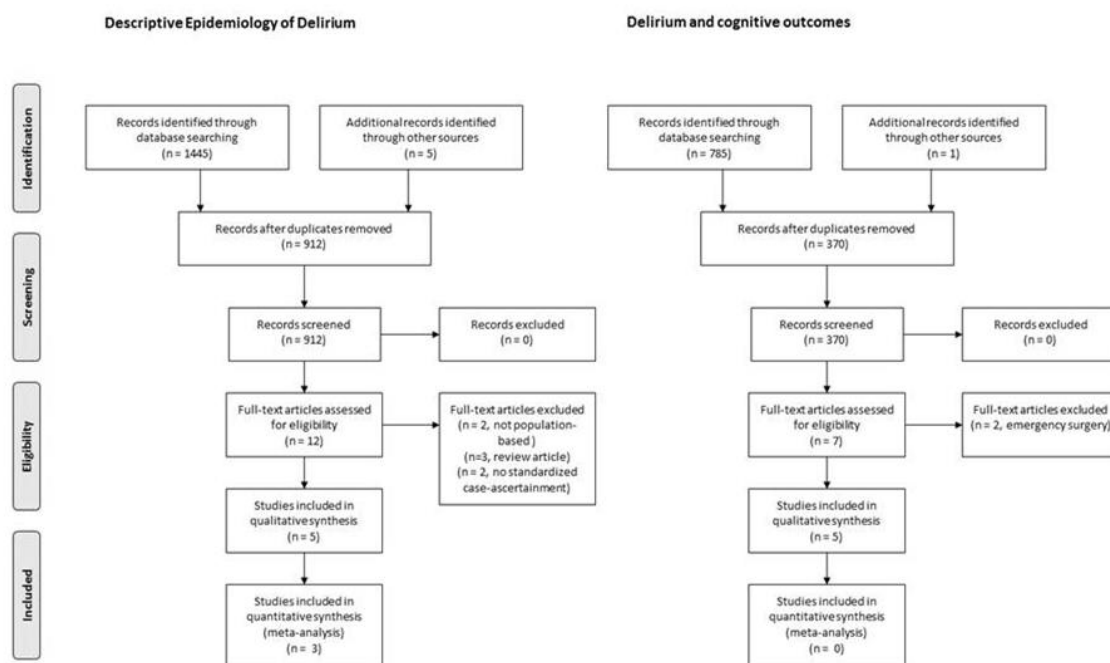
Figure 2-1. Flow diagram indicating identification of eligible studies.

Table 2-3 Population-based studies of delirium prevalence and incidence

Study	Population and setting	Design	Delirium ascertainment	Enriched sample?	Risk of bias
Point Prevalence					
East Baltimore (Folstein et al. 1991)	Census blocks, random sample 18-64 and all residents age≥65	DIS, with clinical assessment of random subsample (n=398) and any others with positive DIS (n=412).	SPE and psychiatric assessment (DSM-III and ICD-9)	Yes	High non-response.
Girona (Vilalta-Franch et al. 2009)	Door-to-door sampling of adults age ≥70 (n=1581 eligible)	All screened participants (n=1460) with MMSE<24 (n=335) and random sample MMSE ≥ 24 (n=314)	Neurologist and psychologist administered CAMDEX.	Yes	Low
CSHA (Andrew et al. 2006)	Random sample all adults age≥65 clustered in 5 regions, over-sampling adults age≥75	Clinical examination of random subsample (n=2914) including all institutionalised adults and screen positive for cognitive impairment (3MS<78/100)	DSM-III-R applied at consensus conference based on neuropsychiatric evaluation.	Yes	Delirium only assigned if no underlying dementia
Period prevalence					
GERDA (Eriksson et al. 2011)	All women aged ≥90 years, 50% of those aged 85-89 years	All participants (n=503) examined with MMSE and OBS scale	DSM-IV applied based on study information, informant / carer interviews, medical records. (one month period)	No	Retrospective.
Vantaa 85+ (Rahkonen et al. 2001)	Recruitment of all adults resident in Vantaa age≥85 years (n=601 eligible)	All participants assessed with informant, with clinical, cognitive and functional examinations	History of delirium by retrospective interview of participant and informant with reference to medical case notes (three year period)	No	Retrospective, high attrition over three years due to death; survivor effect.

East Baltimore Mental Health Study; CSHA Canadian Study of Health and Ageing; GERDA Gerontological Regional Database
DIS Diagnostic Interview Schedule; SPE Standardised Psychiatric Examination;
CAMDEX Cambridge Mental Disorders in Elderly Examination
OBS Organic Brain Syndrome
MMSE Mini-Mental State Examination; 3MS Modified MMSE.

All studies reporting point-prevalence used a basic screening measure, with more detailed characterisation of screen-positive and a random subsample of screen-negative participants. The East Baltimore Survey (Folstein et al. 1991) used a stratified population sample of adults (including all households residents aged ≥65 years) screened with the NIMH Diagnostic Interview Schedule (DIS) and interviewed in more detail using the Standardised Psychiatric Examination (SPE) and a clinical assessment (blind to the previous DIS scores). As mentioned in Section 2.1.2.3, the SPE was an attempt to standardise the psychiatric assessment by using a 'probe and question' structure with a glossary of symptom definitions generating diagnostic categories that could be directly related to DSM-III (Wing et al. 1977) (Romanoski et al. 1988). An analysis of response rates among screen positive and negative persons was reported. Ultimately, only 6 cases of prevalent delirium were identified giving an age-specific prevalence of 10.9 (95% CI 0.0 to 22.5) per 1000 persons aged ≥55 years. It is not clear if any of these cases had co-existent dementia.

The Girona study used another validated interview schedule (Cambridge Mental Disorders of the Elderly Examination, CAMDEX), after screening with MMSE. 1460 individuals aged ≥70 years participated in this door-to-door study (92% of the eligible population according to municipal census records) (Vilalta-Franch et al. 2009). The standardised information gathered allows a diagnosis of delirium and/or dementia to be made. 14 cases of delirium were detected (prevalence = 9.6 (95% CI 4.4 to 14.9) per 1000 persons) 12 of whom also had dementia. The prevalence of delirium in persons with dementia was much higher: 79.5 (95% CI 35 to 126) per 1000 persons.

The Canadian Study of Health and Ageing (CSHA) screened a population aged ≥65 years with the modified Mini-Mental State Examination. DSM-III-R diagnoses were applied through consensus meetings following two independent neuropsychological evaluations (Andrew et al. 2006). Diagnoses of delirium and dementia were considered mutually exclusive. The 21 cases

identified represent a point-prevalence of 6.3 (95% CI 4.1 to 9.6) per 1000 persons. It is likely that this estimate is lower than the other studies because no persons were assigned a delirium superimposed on dementia category.

The eligible population for the GERDA study comprised all women aged ≥90 years and half those aged 85-89 years, of whom 81% were recruited (Eriksson et al. 2011). Participants (n=504) were examined in their usual place of residence using MMSE and delirium symptomatology was assessed using the Organic Brain Syndrome scale (Jensen et al. 1993), which combines neuropsychiatric symptoms with an observational scale and has been shown to perform well against other diagnostic algorithms such as the Confusion Assessment Method (Bjorkelund et al. 2006). Diagnoses pertaining to delirium in the previous month were ultimately decided by a geriatrician with access to all study data, informant and carer interviews and medical records, based on DSM-IV criteria. In this sample, the one-month period prevalence for delirium was 272 (95% CI 235 to 312) per 1000 persons. Delirium prevalence was strongly associated with age (85-89 years 19%; 90-94 years 24%; ≥95 39%) and dementia (OR 5.8 (95% CI 3.5 to 9.5) for clinically diagnosed Alzheimer's disease).

The estimates from the point-prevalence studies are all from enriched subsamples. Therefore, it is not possible to pool the estimates, even if using random-effects meta-analysis. However, there is a consistent finding that population prevalence of delirium is relatively low (even when including participants in care homes). The period prevalence estimates (30% and 20%) are closely associated with age.

2.2.3 Discussion

Overall, it is apparent that there are very few population-based studies that have assessed delirium prevalence. However, it is probable that point-prevalence of delirium in the community is low. In terms of the key epidemiological principles, these results are from unselected populations (by design) and case-ascertainment was broadly in accordance with a standardised approach to delirium diagnosis. In these descriptive prevalence studies, no attempt was made to link with outcome, so attrition (though not missing data) and residual confounding are less of an issue. As for depression, or examples from infectious disease epidemiology, transient syndromes are by nature difficult to capture in field surveys.

Table 2-3 details the risk of bias arising from the design. The Girona study was at lowest risk of bias because it used a door-to-door approach and achieved a high proportion of responses. Moreover, the enriched ascertainment subsample also included screen-negative participants. This allows for a reliable estimate of prevalence back-weighted to the base population. The East Baltimore study had a similar design, but was hampered by low proportion responding. Beyond basic comparisons of the demographic characteristics of responders versus non-responders, it is difficult to estimate the direction of bias in ascertainment. In CSHA, the consensus panel for ascertainment made delirium and dementia mutually exclusive categories, likely leading to significant under-ascertainment of delirium.

There were an insufficient number of studies to consider formal techniques such as meta-regression. However, age and proportion with dementia are likely to be independent predictors of delirium prevalence, even in population-based samples. Because CSHA is the largest study, and this did not include delirium in persons with a dementia diagnosis, the pooled prevalence is also likely to be an underestimate. In addition, it is known from doorstep reports that

intercurrent illness and therefore any associated delirium reduces response rates in epidemiological surveys, so the detected prevalence may be very low by design.

Importantly, these studies describe an approach to characterising a base population, enriching it with groups likely to eventually yield more incident delirium cases (older, persons with pre-existing cognitive impairment). The next steps would be to establish a system whereby acute changes in mental status can be identified (e.g. via general practitioners). Like in the OXVASC study (Section 2.1.1.1), this requires excellent links between hospital and community services. Such linkage has yet to be successfully exploited in delirium, but is crucial if the determinants and effects of delirium are to be most comprehensively investigated.

2.3 Systematic review: delirium and trajectories of cognitive decline

Question:

What cognitive outcomes are associated with delirium and/or acute illness in studies prospectively ascertaining pre-morbid (pre-delirium) cognitive function?

The aim of this section is to review the existing literature relevant to the epidemiology of delirium as it relates to dementia in community populations, addressing the prospective relationship between delirium and dementia in community settings. Section 1.1.2.3 summarised the evidence that delirium is associated with new dementia diagnoses following hospital admission, though also acknowledged that this is likely to be confounded by undiagnosed (pre-morbid) dementia.

This systematic review seeks to examine the relationship between delirium and subsequent cognitive impairment more broadly. This association is best addressed using studies with a specific design, namely those with prospective information on cognitive function prior to the

onset of delirium. In addition to delirium, the prospective follow-up of trajectories of cognitive decline due to acute illness and/or hospitalisation were also of interest.

2.3.1 Methods

The methods also followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al. 2000).

2.3.1.1 *Eligibility criteria*

All prospective studies reporting delirium and dementia were eligible for inclusion. More generally, studies reporting cognitive outcomes before and after an episode of delirium and/or acute illness or hospitalisation were considered. Studies were excluded if they were in children, or related solely to alcohol withdrawal states.

2.3.1.2 *Search strategy and data extraction*

A systematic search of Medline (from 1950) on Pubmed, Embase (from 1980) on embase.com and the Science Citation Index (from 1950) on Web of Science (all until 31st December 2012) was conducted. Conference abstracts indexed in the Science Citation Index were considered. Bibliographies of included articles and other reviews were screened. The second reader for this review was Alessandro Morandi, Ancelle della Carità Hospital, Cremona.

Comprehensive text word, Medical Subject Headings and Emtree terms were used to find relevant studies (search strategies in Appendix Section 10.2). Any estimates of association between delirium and cognitive outcomes (OR, RR, or other more sophisticated approaches, such as change-point modelling) were extracted, along with their standard errors, confounders adjusted for, and measures of attrition.

2.3.1.3 *Data analysis*

The diversity of designs, populations and analytic methods precluded anything other than a narrative synthesis of the data.

2.3.2 Results

The search identified 503 studies, 21 of which merited full text review.[6] Ultimately, six studies were included and their epidemiological characteristics are summarised in Table 2-4.

The Vantaa 85+ cohort study is a population-based investigation of dementia in persons aged ≥85 years resident in Vantaa, Finland. This cohort contributes to the EClipSE study, and further details of this are given in the section below (Section 3.4). Vantaa is the only population-based prospective study to have reported measures of delirium exposure in relation to dementia (Rahkonen et al. 2001). Here, participants were assessed for incident dementia three years after study entry. At follow-up participants and/or their proxy informants were asked about a history of delirium, and investigators had access to hospital records. There was a strong association with dementia (OR 5.3 (95% CI 2.0 to 14)). However, this analysis should be regarded as cross-sectional (albeit over a three year period) and so no prospective relationship can be determined. A more detailed examination of data from this cohort comprises a component of this PhD (Chapter 5).

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[6] This included an article published from this thesis (Davis, 2012), but not considered here.

Table 2-4 The epidemiological characteristics of studies of delirium / critical illness with cognitive outcomes.

	Population	Exposure	Outcome	Risk of bias
(Fong et al. 2009) (Gross et al. 2012)	Memory clinic patients	Retrospective diagnosis of delirium from case notes	Worsening on Blessed information-Memory-Concentration score	Only considered persons with prior cognitive impairment. 59% missing data (54% due to reports of hospitals outside area where delirium could be ascertained).
(Ehlenbach et al. 2010)	Members of Health Maintenance Organization, institutionalised adults excluded	Hospitalisations reported on insurance claims forms	Dementia (DSM-IV; consensus conference)	Not population-based. Not delirium specifically.
(Iwashyna et al. 2010)	'Nationally representative sample', but institutionalised adults excluded	Hospitalisations reported on insurance claims forms	Severe cognitive impairment on 35-scale	Possibly population-based. Not delirium specifically.
(Wilson et al. 2012a)	Urban population based on census	Hospitalisation based on Medicare claims	Rate of change in global cognitive test score	79% response rate for baseline screen. Analysis only conducted on 18% original baseline sample due to missing data (39% could not be linked, 21% died, 19% insufficient follow-up.
(Rahkonen et al. 2001)	Population-based sampling all residents age ≥85.	Participant and informant interview with access to medical records	Dementia (DSM-III-R; individual clinician)	Truly population-based sample. Dementia outcomes not standardised, delirium ascertainment retrospective. High attrition from death.

DSM Diagnostic and Statistical Manual of Mental Disorders

The only other study to specifically consider delirium showed an adverse effect on cognitive trajectories in a group of memory-clinic patients (Fong et al. 2009). In this study, delirium was identified through review of clinical notes, using a previously validated tool. In addition to the study population being restricted to a memory-clinic group, these results are limited by only considering change in a linear model before and after the first episode of delirium, and this may be an over-simplification. However, more complex analyses using random-effects models confirmed faster cognitive decline in a subset (n=263) with longer follow-up (median 3.2 years) (Gross et al. 2012).

A report from the Adult Changes in Thought (ACT) study found critical illness (without specifically considering delirium) was associated with incident dementia (adjusted HR 1.4 (95% CI 1.1 to 1.7)) (Ehlenbach et al. 2010). Similar findings were reported using a change-point model comparing pre- and post-hospitalisation trajectories of cognitive decline (Wilson et al. 2012a).

Consistent with this, participants being followed in the Health and Retirement Study who had an intercurrent episode of severe sepsis (n = 516) also had a higher risk of being subsequently diagnosed with severe cognitive impairment (OR 3.3 (1.5 to 7.3)) (Iwashyna et al. 2010).

2.3.3 Discussion

In the identified studies, delirium has been defined in disparate ways, ranging from direct ascertainment through standardised interview through to review of medical records, much related to pragmatic possibilities. The ideal approach would assess cases prospectively with the contemporaneous application of operationalised diagnostic criteria. An alternative involves a retrospective review of medical records. While this can be validated in terms of its diagnostic accuracy, it is likely to underestimate hypoactive forms of delirium, as well as those not presenting to hospital. Other studies have considered critical illness as a proxy for delirium (and vice versa). It is also worth noting a nested case-control analysis of dementia diagnoses in the General Practice Research Database showing that infectious episodes were associated with subsequent dementia (Dunn et al. 2005).

The sources of bias in these studies can be understood in respect of the four epidemiological principles outlined above. Only one assessed delirium in a population-based sample. HRS started off excluding persons in institutional care, though followed participants if they were subsequently admitted into a care home. The other cohorts had varying degrees of selection. Case-ascertainment was inferential in each study – retrospective or not directly recording

delirium at all. Attrition was partially addressed, but there was a substantial amount of missing data in most of the studies even from baseline. Potential confounding was accounted for to some extent in most of the analyses, and residual confounding discussed.

2.4   Core questions and statement of aims for thesis

This chapter has described some key principles for investigating epidemiological questions. A systematic review of the literature identified a small number of studies of the descriptive epidemiology of delirium in population-based cohorts. A second systematic review has also shown that delirium and/or acute hospitalisation has rarely been considered in cohort studies, but there is a suggestion that it may adversely affect trajectories of cognitive decline. These findings build on the issues raised in Chapter 1, namely that though delirium is common and serious, there is insufficient evidence to understand the temporal relationship between delirium and cognitive decline. Prospectively linking delirium with permanent decrements in cognitive function challenges the current construct of dementia because it suggests that dementia pathophysiology may be affected by processes outside the brain, e.g. peripheral infection. Whether this could occur through mechanisms already known to be pathological in dementia, such as tau phosphorylation or amyloid cleavage, or through entirely novel pathways is a major research question. Taken together, there is a need to leverage information from existing population-based cohort studies of dementia incidence to understand the epidemiological, cognitive, clinical and biological sequelae of delirium. This thesis attempts to provide such an understanding.

Aim: To assess the clinical impact of delirium on long-term cognitive outcomes in descriptive, analytical and biological terms.

Objective 1: Estimate the prevalence of delirium in the general population. This can be achieved by examining the reporting of delirium symptom clusters in population-based cohort studies employing a standardised psychiatric interview schedule.

Objective 2: Assess the association of delirium with cognitive outcomes. By using the delirium measure derived above, along with delirium exposures determined directly in any cohort studies, the prospective association with dementia and cognitive decline can be investigated.

Objective 3: Investigate how these associations relate to underlying dementia pathology. In the population studies with neuropathology specimens, the independent contributions of delirium and dementia pathology to cognitive decline can be modelled. This would allow assessment as to whether any association between delirium and cognitive decline could occur through Alzheimer, vascular or Lewy body pathology, or otherwise through distinct and novel pathways.

Objective 4: Develop novel methods for retrospectively ascertaining delirium. This could be achieved by using extracts from the clinical record of inpatients, where delirium had been concurrently ascertained by an experienced clinician at the bedside (reference standard). Key extracts could be assembled as a vignette, and a consensus expert panel could retrospectively determine a delirium diagnosis (index test).

3 Constituent cohort studies

The data for this thesis are primarily drawn from three cohort studies. This chapter provides a detailed description of these cohorts to give the full context for the findings presented in the following chapters (Chapters 4 to 7). This chapter also contains a specific section on how delirium was defined for this thesis in each study, that is, how delirium was operationalised as an exposure. Detailed neuropathology methods are reported in Appendix Section 10.4.

Vantaa 85+, CC75C, and MRC-CFAS are the three constituent cohorts of this thesis. There are two common features to the design of these cohorts: (i) population-based sampling; and (ii) a brain donation programme with standardised neuropathological assessment of autopsy material.

> **Chapter outline**
>
> - Vantaa 85+
> - Cambridge City over-75s Cohort
> - MRC-Cognitive Function and Ageing Study
> - Epidemiological CLinico-Pathological Studies in Europe Collaboration (EClipSE)

A systematic review conducted in 2005 identified six population-based studies of dementia incidence with neuropathological data (Zaccai et al. 2006). The studies included in this thesis represent half of the population studies ever conducted on the topic, and the entirety of data from European populations. Individual participant data from these three cohorts have been brought together in the Epidemiological Clinico-pathological Studies in Europe (EClipSE) harmonisation project (section 3.4). The provenance of the EClipSE project arose through the recognition that participant-level data could be combined for more powerful analyses, and in

addition to the systematic reviews presented in the previous Chapter, this dataset forms the basis of the primary analysis for this thesis.

The key features of the studies are summarised in Table 3-1. The following sections present the epidemiological details of each cohort. Similarities and differences between the cohorts are explored in section describing the EClipSE project (section 3.4).

Table 3-1 Summary of studies used in this thesis.

Study	Total sample	Site	Age sample	Donors
Vantaa 85+	553	Vantaa, Finland	≥85	290 (52%)
CC75C	2,166	Cambridge, UK	≥75	241 (11%)
CFAS	18,226	UK multicentre*	≥65	456 (3%)

Abbreviations: CFAS Cognitive Function and Ageing Study; CC75C Cambridge City over-75s Cohort.
* CFAS sampled from six geographical areas: four urban (Newcastle, Nottingham, Liverpool, Oxford) and two rural (Cambridgeshire, Gwynedd)

3.1 Vantaa 85+

The aim of the Vantaa 85+ study was to investigate the population health of the oldest-old by assessing burden of illness, functional abilities and service needs of all residents of the city of Vantaa, southern Finland.

3.1.1 Population, setting and study design

Vantaa is a city in southern Finland. All persons aged ≥85 years resident in the city were eligible, based on information from the Population Register Centre (Maistraattit). Participants and their informants were invited to attend baseline assessments by a study neurologist and nurse at the

local hospital, or examined in their own home or institution if necessary. 601 individuals were eligible, and 553 consented to participate in the study. Of these 48 persons not recruited, 11 were due to refusal to participate, 1 could not be contacted and 36 died between agreeing to participate and the first examination. Baseline assessment was in 1991, with follow-up examinations in 1994, 1996, 1999, 2001. Figure 3-1 shows the follow-up schedule and numbers examined at each wave.
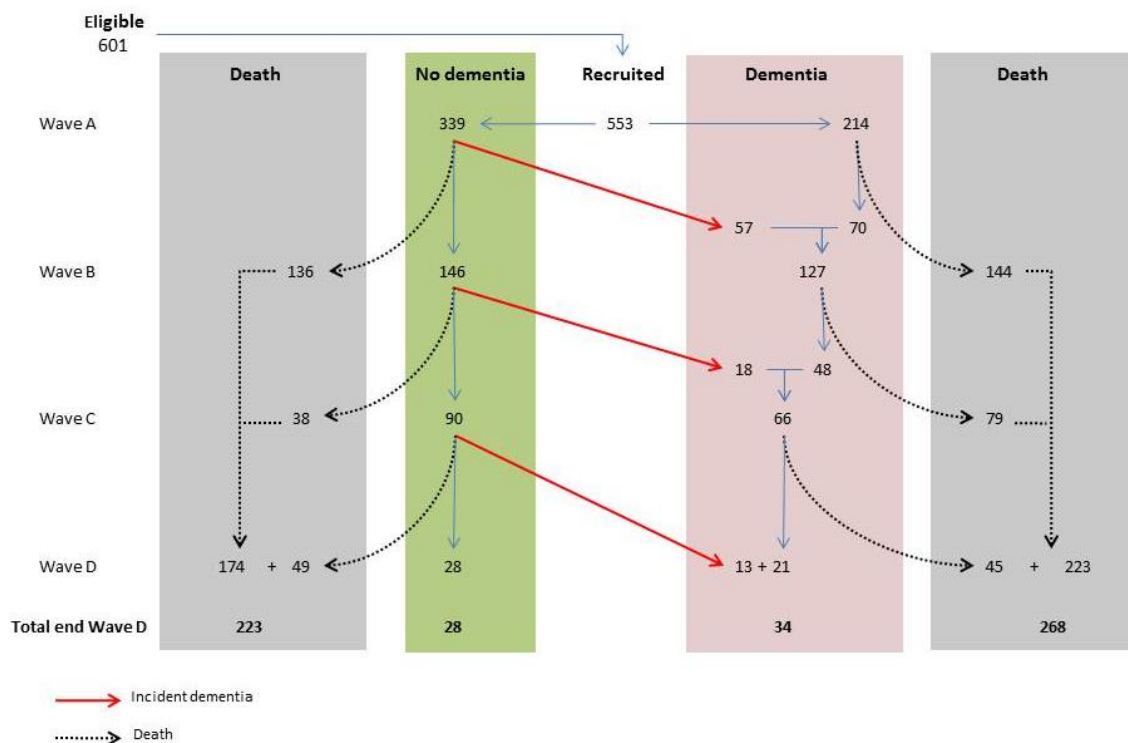
Figure 3-1 Vantaa 85+ cohort flow diagram. Wave A = 1991; Wave B = 1994; Wave C = 1996; Wave D = 1999; (Wave E = 2001, not shown).

3.1.2 Clinical assessments

The standard interview included socio-demographic questions, social networks and well-being. Questions on chronic illnesses and medication were corroborated by access to medical records and physical examination.

Cognition was assessed at every wave using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), the Short Portable Mental Status Questionnaire (Pfeiffer 1975), and the Clinical Dementia Rating Scale (Morris 1993). Depression was assessed using the Depression Status Inventory (Zung 1972). Functional abilities were measured with the Personal and Instrumental Activities of Daily Living scales (Katz et al. 1963; Lawton et al. 1969). Hospital, primary care and social work records were also used to help identify incident dementia in participants between last assessment and death.

3.1.3 Dementia assessments

Dementia diagnosis by DSM-III-R criteria (APA, (1987)) was agreed by two neurologists simultaneously examining each participant. Dementia subtypes were classified using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for Alzheimer's dementia (McKhann et al. 1984) and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences for vascular dementia (Roman et al. 1993).

3.1.4 Neuropathology and genetic assessments

Biological samples included autopsy and neuropathological examination in 290 (52%) of participants (described in more detail below) and bloods (of which 94% have been sequenced).

3.1.5 Impact of the study

Because the oldest-old are generally under-represented in dementia research (Schoenmaker et al. 2004), the descriptive findings alone from the cohort can be regarded as significant contributions to the literature. The key results of the study highlighted the difficulties of clinico-pathological correlations in dementia in unselected populations of the oldest-old (Polvikoski et al. 2001). It challenged the idea that medial temporal lobe atrophy on MRI could differentiate Alzheimer's

from other dementia subtypes (Barkhof et al. 2007). Apolipoprotein ε4 (ApoE) was associated with neocortical amyloid (Polvikoski et al. 1995), strongest in those with dementia (Myllykangas et al. 1999). In demonstrating this, Vantaa 85+ was the first to show that (ApoE) was biologically important in this age group.

In addition to the generalisability of an unselected sample, the main strengths of the study come from the very high participation and the integration of the study with health and social care information. Autopsy data in 52% of the sample is among the highest ever reported. The main weaknesses come from the high attrition early in the study (through death), and the 2-3 year follow-up schedule which might have under-estimated clinically important events.

3.2   CC75C

The Cambridge City over-75s Cohort (CC75C) is one of the largest and longest-running population-based studies of the oldest-old.

3.2.1   Population, setting and study design.

The sampling was designed to recruit persons aged ≥75 years from representative general practices in the city of Cambridge. Dementia prevalence was estimated from a population of 2610 (95% of those eligible) (O'Connor et al. 1989). The baseline cohort to the longitudinal incidence phases comprised slightly fewer participants (n= 2165) through the exclusion of one of the original GP practices because of differential recruitment. These have been followed-up over 2-4 year intervals. The flowchart in Figure 3-2 summarises the main stages to date.
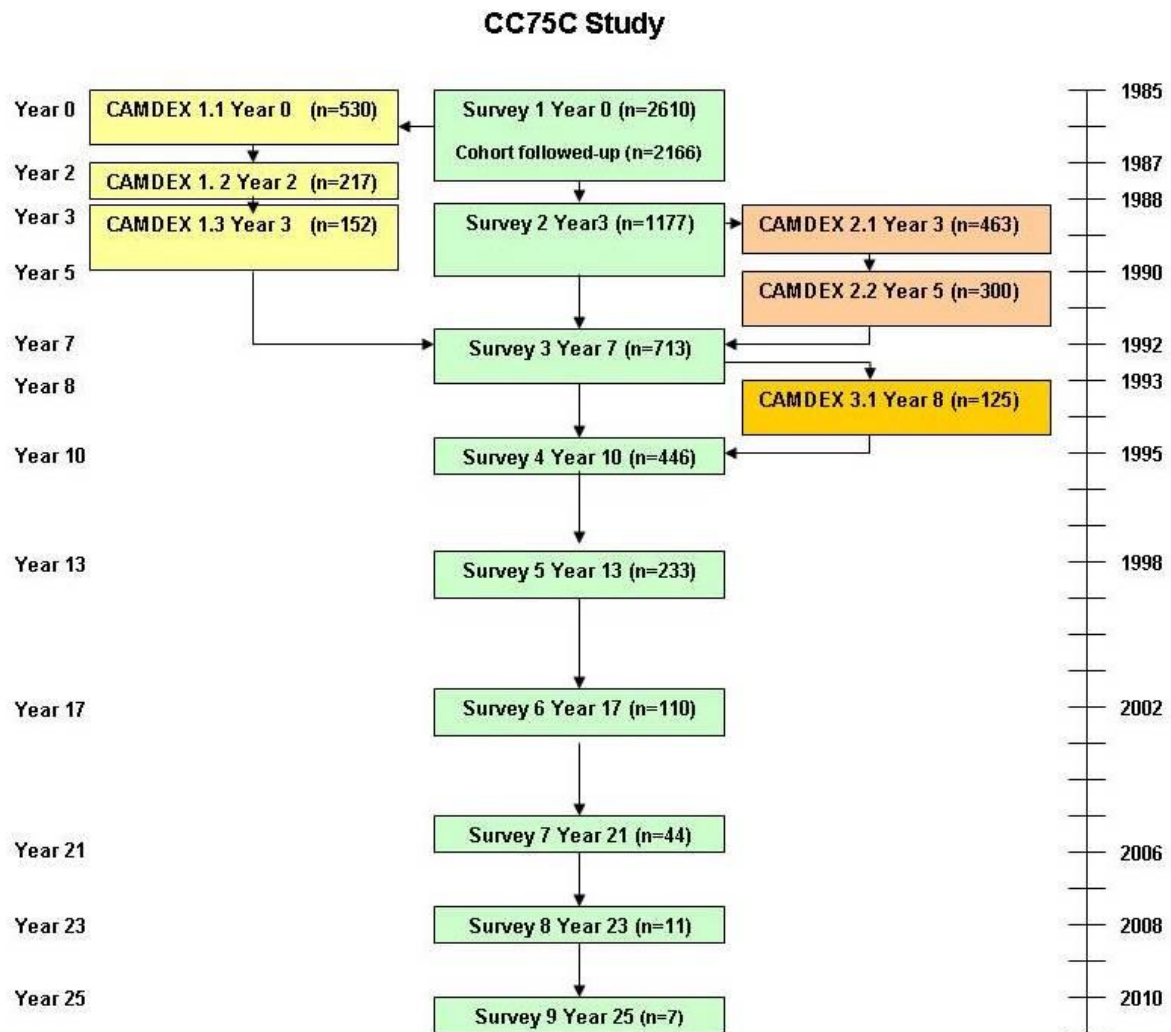
Figure 3-2 CC75C flow pathway (survey 10, 2012 not shown).

3.2.2 Clinical assessments

The structured schedule was administered by trained interviewers. Questions included those on socio-demographic, health-related questions (self-reported illness, healthcare use and medication) and functional capacity. Cognitive assessments were based on the Cambridge Cognitive Examination (CAMCOG) (Huppert et al. 1995) and included the MMSE.

Informant data were collected in subsequent surveys, especially valuable given the high attrition due to mortality. Proxy interviews on a subsample of participants (including brain donors) were

undertaken, known as the Retrospective Informant Interview (RInI). These structured interviews covered physical and cognitive functioning (based on the CAMDEX schedule), as well as information on health and social care needs during the final illness of the participant. These interviews are a major source of information on delirium exposure (see section 3.5).

3.2.3 Dementia ascertainment

After the baseline cognitive screening assessment, those who scored 23 or below in the MMSE, and a sample of those with MMSE scores 24 or 25, were assessed using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth et al. 1986), a structured schedule specifically designed to detect mild dementia. The CAMDEX includes a mental state examination, a psychiatric history, detailed cognitive testing, and an interview with a proxy informant.

In the brain donors, dementia status at death was established by consensus conferences based on DSM-IV, using all available information (but blinded to neuropathology data). Subtype and severity information was also decided by reference to DSM-IV criteria and were consistent with other diagnostic systems, e.g. CAMDEX and NINCDS-ADRDA (Brayne et al. 2009).

3.2.4 Neuropathology and genetic assessments

Bloods were collected from year 10 (survey 4). The brain donation programme was established after survey 2, and was the first population-based study to approach both those with and without dementia in this way. Brain tissue samples were available in 246 (11% of the follow-up cohort), with donors showing no significant differences from the rest of the cohorts in terms of dementia prevalence and age (Brayne et al. 2009).

3.2.5 Impact of the study

CC75C was one of the earliest studies of dementia epidemiology in UK. As well as estimates of prevalence and incidence in a representative sample of oldest-old, it has reported data on the impact of cognitive impairment on health services, long-term care, terminal decline and palliative care. CC75C also added to the understanding of continuous distributions of cognition and cognitive change in the general population. Consistent with the Vantaa 85+ findings, the neuropathology work showed that classical Alzheimer's pathology was demonstrable in persons without dementia. As with Vantaa 85+, the main limitations relate to attrition due to death or incomplete follow-up.

3.3 CFAS

The Medical Research Council-Cognitive Function and Ageing Study (MRC-CFAS, or simply CFAS) is one of the largest population-based studies of dementia epidemiology to date. The aims of the study have evolved since its inception, and cover a wide range of themes, including descriptive epidemiology, neuropathology, molecular epidemiology, and public health policy.

3.3.1 Population, setting and study design

CFAS is a multi-centre study. Four centres sampled from urban areas: Newcastle, Nottingham, Oxford and Liverpool), and two sampled from rural areas: Cambridgeshire and Gwynedd (Figure 3-3). Five sites are identical, and one (Liverpool) started before the others and until its third wave, had a different sampling and assessment schedule. The core design for case ascertainment in the five identical sites followed a two-stage framework. A screening examination was followed by a more detailed assessment of the 20% with the lowest cognitive scores and a random subsample from the remaining 80%. Individuals were followed as

frequently as possible (every 1-2 years in the brain donor sample) and at year 10, the entire cohort was re-examined (Figure 3-4). Liverpool started recruitment in 1989, the other sites from 1991.

Figure 3-3. Geographic sampling areas in CFAS (used with permission).

Family Health Service Authority (FHSA) lists were used as the sampling frame within a defined geographical area, and this specifically included persons resident in institutions. The eventual sample was stratified to have equal numbers aged 65 to 74 and aged 75 and over, resulting in around 2500 participants in each area (in Liverpool, around 5000 participants stratified by 5 year age band and sex).

The follow-up waves for the identical sites are shown in Figure 3-4. The first phase consisted of the baseline prevalence screen and detailed assessment, with higher risk participants followed-up more intensively for incident dementia.
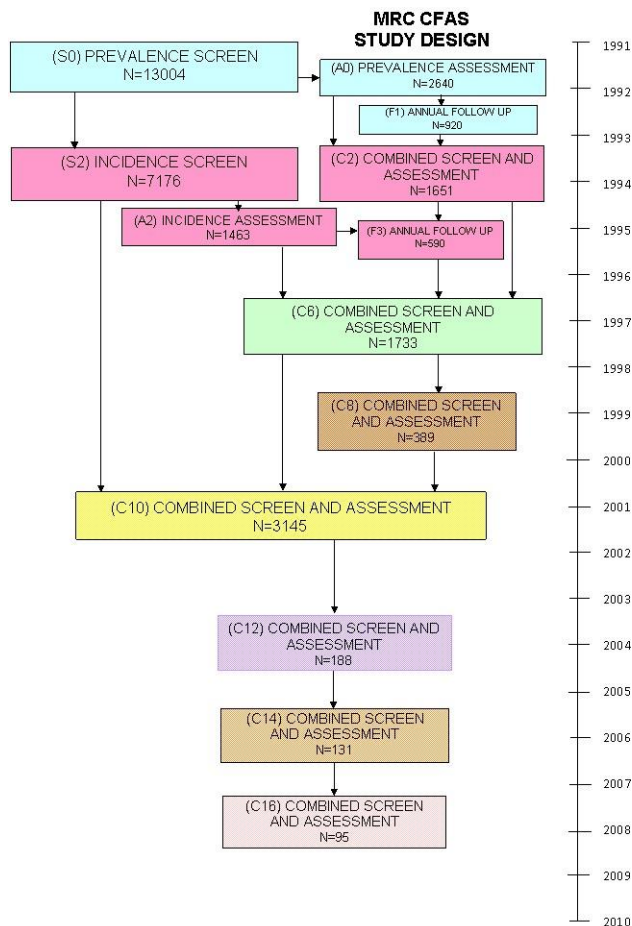
Figure 3-4. CFAS cohort flow pathway (Liverpool not shown). C12-C16 only for those agreeing to brain donation.

Detailed analyses of attrition and loss to follow-up have been undertaken. Individuals who refused were shown to have higher mortality than participants and the effect of this over varying timeframes has been investigated (Matthews et al. 2004; Matthews et al. 2006).

3.3.2   Clinical assessments

Interviews were carried out in participants' own home by trained lay interviewers using laptops and automated software. Interviewers had undergone a continuous process of training with regular meetings and rating sessions. The assessment interview was based on the Geriatric Mental State Examination (GMS) (Copeland et al. 1986), and as such is a structured schedule

amenable to administration by non-clinicians. The standardised GMS comprises measures that explore psychiatric symptoms of organicity, depression, anxiety and psychosis. In persons perceived as being too frail, ill or tired, a 'priority mode' could be activated to focus on a minimum dataset. All information was based on self-report, but informant proxies were also interviewed (in the History and Aetiology Schedule). Each interviewer undertook assessments blinded to the data acquired in previous phases. As for CC75C, proxy informants of brain donors were interviewed after a participant had died, using a similar RInI questionnaire. It has been shown that retrospective informant data correlates well with cognitive scores measured in late life (Marioni et al. 2011).

Throughout CFAS, the main cognitive measures were the mini-mental state examination, supplemented with additional questions from the CAMDEX schedule.

3.3.3   Dementia ascertainment

The structured interview schedule collected information on psychiatric symptoms necessary for categories to be assigned based on a computerised algorithm, thereby directly operationalising the diagnostic criteria. This approach has been validated against clinical diagnoses based on DSM-III-R (Kay et al. 1998).

3.3.4   Neuropathology and genetic assessments

All persons attending the year 6 assessment were approached for blood specimens. Apolipoprotein E effects on dementia risk (Keage et al. 2010) and neuropathology (Nicoll et al. 2011). The brain donation programme was a component of the study from the outset, oversampling dementia cases by design. Some participants intending to donate brain tissue are still being followed, but 456 brains (3%) comprise the most recently analysed dataset (Matthews et al. 2009; Savva et al. 2009).

3.3.5 Impact of the study

CFAS is the largest epidemiological study of its kind, covering the descriptive epidemiology of dementia (MRC CFAS 1998; Matthews et al. 2005), as well as intermediate cognitive states (Stephan et al. 2008). CFAS has also been instrumental in exploring the relationship between cognitive impairment and mortality, disability, carer burden and health care costs (Melzer et al. 1999; MRC CFAS 2000; Neale et al. 2001; Spiers et al. 2005; Comas-Herrera et al. 2007). The descriptive epidemiology of other AGECAT-derived psychiatric syndromes, e.g. depression, has been reported (McDougall et al. 2007; Kvaal et al. 2008). CFAS has also added to our understanding of neurocompensation and cognitive reserve, particularly with respect to education (Brayne et al. 2010). As detailed elsewhere in this thesis CFAS has made a sizeable contribution to the understanding of the neuropathological correlates of dementia in unselected populations.

3.4 EClipSE

The Epidemiological Clinico-pathological Studies in Europe (EClipSE) collaboration represents the data harmonisation of these three population-based cohort studies (Table 3-1) (EClipSE Collaboration 2009). The principal aim of the project is to increase the statistical power of the studies using individual patient data. This allows for more sophisticated investigations of clinico-pathological relationships, including interactions between variables. It is the largest collection of brains from unselected populations with 987 participants in the current dataset.

3.4.1 Similarities across the cohorts

All three cohorts are population-based studies, and each study started roughly the same time (within six years of each other). Though CFAS recruited persons aged 65 and older, persons over

75 were over-sampled, so, together, these cohorts are representative of the oldest-old from the era. Two studies are from the UK, and relied on similar population-registration systems and sampling techniques. CC75C and Vantaa 85+ targeted whole populations aged ≥75 and ≥85 respectively, with no sampling necessary. Each study was linked to national statistics services that allowed tracking of participant mortality.

3.4.2   Differences across the cohorts

There are some important differences between cohorts. Firstly, there may be differences that arise from cultural, linguistic or geographical reasons. The distribution of years of education differs markedly across cohorts. In Vantaa, the median years of education was 4, and 52% of participants had exactly this number of years, making it more difficult to account for the effects of education on clinical and pathological outcomes (Brayne et al. 2010).

The operationalisation of dementia was different in each study. Vantaa relied on two assessments by neurologists at each study visit, reaching agreement with respect to DSM-III-R. For brain donors, CC75C used a multidisciplinary consensus after participants had died, based on all available information including informant interview data, based on DSM-IV. CFAS used the AGECAT algorithm derived from DSM-III-R and for those without full interview data all available clinically relevant data blinded to neuropathology was used to determine dementia status at death (e.g. death certification, informant interviews). One other difference is that Vantaa participants were examined by a neurologist, so there is a greater level of clinical detail compared to self-reported conditions in the UK cohorts.

3.4.3   Representativeness of brains

The proportion of participants undergoing brain donation ranged from 3% for CFAS, 10% for CC75C, and 52% for Vantaa 85+. Whereas the opportunity for brain donation was routinely offered to Vantaa participants, the UK cohorts over-sampled for cognitive impairment as the

donation process was offered to the more intensively assessed groups (except Nottingham, where all participants were approached). Therefore, despite the proportion of brain donors CFAS being low, the sampling is such that the overall representativeness of the cohort was maintained. In Vantaa 85+, brain donors are similar to persons not donating for clinical parameters: age at death, sex, education, dementia status at death, duration of dementia. Other than a greater proportion of persons with cognitive impairment and dementia, CC75C and CFAS brain donors were otherwise representative of the rest of the cohort in terms of age at death.

3.4.4 Clinical data

Demographic data include date of birth, sex, marital status, years of education, social class, place of residence. Measures of social contact and religious participation were also available in each study. In addition, physical health, personal and instrumental activities of daily living, and psychiatric symptomatology are available.

The MMSE is the primary measure of cognition across all studies and interviews. Other neuropsychological data are available, more so in CC75C and CFAS, though these are not directly comparable to the other measures in Vantaa 85+. Substantial data from informant interviews are also available in the UK cohorts, and these constitute much of the information on delirium exposures (Section 3.5 and Chapter 0).

3.4.5 Neuropathological and genetic data

Each study assessed neuropathology in paraffin-embedded brain tissue, blind to clinical status. The median post-mortem interval was less than 24 hours, but with some variation across studies. CC75C and CFAS used the full Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (Mirra et al. 1991) along with Braak staging as a semi-quantitative measure of neurofibrillary tau. Vascular pathology was assessed in a variety of ways, including microvascular and large artery disease. Lewy bodies in the substantia nigra were assessed with haematoxylin and

eosin, but also included immunohistochemical staining against α-synuclein (or ubiquitin in some of the earlier CC75C specimens). Vantaa 85+ also reported neuronal loss in the substantia nigra as a marker of Lewy-body disease. CFAS and CC75C participants have a CERAD neuropathological classification of dementia subtype. ApoE genotype was available on 70% (n=680) of the sample. The neuropathological methods are detailed further in section 10.4 and in Chapter 5.

3.4.6   Comment

The EClipSE collaboration represents a unique dataset, with an opportunity to undertake analyses on clinic-pathological correlations in the largest collection of brains from unselected populations created to date. Other work in the field has tended to focus on selected populations (e.g. tertiary referral centres), though there may be several filters before arriving at a study sample. Though the characteristics of donors are comparable to non-donors, oversampling of cognitively impaired participants in CFAS led to an enriched sample in this respect. Nonetheless, the broad representativeness of the participants remains high. Previous work in each study contributing to EClipSE has offered significant advances to our understanding in the field – precisely because the findings are drawn from unselected samples.

The central aim of this thesis is to understand how delirium inter-relates with longitudinal trajectories of cognitive change, dementia and neuropathological status at death.

3.5   Delirium operationalisation

A core task for this thesis was gathering all possible sources of information on delirium, or possible delirium, from each of the cohort studies. No study prospectively identified incident delirium. Therefore detailed characterisation of delirium phenomenology, severity, duration and

aetiology was not possible in these population studies. Nonetheless, informant data and information from medical case notes provided indirect information about delirium and other changes in mental status in the context of acute illness such that a variable corresponding to likely delirium exposure could be derived by integrating information from all these sources. Table 3-2 summarises the available sources.

Table 3-2. Summary of data sources for derivation of delirium exposure.

Study	Sources	In whom	When
Vantaa 85+	At every interview, history of delirium asked on direct questioning to participant and informant, with reference to medical records and DSM-III-R checklist.	Every participant	At baseline and in every subsequent interview (Years 0, 3, 5, 8, 10)
CC75C	Delirium part of CAMDEX	MCI subset	Years 0, 2, 3, 5
	CAMDEX-informant at RInI	Brain donors	Shortly after death
CFAS	GMS questions	Every participant	Throughout
	HAS	20% subset	Throughout
	RInI	Brain donors	Shortly after death

CAMDEX Cambridge Mental Disorders of the Elderly Examination
RInI Retrospective Informant Interview
GMS Geriatric Mental State, HAS History and Aetiology Schedule

In Vantaa 85+, ascertaining history delirium was an explicit component of the study from the outset (Rahkonen et al. 2001). History of delirium was specifically asked about at baseline and at each follow-up. Participants and their informants were asked about symptoms of delirium according to the DSM-III-R checklist. Participant recall was corroborated with records from primary and secondary care, which were available at the time of interview. A study diagnosis of delirium history prior to recruitment, or at subsequent waves, was determined if the examining clinicians deemed that the evidence overall supported a diagnosis of delirium history.

The relevant questions from the interview schedules in CC75C and CFAS are given in Appendix Section 10.3. Delirium symptoms were a component of the CAMDEX schedule used in CC75C.

This was applied to a random subset of participants with MMSE scores 24 or 25 during the first five waves. An adaptation of the CAMDEX schedule formed part of the retrospective informant interview (RInI) and these questions were concerned with symptoms observed in the time since last study assessment and death, including the final illness.

In CFAS, the History and Aetiology Schedule (HAS) was an informant questionnaire applied to a subset of participants at each prevalence and incidence screen and assessment. In addition, questions from the GMS on attention and clouding of consciousness were used to infer delirium status. As with CC75C, information from the RInIs was used to assess delirium status in the last phase of life. These interviews have been vital sources in the work on terminal cognitive decline.

3.6   Summary and orientation to subsequent chapters

This chapter has described the cohorts from which the analyses in this thesis have been based. Chapter 4 details how these component questions were operationalised to construct a delirium diagnosis in CFAS that could be validated against mortality and dementia risk. Chapter 5 shows how these findings were replicated in Vantaa 85+, with further analysis of the impact of delirium on trajectories of cognitive decline. The neuropathological basis of this relationship is explored using 987 brains from the EClipSE (Chapter 6). Chapter 7 describes the validation of a chart-based method for deriving a retrospective diagnosis for delirium. This gives new possibilities for this technique to furnish existing and on-going cohort studies with a measure of delirium.

4 Descriptive epidemiology of delirium in CFAS

4.1 Summary

In the general population, the epidemiological relationships between delirium and adverse outcomes are not well defined. The aims of this chapter cover: (1) construction of an algorithm for the diagnosis of delirium using the Geriatric Mental State (GMS) examination; (2) testing the criterion validity of this algorithm against mortality and dementia risk; (3) reporting the age-specific prevalence of delirium as determined by this algorithm.

Participant and informant data in a randomly weighted subsample of the MRC Cognitive Function and Ageing Study were taken from a standardised assessment battery. The algorithmic definition of delirium was based on the DSM-IV classification. Outcomes were: proportional hazard ratios for death; odds ratios of dementia at 2-year follow-up.

Data from 2197 individuals, representative of a population of 13004, were used (median age 77 years, 64% women). Delirium was associated with a new dementia diagnosis at 2 years (OR 8.82, 95% CI 2.76 to 28.2) and death (HR 1.28, 95% CI 1.03 to 1.60), even after adjustment for acute illness severity. Similar associations were seen for subsyndromal delirium. Age-specific prevalence increased with age from 1.8% in the 65-69 year age group to 13.5% in the ≥90 age group (p<0.01 for trend). For subsyndromal delirium, age-specific period prevalence ranged from 8.2% (65-69 years) to 40.3% (≥90 years).

These results demonstrate the possibility of constructing an algorithmic diagnosis for delirium using data from the GMS schedule, with criterion validity for mortality and dementia risk. These are the first population-based analyses able to account prospectively for both illness severity and a previous study-diagnosis of dementia.

4.2 Introduction

Delirium is a serious neuropsychiatric syndrome presenting with inattention and global changes in cognition (MacLullich et al. 2011). Delirium arises as a consequence of a neurological or systemic illness. It is well-recognised that there is an inverse relationship between predisposing (ageing, cognitive impairment) and precipitating (illness severity) factors (O'Hanlon et al. 2013). Delirium is therefore a sensitive marker of acute illness in older people. This association with acute illness has resulted in the vast majority of delirium studies being undertaken in hospital cohorts (Khan et al. 2012). However, this introduces selection biases as not all persons with delirium may reach medical attention and comparisons to pre-morbid cognitive functions are difficult.

In hospital samples, a major concern is that delirium contributes to persistent cognitive deficits, independently of predisposing and precipitating factors (Witlox et al. 2010). This has also been considered for subsyndromal delirium, where individuals have one or more of the diagnostic features of delirium (Cole et al. 2003a). Indeed, any examination of the utility of a delirium definition should incorporate criterion validity tests for mortality and future dementia. In prospective community cohort studies, adverse cognitive outcomes have been associated with hospitalisation *per se* (Ehlenbach et al. 2010; Iwashyna et al. 2010; Wilson et al. 2012a), though none has been able to specify if delirium is a key determinant (Section 2.3).

Even in the older population, the point-prevalence of delirium in the community is likely to be low, though this understanding is based on a systematic review identifying only three prevalence estimates in population samples (Section 2.2) (Davis 2013). Furthermore, epidemiological studies may under-estimate acute illness and/or prevalent delirium as people who are unwell are less likely to be interviewed. However, the period-prevalence is higher and the same systematic review identified the Gerontological Regional Database (GERDA) study reporting 27% of persons aged 85 and older in the general population with delirium in the previous month (Eriksson et al. 2011).

This suggests that whole population samples could efficiently investigate delirium if stratified subsamples at higher risk for cognitive impairment are more intensively studied.

Delirium is clinically defined by application of a psychiatric reference standard such as the DSM, where the core features are altered consciousness, cognitive and/or perceptual disturbance, acute and fluctuating change, in relation to a general medical condition (Section 1.3). Based on this, there is an opportunity to construct an algorithmic diagnosis for delirium in population-based cohort studies collecting psychiatric symptoms. Such an approach is well-established in dementia, but yet to be systematically applied in delirium, and particularly not in population studies. Accordingly, using data from the population-based Medical Research Council Cognitive Function and Ageing Study (CFAS) the aims here are to: (1) construct an algorithm for the diagnosis of delirium in population-based studies using the Geriatric Mental State (GMS) examination based on clinical principles; (2) test the criterion validity of this algorithm against mortality and dementia risk; (3) report the age-specific prevalence of delirium as determined by this algorithm.

4.3 Methods

4.3.1 Population

Data from the MRC Cognitive Function and Ageing Study (CFAS) were used. The principal methods for CFAS have previously been presented in detail in Section 3.3. In brief, CFAS was a multi-centre study, with sampling from four urban (Newcastle, Nottingham, Oxford and Liverpool), and two rural areas (Cambridgeshire and Gwynedd) in the UK. The present report only concerns the five identical sites (excluding Liverpool). Family Health Service Authority (FHSA) lists were used as the sampling frame within a defined geographical area, and this specifically included people resident in institutions. Figure 4-1 shows the two stage sampling

process for case ascertainment. A screening examination was started in 1991 (S0, n=13004). Then, a stratified sample consisted of approximately 20% selected depending on centre, age (equal numbers aged 65–74 and ≥75), and cognitive ability (weighted toward the more cognitively frail, based on the screening assessment), and a random subsample from the remaining 80% (A0, n=2640). Interviews of participant informants were also undertaken (H0, n=2197). Participants were followed at two years, with further subsets thereafter, including a full sweep at 6 and 10 years. The number of participants at baseline and at the first two-year follow-up is shown in Figure 4-1. Mortality outcomes were notified through reports linked to the Office of National Statistics.
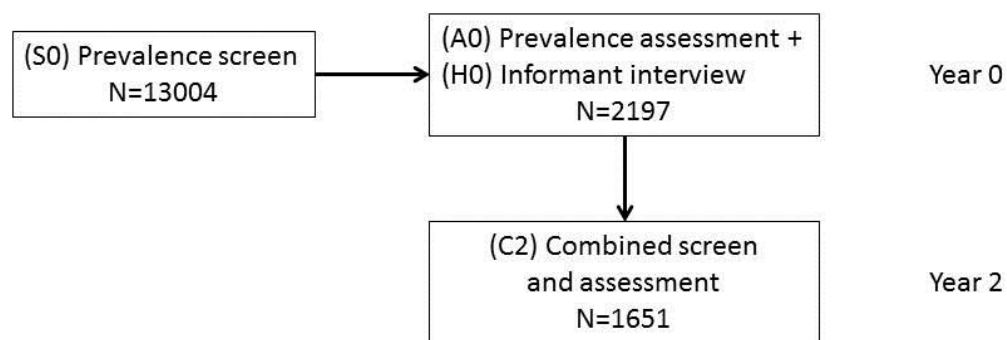
Figure 4-1. Assessment and follow-up schedule for the first two years of CFAS.

4.3.2   Interviews

Interviews were carried out in participants' own home (including care homes) by trained interviewers. At screening, information on socio-demographic, physical and behavioural status was collected in addition to health (including self-reported chronic conditions) and cognitive function, assessed using the MMSE. The assessment interview was based on the GMS (Copeland et al. 1986), and as such is a structured schedule amenable to administration by trained non-clinicians.

The GMS comprises measures exploring psychiatric symptoms of organicity, depression, anxiety and psychosis, with ratings for each derived using the AGECAT algorithm. The study diagnosis of dementia was based on the GMS B3 AGECAT algorithmic differential diagnosis, where the dementia component is organicity at case level O3 and above. This approach has been validated against clinical diagnoses based on DSM-III-R (Kay et al. 1998). All information was based on self-report and cognitive testing using the CAMDEX. Informant proxies were also interviewed in a standardised manner using a set of questions complementary to the GMS known as the History and Aetiology Schedule (HAS). Informants were asked questions exploring psychiatric symptom clusters occurring in 'recent weeks and months'. Each interviewer for C2 undertook assessments blinded to data acquired in the baseline phase (S0/A0/H0).

Questions from A0 and H0 (Figure 4-1) pertaining to delirium symptoms are shown in Table 4-1. These were used to define an algorithm for a study definition of delirium based on DSM-IV, where participants were required to demonstrate all three of: (i) acute change; (ii) fluctuation); (iii) inattention and/or drowsiness (Box 4-1). Subsyndromal delirium was defined as having at least one of these features. In addition, interviewers were asked to judge if responses were affected by their subjective rating of any acute illness in the participants (categorised as: none, mild, moderate, or severe).

Table 4-1. The prevalence of delirium symptom clusters at baseline.

Symptom	Interview question (yes / no)	N (2197)	%
Acute change	Has there been sudden worsening in mental confusion in recent weeks or months, which has continued to the present time? (informant)	199	9.1%
Fluctuation	Are there episodes lasting days or weeks when his/her thinking seems quite clear and then becomes muddled? Are there long periods during the day when s/he is lucid and not confused (that is, knows where s/he is and knows what s/he is doing and saying)? Does s/he get confused at night, wander about or talk nonsense? Or at any other time? What about during the day time?	264	12.0%
Inattention	Impaired ability to focus sustain and shift attention	230	8.7%*
Drowsiness	Disturbance of consciousness, that is either being sleepy, or awake but unaware of their surroundings Judged delirium Is the subject drowsy now?	142	6.5%
Delirium judgment	Could a physical illness (not drugs or alcohol intoxication) be sufficient explanation for the subject's mental or psychiatric symptoms (e.g. delirious due to acute infection)?	34	1.6%

*Question comes from prevalence assessment A0, denominator 2640, all other questions from History and Aetiology Schedule

Box 4-1. Delirium algorithm

Delirium	= (Acute change) + (Fluctuation) + (Inattention and/or drowsiness)
	OR
	= Judgment: a physical illness … be sufficient explanation for the subject's mental or psychiatric symptoms (e.g. delirious due to acute infection)

4.3.3   Statistical analyses

Stata 12.1 (StataCorp) was used for all analyses. The criterion validity of the delirium algorithm was tested in two ways: (i) hazard for mortality and (ii) odds of a new diagnosis of dementia at two year follow-up. The association between delirium and mortality was evaluated using Cox proportional hazards models, adjusted by age, sex and prevalent dementia. The association between delirium and dementia was assessed using logistic regression where the outcome was new dementia at two-

year follow-up (C2, Figure 4-1) in the population known to be dementia-free at baseline, adjusted by age and sex (A0, Figure 4-1). Each delirium symptom was tested for both outcomes, as well as the overall algorithmic diagnosis. Testing the criterion validity of the algorithmic diagnosis also adjusted for interviewers' rating of acute illness severity. Post-estimation tests included Hosmer-Lemershow goodness-of-fit and Schoenfeld residuals for logistic and Cox models respectively. The exact procedures for conducting regression analyses are described in the box below.

Box 4-2. Statistical procedures for multiple regression.

1. Decide outcome of interest (dependent variable)

    - The nature of the outcome and the structure of the data determine the type of regression analysis, e.g.

        - Binary = logistic regression

        - Rate ratios = Poisson regression

        - Time-to-event = e.g. proportional hazards regression

        - Continuous = linear regression

2. Selection of independent variables

    - Should be clinically justified, usually include age and sex

    - Over-adjustment is clinically and statistically possible. A maximum number of covariates is based on the sample size, usually considered in a ratio of 1:10.

3. Inspection of distributions

    - Continuous variables: Gaussian? Or is transformation necessary? Unusual distributions might merit categorisation, but this results in loss of power and cut points should be clinically meaningful

    - Categorical variables: ordinal variables modelled as individual parameters, rather than as one quantity unless the grades are statistically and clinically meaningful.

4. Estimate model

    - Each independent variable on outcome

    - correlations between each pair of covariates, considering clinical aspects each time

    - No automated variable selection (e.g. forward or backward stepwise approaches)

    - Final model based on parsimony and likelihood ratio testing

5. Post-estimation testing (exact methods vary with regression technique)

    - Inspection of residuals

    - Formal tests, e.g. goodness-of-fit or Schoenfeld residuals

4.4 Results

The subsample selected for this analysis included 2197 individuals assessed by both the GMS (participant) and HAS (informant) schedules at the assessment interview (A0). Median age was 77 (interquartile range 71-84), and 1403 (64%) were women. In this weighted subsample of the whole baseline cohort, 511 (23%) had prevalent dementia. Table 4-1 lists the delirium symptom clusters and questions used to explore these, along with the prevalence of individual symptoms. Table 4-2 gives the raw numbers for delirium in relation to prevalent and incident dementia and death over the two year period.

Table 4-3 shows the results of the Cox proportional hazards survival analyses, adjusted by age, sex and prevalent dementia. In this weighted subsample, each delirium symptom was independently associated with higher mortality. This was also the case for the algorithmic diagnosis, even after adjustment for acute illness severity (HR 1.28, 95% CI 1.03 to 1.60). A similar risk for subsyndromal delirium was apparent (HR 1.41, 95% CI 1.23 to 1.62).

Table 4-2. Cases of delirium and dementia, along with outcomes at 2 years.

	No delirium (n=2075)			Delirium (n=122)		
	cases	denominator	%	cases	denominator	%
Dementia at baseline	425	2065	*21*	86	119	*72*
Death before 2 years	334	2065	*16*	53	119	*45*
Incident dementia at 2 year follow-up	102	1129	*9*	9	20	*45*

Groups described here are from the assessed population, i.e. 20% most cognitively impaired at screen, plus random sample of remainder.
Delirium defined through algorithm
Dementia diagnoses from AGECAT.

Table 4-3. Survival models for delirium

	N	HR	LCI	UCI	P value
Delirium symptom clusters					
Inattention	2637	1.36	1.16	1.58	<0.01
Acute change	2184	1.57	1.33	1.85	<0.01
Fluctuation	2184	1.40	1.21	1.62	<0.01
Drowsiness	2184	1.31	1.08	1.57	<0.01
Judged delirium*	2184	1.92	1.35	2.74	<0.01
Algorithm Delirium: final model	2159				
Delirium		1.28	1.03	1.60	0.03
Dementia		1.83	1.63	2.06	<0.01
Age (per year)		1.08	1.08	1.09	<0.01
Sex (female vs male)		0.68	0.61	0.75	<0.01
Illness severity					
None		(Ref)			
Mild		1.47	1.15	1.88	<0.01
Moderate		1.52	1.10	2.12	<0.01
Severe		3.14	2.23	4.42	<0.01
Subsyndromal delirium: final model	2159				
Subsyndromal delirium		1.41	1.23	1.62	<0.01
Dementia		1.62	1.42	1.85	<0.01
Age (per year)		1.08	1.07	1.09	<0.01
Sex (female vs male)		0.67	0.61	0.75	<0.01
Illness severity					
None		(Ref)			
Mild		1.32	1.03	1.70	0.03
Moderate		1.50	1.10	2.06	0.01
Severe		2.94	2.10	4.12	<0.01

HR hazard ratio, LCI UCI 95% lower and upper confidence intervals respectively

This table shows Cox proportional hazard models for death.

The upper part of the table shows individual symptom clusters, and their association with mortality (adjusted for age, sex, baseline dementia and illness severity).

* 'Judged delirium' refers to the overall impression of the interviewer that a participant had delirium.

The middle part describes the full model for full syndromal delirium and the same adjusted covariates

The middle part describes the full model for subsyndromal delirium and the same adjusted covariates

Table 4-4 gives the results of the logistic regression analyses assessing the odds of a dementia diagnosis at two year follow-up, adjusted by age and sex. In this weighted subsample, all delirium symptoms were associated with odds ratios greater than 1.0, but this was only statistically significant for acute change, fluctuation and drowsiness. The algorithmic diagnosis was significantly associated with a two year dementia diagnosis (OR 8.82, 95% CI 2.76 to 28.2). The estimate for subsyndromal delirium was half that of full syndromal delirium (OR 4.31, 95% CI 2.41 to 7.73).

Table 4-4. Logistic models for 2 year dementia

	N	OR	LCI	UCI	P value
Delirium symptom clusters					
Inattention	1347	1.90	0.77	4.69	0.16
Acute change	1149	7.63	3.47	16.75	<0.01
Fluctuation	1347	6.84	3.67	12.77	<0.01
Drowsiness	1347	4.83	2.50	9.35	<0.01
Judged delirium	1149	4.44	0.78	25.26	0.09
Algorithmic Delirium: final model	1140				
Delirium		8.82	2.76	28.2	<0.01
Age (per year)		1.11	1.08	1.14	<0.01
Sex (female vs male)		0.96	0.61	1.50	0.85
Illness severity					
None		(Ref)			
Mild		1.66	0.57	4.79	0.35
Moderate		1.41	0.31	6.37	0.66
Severe		(omitted)			
Subsyndromal delirium: final model	1140				
Subsyndromal delirium		4.31	2.41	7.73	<0.01
Age (per year)		1.10	1.07	1.14	<0.01
Sex (female vs male)		0.94	0.60	1.47	0.78
Illness severity					
None		(Ref)			
Mild		1.02	0.35	2.95	0.98
Moderate		1.54	0.41	5.77	0.52
Severe		(omitted)			

OR odds ratio, LCI UCI 95% lower and upper confidence intervals respectively

This table shows logistic regression models for dementia at two year follow-up.

The upper part of the table shows individual symptom clusters, and their association with dementia (adjusted for age, sex, baseline dementia and illness severity).

* 'Judged delirium' refers to the overall impression of the interviewer that a participant had delirium.

The middle part describes the full model for full syndromal delirium and the same adjusted covariates

The middle part describes the full model for subsyndromal delirium and the same adjusted covariates

The age-specific period prevalence of delirium is given in Table 4-5 and Figure 4-2. The overall

period prevalence in this enriched cognitive impairment subsample is estimated at 5.6% (95% CI

4.6 to 6.5). Age-specific prevalence increased with age from 1.8% in the 65-69 year age group to 13.5% in the ≥90 age group (p<0.01 for trend). For subsyndromal delirium, age-specific period prevalence ranged from 8.2% (65-69 years) to 40.3% (≥90 years). In persons with prevalent dementia, 16.8% (95% CI 13.6 to 20.1%) had superimposed delirium.

Table 4-5. Age-specific period prevalence of algorithmic delirium and subsyndromal delirium.

Age (years)	N	Delirium Prevalence (%)	95% CI	N	Subsyndromal delirium Prevalence (%)	95% CI
65-69	8 / 453	1.8	0.6 – 3.0	45/549	8.2	5.9 – 10.5
70-74	20 / 491	4.1	2.3 – 5.8	69/602	11.5	8.9 – 14.0
75-89	19 / 399	4.8	2.7 – 6.9	75/472	15.9	12.6 – 19.2
80-84	31 / 418	7.4	4.9 – 9.9	143/517	27.7	23.8 – 31.5
85-89	23 / 280	8.2	5.0 – 11.4	113/334	33.8	28.7 – 38.9
≥90	21 / 156	13.5	8.1 – 18.8	71/176	40.3	33.1 – 47.6
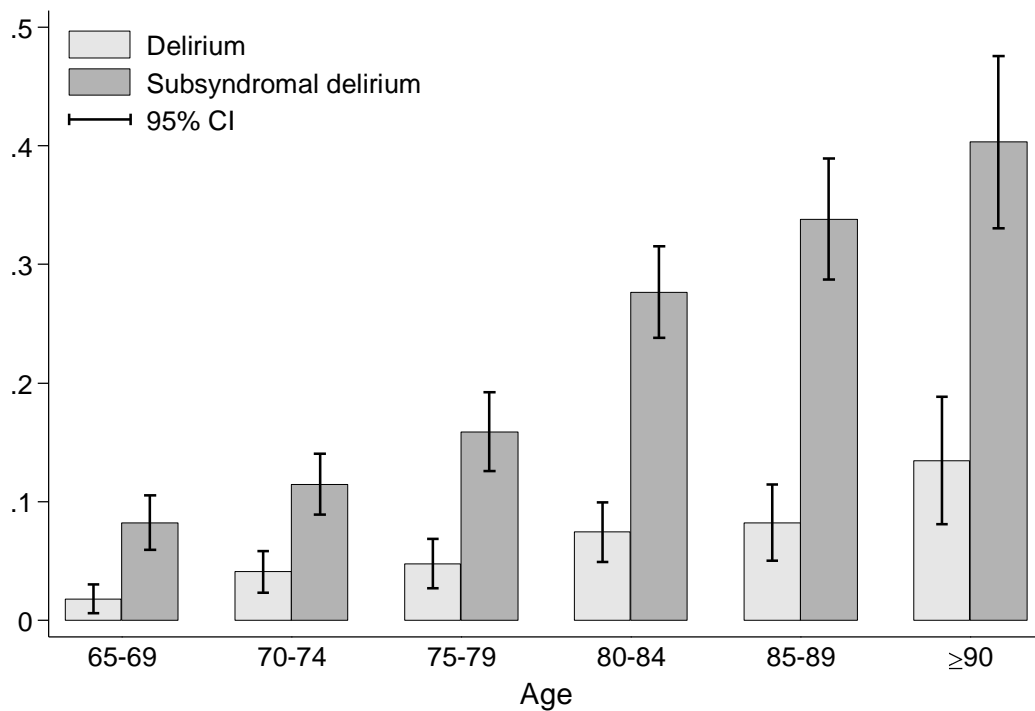
Figure 4-2. Prevalence of delirium and subsyndromal delirium, by age group.

4.5 Discussion

These results demonstrate the possibility of constructing an algorithmic diagnosis for delirium within a population-based framework using data from the GMS schedule including self and informant reported responses. This algorithm has criterion validity for mortality and dementia risk. These are the first population-based analyses able to account for both illness severity and prior prevalent dementia, suggesting that delirium has a deleterious effect on mortality and dementia risk beyond that expected from precipitating and predisposing factors alone. These findings also highlight the importance of age in the prevalence of delirium with the highest prevalence in the oldest-old group (i.e., ≥90 years).

The strengths of this study derive from its large population-based sample size and availability of serial cognitive assessments in relation to incident dementia. The major limitation is that the algorithm was not validated with concurrent clinical diagnosis. Furthermore, the period over which informants were asked to comment on delirium symptoms was not strictly defined ('in recent weeks and months') and may be overstated due to recall bias. The lack of assessments by clinicians also limits the precision of the data. Though the CFAS sample was population-representative in 1991, the age-specific prevalence of dementia is lower in 2011 (Matthews et al. 2013) and so secular trends may constrain the accuracy of current delirium prevalence estimates.

The estimated age-specific prevalence is lower than the only other estimate from GERDA, even though diagnoses included information from community medical records (Eriksson et al. 2011). Previously, the only population-based cohort to have assessed a delirium measure in relation to adverse outcomes is the Vantaa 85+ study (Rahkonen et al. 2001; Davis et al. 2012), described below in Chapter 5. In Vantaa 85+, delirium history was assessed at each interview by a neurologist with access to an informant and medical records, amounting to an estimate of period prevalence for the intervening 2-3 years between waves. The present analysis is much larger

(CFAS=2197representative of 13004 individuals, versus Vantaa=553). Though medical records were not available here, the advantage in CFAS is the possibility of accounting for illness severity, even though this assessment was subjective. The point estimates for mortality (CFAS HR 1.55 (when unadjusted by illness severity) versus Vantaa HR 1.61) and two-year dementia risk (CFAS OR 8.82 versus Vantaa OR 8.65) are effectively the same. Though delirium diagnoses were derived through different approaches, this suggests the core features of inattention, altered arousal and acute fluctuations in cognitive function represent an adverse state for future outcomes regardless of the exact methods for operationalising the syndrome.

In conclusion, these data add to the small literature on the population-based epidemiology of delirium. That delirium appears to be associated with increased dementia strengthens the argument that interventions for delirium may have an impact on the burden of cognitive impairment. Nonetheless, the core elements of the delirium-dementia relationship still require further exploration, particularly in the general population (Brayne et al. 2012). At the least, these findings indicate that it is possible to identify population samples with delirium and subsyndromal delirium at higher risk for dementia.

5 Clinical impact of delirium in Vantaa 85+

5.1 Summary

Recent studies suggest that delirium is associated with risk of dementia, and also acceleration of decline in existing dementia. However, prior studies may have been confounded by incomplete ascertainment of cognitive status at baseline. Here a true population sample was used to determine if delirium is a risk factor for incident dementia and cognitive decline. The effect of delirium was also examined at the pathological level by determining associations between dementia and neuropathological markers of dementia in patients with and without a history of delirium.

The Vantaa 85+ study examined 553 individuals (92% of those eligible) aged ≥85 years at baseline, 3, 5, 8 and 10 years. Brain autopsy was performed in 52%. Fixed and random-effects regression models were used to assess associations between (1) delirium and incident dementia and (2) decline in Mini-Mental State Examination scores in the whole group. The relationship between dementia and common neuropathological markers (Alzheimer-type, infarcts, Lewy-bodies) was modelled, stratified by history of delirium.

Delirium increased the risk of incident dementia (odds ratio 8.7, 95% confidence interval 2.1 to 35). Delirium was also associated with worsening dementia severity (odds ratio 3.1, 95% confidence interval 1.5 to 6.3) as well as deterioration in global function score (odds ratio 2.8, 95% CI 1.4 to 5.5). In the whole study population, delirium was associated with loss of one more Mini-Mental State Examination point per year (95% confidence interval 0.11 to 1.89) than those with no history of delirium.

In persons with dementia and no history of delirium (N=232), all pathologies were significantly associated with dementia. However, in individuals with delirium and dementia (N=58), no

relationship between dementia and these markers was found. For example, higher Braak stage was associated with dementia but no delirium (odds ratio 2.0, 95% confidence interval 1.1 to 3.5, p = 0.02), but in those with a history of delirium, there was no significant relationship (odds ratio 1.2 (95% confidence interval 0.2 to 6.7, p=0.85). This trend for ORs to be closer to unity in the delirium and dementia group was observed for neuritic amyloid, apolipoprotein ε status, presence of infarcts, α-synucleinopathy, and neuronal loss in substantia nigra.

These findings are the first to demonstrate in a true population study that delirium is a strong risk factor for incident dementia and cognitive decline in the oldest-old. However, in this study, the relationship did not appear to be mediated by classical neuropathologies associated with dementia.

5.2 Introduction

Delirium is a severe, acute neuropsychiatric syndrome that affects at least 15% of hospitalised older adults (Inouye 2006; Siddiqi et al. 2006; Young et al. 2007; MacLullich et al. 2011). There has been much interest in whether delirium may be a marker for future dementia risk. In a population of memory clinic patients already diagnosed with dementia, delirium was associated with faster decline in cognitive test scores (Fong et al. 2009). Higher rates of dementia diagnosis were also observed in persons with postoperative delirium following elective hip surgery (relative risk 1.9, 95% CI 1.1 to 3.3) (Kat et al. 2008). These results are consistent with a systematic review of dementia outcomes following hospitalisation with delirium (Witlox et al. 2010). However, because dementia itself is a major risk factor for delirium, and around half of dementia is undiagnosed in hospital settings (Sampson et al. 2009), the key question of whether delirium is a risk factor for new onset dementia remains unanswered (MacLullich et al. 2009). Moreover, studies of selected hospital and memory-clinic samples may be biased toward more severe

disease. Capturing the full range of dementia risk following delirium within a population-based design would provide more generalisable risk estimates.

The Vantaa 85+ study is a true population-based cohort study and is the only one to have explicitly measured delirium. This chapter address two main questions. First, does delirium increase the risk of incident dementia in this population? Second, in those with dementia, is a history of delirium associated with an increased with an increased burden of standard neuropathology markers of dementia? Whether delirium was associated with accelerated cognitive decline and increased severity of dementia was also determined.

5.3   Methods

5.3.1   Sample characteristics

The Vantaa 85+ Cohort study methods have previously been reported in Section 3.1. Briefly, the study population comprised 553 persons, representing 92% of the 601 adults aged ≥85 years living in Vantaa in 1991. Participants were recruited from the whole population, unrestricted by residential or health status. Follow-up for incident dementia and other markers of health status occurred at 3 (n=277), 5 (n=155), 8 (n=65), and 10 (n=25) years. The study received approval from the Ethics Committee of the City of Vantaa.

5.3.2   Clinical assessments

Dementia diagnosis by DSM-III-R criteria (APA, (1987)) was agreed by two neurologists simultaneously examining each participant. Dementia subtypes were classified using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for Alzheimer's dementia (McKhann et al. 1984) and

National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences for vascular dementia (Roman et al. 1993). Further details on the clinical and cognitive assessments were described in Section 3.1.2.)

At each interview, the examining neurologists assessed participants and informant(s) for a history of any episodes of delirium, specifically assessing: changes in cognitive functioning, level of alertness, psychotic and perceptual symptoms, with reference to a checklist of DSM-III-R criteria for delirium diagnosis (Rahkonen et al. 2001). The reported history and number of episodes of delirium were corroborated with hospital case notes that were available at the time of assessment, and any additional likely episodes of delirium not recalled by participants or informants were ascertained through detailed inspection of hospital case and primary care case notes. Therefore, the study-ascertainment of delirium was retrospectively derived from multiple sources and the overall diagnosis accepted if the examining neurologists judged there was sufficient evidence from participant and informant recall and/or indication in the medical notes.

At baseline and at each subsequent wave, the presence of the following conditions was assessed through interview and medical records: myocardial infarction; congestive heart failure; peripheral vascular disease, cerebrovascular disease; chronic lung disease; connective tissue disease; hemiplegia; diabetes mellitus, diabetes with complications; tumours; leukaemia; and lymphoma.

5.3.3 Mortality

Dates of death were collected through Statistics Finland.

5.3.4 Neuropathology

Brains were fixed in phosphate-buffered 4% formaldehyde solution for at least two weeks. All specimens were macroscopically examined by one pathologist, blind to all clinical data, using a standardised dissection and sampling protocol. Cerebral infarcts and lacunes were identified by

examination of the surface of the brain and from 1-cm-thick coronal slices of the cerebral hemispheres, from 5-mm-thick transverse slices of the brain stem, and sagittal slices of the cerebellum, histologically verified. In addition, a standardised set of samples were obtained from the middle frontal, superior temporal and middle temporal gyri, inferior parietal lobule, uncal region, hippocampal body, cingulate gyrus, occipital lobe (including the primary visual cortex) and midbrain. The protocols for quantifying Alzheimer-type (Braak stage (0 to 6); neuritic amyloid plaque (none 0 to severe 3)) (Polvikoski et al. 1995; Polvikoski et al. 2006), infarcts (present or absent) (Rastas et al. 2007; Ahtiluoto et al. 2010), and Lewy body (neuronal loss in substantia nigra (none 0 to severe 3); α-synucleinopathy (none 0 to severe 3) (Oinas et al. 2009)) pathologies have been described in detail (see Appendix Section 10.4.1).

5.3.5   Genetic testing

Apolipoprotein E (ApoE) genotyping was performed using both polymerase chain reaction and solid-phase mini-sequencing techniques (Syvanen et al. 1993; Polvikoski et al. 2006).

5.3.6   Statistical analyses

Stata 11.1 (StataCorp) was used for all analyses. Logistic regression was used to determine if episodes of delirium were associated with new onset of dementia. Because dementia neuropathology tends to be mixed in unselected populations (Matthews et al. 2009), assessment of the associations between delirium and clinical dementia subtypes was not attempted. Only episodes of delirium occurring at least one wave before participants last known as having no dementia were regarded as an exposure; controls were persons in whom dementia was never detected. Logistic regression was also used to assess worsening in Clinical Dementia Rating score in relation to a history of delirium before that wave. Similar analyses were conducted for functional sequelae, where outcomes in logistic models represented worsening in global function score. The association between delirium history at baseline and mortality was determined using a

Cox proportional hazards model. All models were adjusted for age, sex and co-morbidities (using equivalent weightings from the Charlson co-morbidity index) (Charlson et al. 1987). Confidence intervals (CI) of 95% were employed, and are reported in the results. Post-model testing included examination of Pearson residuals for logistic models and Schoenfeld residuals, and log-log survival plots for proportional hazards models. Each regression model followed the procedures outlined in Box 4-2.

Longitudinal change in MMSE was modelled using random-effects linear regression for both MMSE at study entry (intercept) and rate of change in MMSE (slope), having first compared model fit for fixed intercepts and slopes using maximum likelihood estimates. 'Time in study' was used as the time metric. Covariance matrices were unstructured. The effect of delirium history at baseline, mean-centred age at baseline, sex, baseline functional status on intercept and slope was considered, and model fit assessed using likelihood ratio tests. The final model included adjustment for these variables for MMSE at study entry with an additional term adjusting for the influence of delirium history at baseline on rate of MMSE change. Finally, a quadratic term for the time metric was tested. After fitting models, assumptions were checked by constructing Q–Q plots of the standardised residuals.

In keeping with previous methods, neuropathological variables were dichotomised into 'high' or 'low' values (Savva et al. 2009; Brayne et al. 2010). This approach allows for simpler interpretation and is more likely to be robust. The relationships between these markers (exposure) and dementia (outcome) were evaluated using logistic regression models, adjusted for sex and age at death (Savva et al. 2009). These associations were then assessed, stratified by delirium history, to determine if the odds ratio for the dementia-pathology association differed between those with and without a history of delirium. The possibility of a statistical interaction was also tested using a multiplicative interaction term (delirium*pathology).

5.4 Results

5.4.1 Participant characteristics

Participant characteristics are summarised in Table 5-1. Figure 3-1 (page 64) shows the flow diagram for the study, and Figure 5-1 illustrates the subset with delirium. At baseline, there were 71 persons (13%) with a history of delirium. There were no differences in age, sex or years of education between those with and without a history of delirium. However, persons with a history of delirium were more likely to have prevalent dementia (77% versus 33%, p<0.01) and lower MMSE scores (15/30 versus 21/30, p<0.01). A delirium episode was recorded at least once during the study in 121 persons (22%). Brain autopsy data were available in similar proportions of individuals with and without an episode of delirium (54% and 48% respectively, p=0.26).

Table 5-1. Clinical characteristics of participants at baseline.

	No history of delirium		≥ 1 episode of delirium		P value
N at baseline (%)	482	(87%)	71	(13%)	
person.years	1901		164		
Mean age (SD)	88	(2.9)	90	(3.1)	1.00
Sex (% women)	385	(80%)	55	(77%)	0.64
Proportion with >4 years education (%)*	98	(23)	10	(17)	0.31
Mean time in study (years, IQR)	3.2	(1.6—5.9)	1.9	(0.9—3.2)	<0.01
Co-morbidity score at baseline (IQR)†	3	(1—4)	3	(2—5)	<0.01
Functionally independent at baseline (%)	321	(67%)	24	(34%)	<0.01
Prevalent dementia	159	(33%)	55	(77%)	<0.01
MMSE					
Baseline (IQR)	21	(17—26)	15	(10—19)	<0.01
Last follow-up (IQR)	19	(11—24)	13	(9—17)	<0.01

A total of 121 participant s experienced delirium at any time during the study (22%). Of these, 58 were brain donors (48%) and 232 brain donors had no history of delirium (54%) (*P*=0.26)

† Comorbidity index uses the same weightings as the Charlson index. The maximum score is 19. Functionally independent refers to those who reported being fully independent or needing minor assistance to complete activities of daily living.
* Years of education undetermined in 71 participants.
The proportion of brain donor is given for persons experiencing delirium at any point during study.
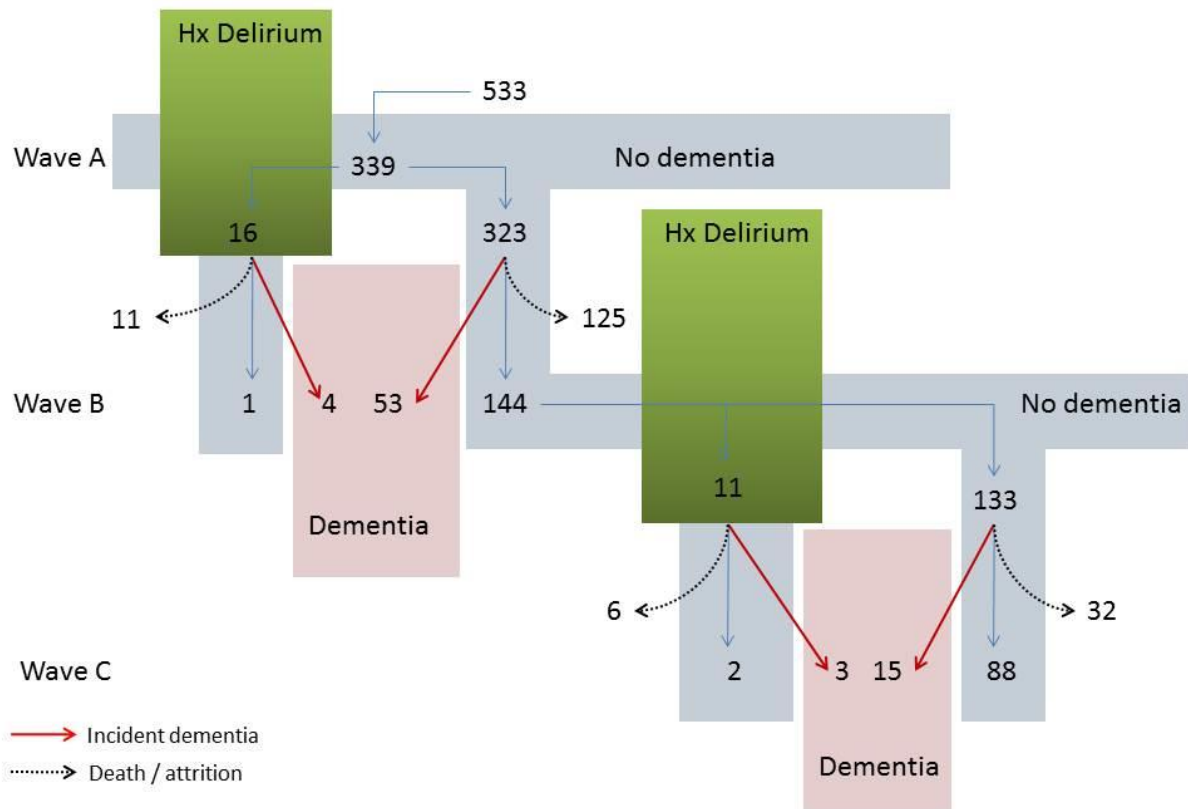
Figure 5-1. Flow diagram showing history of delirium in relation to subsequent diagnosis of dementia.
Participants without dementia are represented in the blue area. Those reporting a history of delirium are in the green boxes. Persons with or without a delirium history can receive a subsequent diagnosis of dementia (red box).

5.4.2 Delirium and dichotomous outcomes

A history of delirium at any wave in persons with no dementia was associated with a significantly higher risk of new dementia at the following wave (OR 8.7, 95% CI, 2.1 to 35) (Table 5-2). For all participants, delirium was also associated with a worse Clinical Dementia Rating score at follow-up (OR 3.1, 95% CI, 1.5 to 6.3) as well as deterioration in global function scores (OR 2.8, 95% CI, 1.4 to 5.5) (Table 5-2). A history of delirium at study entry was associated with increased mortality, even after adjustment for co-morbidities (hazard ratio (HR) 1.6, 95% CI, 1.2 to 2.1).

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Table 5-2. The association of between delirium and dichotomous clinical outcome.

Outcome	Delirium (n)	No delirium (n)			LCI	UCI	P value
Dementia [a]	10	311	OR	8.65	2.13	35.12	<0.01
Dementia worsening [b]	38	226	OR	3.06	1.49	6.29	<0.01
Functional worsening [b]	42	230	OR	2.76	1.38	5.52	<0.01
Mortality [c]	71	469	HR	1.61	1.25	2.10	<0.01

The results of four separate models where delirium is the exposure of interest, adjusted by age, sex and comorbidity, given with 95% confidence intervals (LCI, UCI)

[a] The dementia outcome gives the odds ratio that a person with a history of delirium but no dementia was then diagnosed with incident dementia at the following wave.

[b] The odds ratio of worsening in dementia (at least one point decline in clinical dementia rating scale) or function (at least one category decline in five-point scale from independent to fully dependent for all care needs) between baseline and first follow-up in persons also experiencing delirium.

[c] Association between comorbidity and mortality is also significant in this model (HR, 1.24; 95% CI 1.18 to 1.30) per point on comorbidity index.

All Pearson and Schoenfeld residuals $P > 0.1$.

5.4.3 Delirium and decline in MMSE score

MMSE trajectory was best described by a quadratic model when contrasted with a linear model (Table 5-3). Figure 5-2 shows the predicted trajectories from the model fitted. MMSE scores at baseline were estimated at 28.6 (95% CI, 26.5 to 30.8), representing cognitive function for an individual with zero value on all covariates. In the whole population, cognitive function declined at 0.75 points per year (95% CI, 0.49 to 1.0), with a change in rate of decline of 0.07 points (95% CI, 0.49 to 1.0). Baseline MMSE scores of individuals with history of delirium were 3.0 points (95% CI, 1.4 to 4.5) lower than MMSE scores of individuals without any delirium. A history of delirium was associated with a significantly faster rate of decline in MMSE scores with decline of 1.0 (95% CI, 0.11 to 1.89) MMSE point per year compared to those without delirium.

Table 5-3. Random-effects model of MMSE change.

	β	LCI	UCI	P value
Intercept	28.64	26.46	30.81	<0.01
Delirium	-2.95	-4.47	-1.43	<0.01
Age	-0.15	-0.32	0.02	0.08
Sex	-1.21	-2.33	-0.08	0.04
Functional status	-2.86	-3.24	-2.48	<0.01
Slope	-0.75	-1.00	-0.49	<0.01
Delirium effect on rate	-1.00	-1.89	-0.11	0.03
Slope acceleration	-0.07	-0.10	-0.04	<0.01

Estimates are given with 95% lower and upper confidence intervals (LCI and UCI).

The model is mean-centred on age at baseline and 'time-in-study' is the time metric.

All estimates are adjusted for MMSE at study entry.

The upper part of the table shows estimates for the intercept, first estimating the intercept when all covariates = 0. The estimate changes with the addition of each covariate, subtracting the appropriate β coefficient where: delirium=yes; age per year; sex=female; functional status per increase in five-point scale.

The lower part of the table gives coefficients estimating rate of change (per year) with the effect delirium has on this gradient. The slope acceleration is the quadratic term describing the overall trajectory of the model.
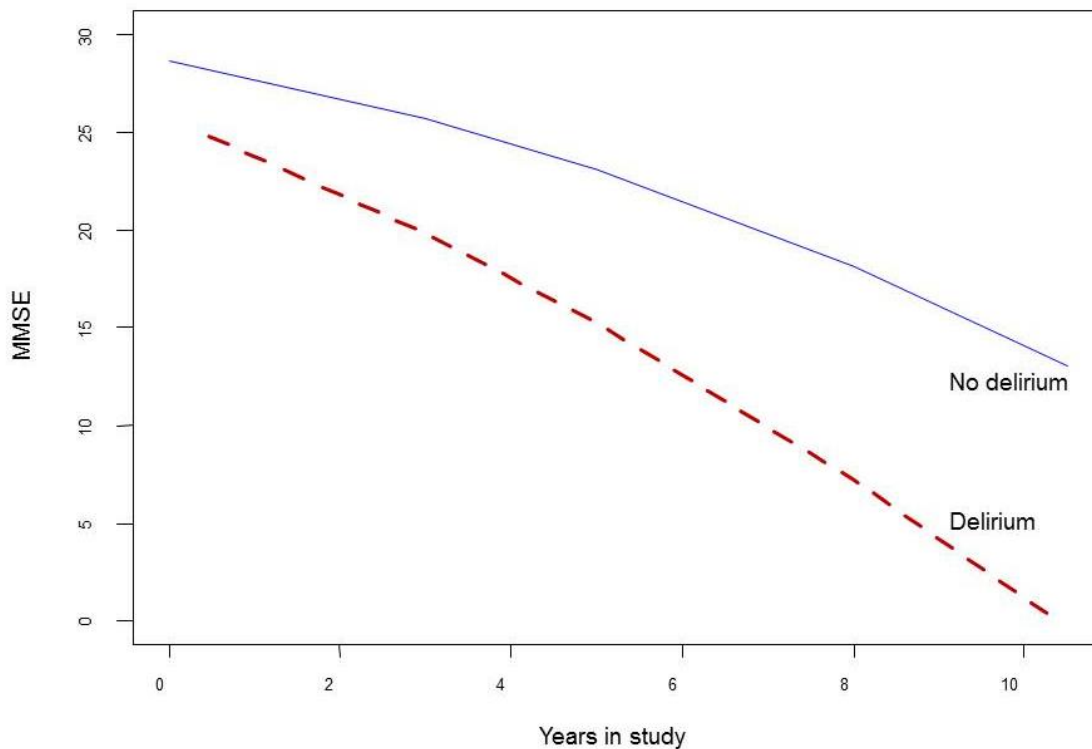
Figure 5-2. Predicted trajectory of MMSE change for those with or without a history of delirium at baseline.

5.4.4 Delirium, dementia and neuropathological markers of dementia

All neuropathological markers were significantly associated with dementia. However, when stratifying the group by history of delirium, the relationship between dementia there were no significant associations between dementia and neuropathology and genotype markers (all ORs closer to unity) (Figure 5-3). For example, higher Braak stage was associated with dementia but not delirium (OR 2.0, 95% CI 1.1 to 3.5, p = 0.02), but in those with a history of delirium, there was no significant relationship (OR 1.2, 95% CI 0.2 to 6.7, p = 0.85). This pattern was observed consistently with neuritic amyloid, ApoE status, presence of infarcts, α-synucleinopathy, and neuronal loss in substantia nigra. While this raises the possibility that the relationship between dementia and neuropathological markers is modified by a history of delirium, the investigation is under-powered to be sure of any relationship using an interaction term (Table 5-4). Delirium history was not itself associated with any of the neuropathological markers of dementia or ApoE status among the brain donors.

Table 5-4. Testing interaction terms between delirium and pathology on dementia outcomes

Parameter	P value
Delirium * Braak stage	0.79
Delirium * Amyloid burden	0.65
Delirium * Infarcts	0.22
Delirium * Neuronal loss in substantia nigra	0.94
Delirium * α-synucleopathy in substantia nigra	0.65
Delirium * ApoE status	0.59
All pathological variables dichotomised into highest versus lowest half (or present/absent in the case of infarcts and Apo ε4 status.	
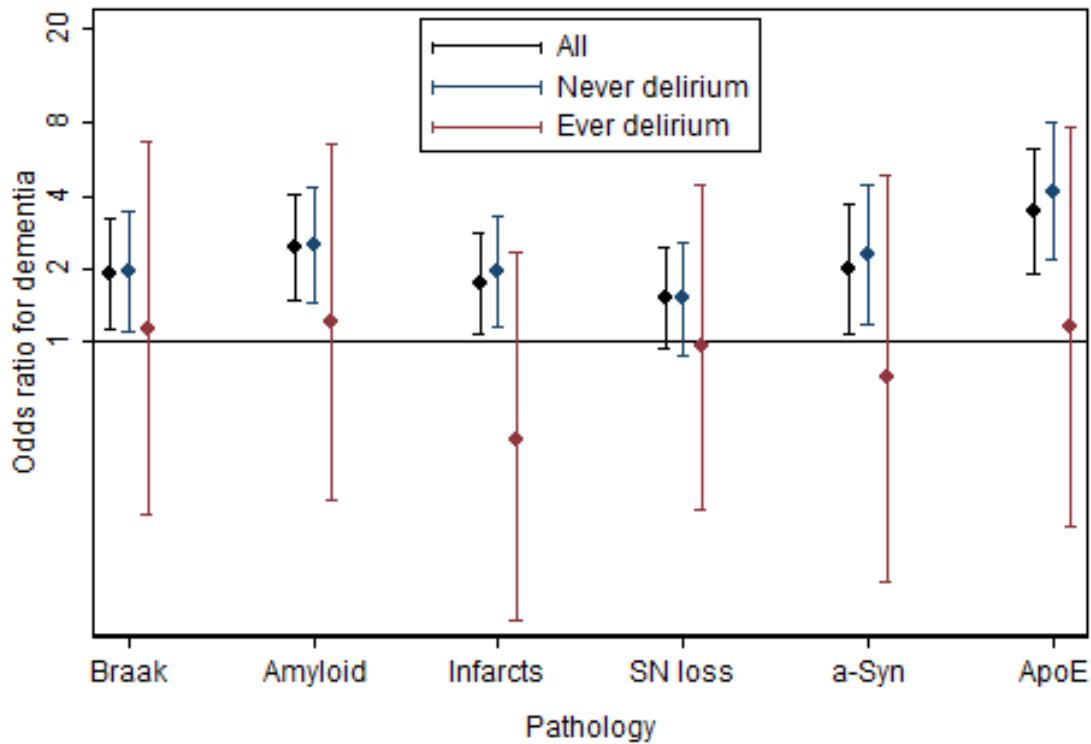
Figure 5-3. Relationship between delirium, dementia and neuropathology or genotype.
Display of logistic regression models, with 95% confidence intervals. The y-axis is log-scaled. Models show association between dementia and pathology (or genotype), adjusted by age at death and sex. Markers were treated as dichotomous variables (high/low). For each marker, the relationship is given for the whole population, and then stratified by delirium history (n=58 with history of delirium; n=232 no history of delirium). SN = substantia nigra; Syn = synucleinopathy; ApoE = apolipoprotein E.

5.5   Discussion

5.5.1   Key findings

This is the first study to my knowledge to examine the hypothesis that delirium is a risk factor for dementia using a true population-based sample of older individuals. The results strongly support this hypothesis. Additionally, in individuals with existing dementia, delirium was associated with worsening dementia severity, worsening global functional status and higher mortality. Moreover, in the whole population, a history of delirium was significantly associated with an accelerated decline in MMSE scores. This is also the first prospective cohort study to examine the potential effects of delirium history on the relationships between dementia and its

neuropathological markers. Individuals with dementia and no history of delirium had strong associations with Alzheimer-type, infarcts and Lewy body pathology. In contrast, those with dementia and a history of delirium showed no such relationships. Though this is an intriguing finding, the study was not powered to determine if delirium is genuinely associated with an altered pattern of pathology.

5.5.2   Strengths and limitations

This study has several strengths. This cohort has high generalisability for the oldest-old, and has a high rate of brain autopsy (Zaccai et al. 2006). The characteristics of the brain donors show no evidence of systematic bias (Brayne et al. 2010). While it has been shown that neuropathological assessments can reliably be made by a single or multiple rater(s) (Mirra et al. 1994), it is possibly an advantage that all scoring was interpreted by the same neuropathologist. There were multiple waves of measurement over a decade; this allows accurate assessment of longitudinal change.

Some limitations of the present study should be acknowledged. Only changes from age ≥85 years could be studied and this resulted in substantial losses to follow-up due to mortality. There is likely to be a survivor effect and this may result in selective differences in clinical and genetic characteristics. Depression also has a complex relationship with cognitive assessment and dementia, and no attempt was made to address this in the present analysis. The results of the random-effects models produced estimated parameters comparable to other population-based studies of general cognitive decline (Terrera et al. 2008). However, similar to many prospective studies of ageing, attrition was significant, and data missing-not–at-random was not accounted for. Despite the fact that autopsy rates were high, the absolute number of cases in each category of delirium exposure remained relatively low.

Self-reported (or informant-reported) delirium may be subject to recall bias, though this is mitigated by corroborating the history with medical records during the interview. Though the

history of delirium was specifically assessed at each wave, this approach is not as accurate as clinician assessment during delirium and is likely to under-detect delirium given that diagnosis rates in routine clinical practice are generally considerably below the true prevalence (Flaherty et al. 2007). In the absence of robust delirium ascertainment being embedded in routine hospital care, only a prospective study in which researchers could assess every patient for delirium during every hospital admission could overcome this issue. This is impractical, however, and combining patient and informant interviews with inspection of case notes is a pragmatic alternative. Indeed, medical records have been validated for the diagnosis of delirium history (Inouye et al. 2005), and the diagnostic accuracy for past episodes is likely to be higher if case notes are reviewed in conjunction with clinical interview as is the case in the present study.

5.5.3   Results in context

The present results are consistent with studies reporting cognitive decline after delirium or intercurrent illness where there have been pre-morbid assessments of cognition (Section 2.3). As reviewed above, follow-up of memory-clinic patients showed delirium was subsequently associated with greater decline in cognitive test scores (Fong et al. 2009). In addition, a report from the Adult Changes in Thought study found that critical illness (without specifically considering delirium) was associated with incident dementia (HR 1.4 (95% CI, 1.1 to 1.7)) (Ehlenbach et al. 2010). Participants in the Health and Retirement Study who had an intercurrent episode of severe sepsis also had a higher risk of being subsequently diagnosed with severe cognitive impairment (OR 3.4 (95% CI, 1.5 to 7.3)) (Iwashyna et al. 2010). The larger effect size in the present study may reflect the older age in this cohort.

5.5.4   Possible mechanisms

The results are also consistent with the emerging evidence from animal models of delirium demonstrating that in vulnerable animals, systemic inflammatory insults can cause transient,

reversible deterioration in cognition and significant acceleration in disease progression after the transient impairments have resolved (Cunningham 2011) (Section 1.4.1). A single, moderate dose of LPS, consistent with the level of inflammatory insult which typically induces delirium in vulnerable humans, has been shown to induce *de novo* neuronal death in animals with existing neurodegenerative disease (Cunningham et al. 2005; Field et al. 2012), and to accelerate the progression of disease without obvious effects on extracellular amyloidosis (Cunningham et al. 2009). In this context, it is of note that a case-control autopsy study of persons who died with delirium showed differential increases in IL-6 and CD68-positive microglia (Munster et al. 2011) (Section 1.4.2.4) Consistent with these findings, the present study suggests the possibility that dementia following delirium may not be as strongly linked with classical dementia neuropathological markers as dementia in those without a history of delirium, but further work is needed.

5.5.5   Conclusions

This study confirmed that delirium is associated with general cognitive decline, with an 8-fold increase in incident dementia and accelerated decline in MMSE scores. Previous investigations for other dementia risk factors (Daviglus et al. 2011) have often been dwarfed by the relationship of dementia with older age itself. The strong association with delirium, even after adjusting for age, in a general population underscores the clinical importance of delirium in relation to dementia risk. Future research should seek to include prospective delirium measures in cohort studies of dementia, correlating these with neuroimaging and neuropathology findings. Up to 30% of delirium has been estimated to be preventable (Inouye et al. 1999) and definitive data would come from intervention trials where the outcome is secondary prevention of dementia. The present study suggests that this would be a plausible approach.

6 Delirium modifies the relationship between cognitive decline and dementia neuropathology

6.1 Summary

Delirium is associated with accelerated cognitive decline. The pathological substrates of this relationship are not yet known, that is, whether they are the same as those associated with the dementias, independent or inter-related. Here, the hypothesis that the accelerated cognitive decline observed following delirium is independent of classical dementia neuropathology was examined.

In three population-based cohorts (the Epidemiological Clinico-pathological Studies in Europe Collaboration), the effects of delirium episodes on cognitive change was examined. These associations were then analysed in relation to the extent of neurofibrillary tangles, amyloid plaques, vascular lesions and Lewy bodies in neuropathological autopsies (N=987). Change in Mini-Mental State Examination scores (MMSE) over six years before death was modelled using random-effects linear regression, and interactions between delirium and pathology burden were assessed.

Mean MMSE six years before death was 25 points. Individuals with delirium had worse initial scores (-2.75 points, $p<0.01$). Cognitive decline attributable to delirium was -0.37 MMSE points/year ($p<0.01$). Decline attributable to dementia pathology was -0.39 MMSE points/year ($p<0.01$). However, the combination of delirium and dementia pathology resulted in the greatest decline, where the interaction contributed a further -0.16 MMSE points/year ($p=0.01$). The additive nature of these variables resulted in individuals with both delirium and dementia pathology declining 0.72 MMSE points/year faster than age, sex and education-matched controls.

Delirium in the presence of dementia-related neuropathologies is associated with accelerated cognitive decline beyond that expected for delirium or the neuropathology itself. This suggests additional unmeasured but related neuropathological processes are initiated by delirium. Age-related cognitive decline has many contributors, and these findings at the population level support a role for delirium acting independently and additively to classical dementia neuropathology.

6.2 Introduction

Understanding the pathological basis of cognitive impairment in whole populations is a prerequisite to mitigating the increasing public health burden of dementia (Brayne et al. 2012). Many strands of investigation presuppose that Alzheimer, vascular and Lewy body pathologies are the predominant causes of dementia. This paradigm has directed the search for biomarkers, treatments and potential prevention strategies. Yet evidence indicates that these 'classical' pathologies do not fully account for the clinical syndrome, especially in populations of the oldest-old (Bennett et al. 2006; Matthews et al. 2009; Savva et al. 2009; Schneider et al. 2009; Cholerton et al. 2013).

Delirium is a syndrome of acute brain dysfunction characterised by inattention and other mental status impairments. An emerging literature demonstrates that delirium is a strong predictor of new-onset dementia as well as acceleration of existing cognitive decline (Fong et al. 2009; MacLullich et al. 2009; Davis et al. 2012; Pandharipande 2013). This is consistent across several different settings: after hospitalisation (Witlox et al. 2010); in those with dementia (Fong et al. 2009; Gross et al. 2012); in post-operative patients (Saczynski et al. 2012); and in a community population (Davis et al. 2012) (Section 2.3). However, whether delirium accounts for additional, inter-related or unexplained pathological injury contributing to dementia has not previously been

examined. It is possible that when dementia follows delirium it has a different pathological profile compared to dementia that develops without delirium. Therefore, understanding how delirium affects the evolution of dementia, in the context of a particular burden of pathology, may offer new insights into independent mechanisms explaining cognitive decline after delirium.

In this chapter, the challenge was to examine a key hypothesis: that faster cognitive decline associated with delirium would act independently of the cognitive decline associated with classical dementia pathology. Accordingly, the extent to which delirium and classical dementia pathology contributed to associated cognitive decline in three unselected population-based cohort studies with neuropathology autopsy data was investigated: the Medical Research Council Cognitive Function and Ageing Study (CFAS); the Cambridge City over-75s Cohort (CC75C) and Vantaa 85+ study. These 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 inter-relation with dementia pathology in the general population.

6.3 Methods

The individual studies have previously been described in detail in Chapter 3 (Brayne et al. 2006; Polvikoski et al. 2006; Fleming et al. 2007), and participant-level data have been harmonised as the Epidemiological Clinico-pathological Studies in Europe (EClipSE) Collaboration (EClipSE Collaboration). Briefly, participants were sampled from general practitioners' registers (CFAS and CC75C, UK) and the Population Register Centre (Vantaa, Finland). CFAS, CC75C and Vantaa 85+ recruited persons aged ≥ 65, ≥ 75 and ≥ 85, respectively. Individuals were assessed mostly at two to four year intervals, with some subsamples having annual evaluation. The Mini-Mental State Examination (MMSE) (Folstein et al. 1975) was performed in all three studies. Additional neuropsychological batteries were also performed, with some differences among the

studies (section 3.4.4.). Previous work has shown that participants in the brain donor programs showed no systematic differences in clinical characteristics compared with other participants in the cohorts (Brayne et al. 2010), though donors in CFAS were selected by stratified random sampling, weighted to those who were older and cognitively impaired (section 3.4.3.). Each study had ethical approval.

6.3.1   Delirium assessments

In CFAS and CC75C, delirium symptoms were a feature of the standardised interview schedules administered by trained interviewers. These schedules were able to assign diagnostic groups based on validated structured algorithms for psychiatric disorders, themselves based on DSM-III-R or related classifications. Questions included: "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 … be sufficient explanation for the subject's mental or psychiatric symptoms (e.g. delirious due to acute infection)?" A full list of relevant questions is given in appendix section 10.3.

At each Vantaa interview, the examining neurologists assessed participants and informant(s) for a history of any episodes of delirium, with reference to a checklist of DSM-III-R criteria for delirium diagnosis (Rahkonen et al. 2001). The reported history was corroborated with medical case records that were available at the time of assessment (details in section 3.1.2. and Chapter 5).

6.3.2   Neuropathology analyses

Paraffin-embedded brain tissue samples were used to assess neuropathological markers, blind to clinical data. Each study reported Braak stage, as a semi-quantitative measure of tau neurofibrillary tangles, and neocortical amyloid plaque burden from the Consortium to Establish a Registry for Alzheimer's Disease protocol (Mirra et al. 1991). The presence of infarcts (>

10mm), lacunes and haemorrhage were histologically assessed using haematoxylin and eosin. Lewy bodies in the substantia nigra were assessed with haematoxylin and eosin, but also included immunohistochemical staining against α-synuclein (or ubiquitin in some of the earlier CC75C specimens) (full details given Appendix Section 10.4).

6.3.3 Statistical analyses

All analyses were conducted in Stata 12.1 (StataCorp, Texas). The exact steps are enumerated in the box below. Consistent with previous approaches, delirium exposure was operationalised as 'never' or 'ever' (Davis et al. 2012). Change in MMSE before death was modelled using a time-to-death random-effects model (Piccinin et al. 2011). Estimating the final trajectory towards death was of interest as this makes relationships with pathological data easier to define. The mean time from the start of the trajectory identified by the model to death was 5.2 years, and so the start point (intercept) for this trajectory was set (centred) at 6 years. This start point is not so near point of death such that rates of change (slopes) cannot be estimated, yet not so far from death that the pathology 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 (Wilson et al. 2007; MacDonald et al. 2011; Wilson et al. 2012b), and in the range observed in other analyses (3 to 8 years) (Muniz-Terrera et al. 2011). Models were adjusted by age at death (centred at mean age = 90 years), sex (0=men, 1=women), years of education (0-3; 4-7; 8-11; 12 or more) and study. Missing data were assumed to be missing-at-random, given that outcome ascertainment was essentially complete in this brain donor cohort.

The four classical dementia neuropathological parameters which contribute the greatest population attributable risk for dementia (Matthews et al. 2009) were examined: Braak stage (neurofibrillary tangles), neocortical amyloid plaques, vascular pathology (large artery infarcts,

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lacunes or haemorrhage) and Lewy bodies in the substantia nigra. In keeping with previous methods, neuropathological variables were dichotomised ('none-mild' = 0; 'moderate-severe' = 1) (Savva et al. 2009; Brayne et al. 2010; Davis et al. 2012). This approach allows for simpler interpretation and is more likely to be robust. Individuals were assigned a 'pathology burden score' based on the number of times they scored in the higher category for each of the four markers. Therefore, the overall pathological burden score ranged between 0 and 4, i.e. being in the lower category for all markers (pathology burden score = 0), in the upper category of all four markers (pathology burden score = 4) or some combination. Finally, interactions between delirium and pathology burden ([delirium history]*[pathology score]) in terms of their effect on both the start point (-6 years before death) and rate of change of MMSE were calculated.

Box. Summary of statistical approach to random-effects modelling

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Formatting data
1. Arrange all datasets in long format, where each row represents an observation at a given time point. Each participant will therefore be represented by multiple rows.
2. Calculate age of participant at each observation, including age at death.
3. Calculate the 'time to death' for each row.
4. Ascertain distribution of 'time to death' term, and centre the data based on mean so that the mean is 0.
5. Generate terms to estimate slope parameters, multiplying time-to-death by variables of interest: e.g., [time-to-death]*[age], or [time-to-death]*[delirium status]

Models
6. Run an intercept-only model, checking maximum likelihood and pseudo-r^2. Inspect both fixed and random effects.

6.4   Results

There were 987 participants (290 from Vantaa 85+, 241 from CC75C, 456 from CFAS) with neuropathology data. Table 6-1 describes the characteristics of the sample. Mean age at death was 90 years (SD 6.4) and persons with delirium were slightly older, more likely to be women and have more years of education. Neocortical amyloid plaques, vascular pathology or Lewy

bodies were not significantly different in individuals with and without a history of delirium. Persons with delirium had higher Braak stage, though this difference did not persist after adjusting for dementia status.

Table 6-1. Characteristics of study participants, according to history of delirium[1]

	No delirium[1]		Delirium[1]		P value
N	708		279		
Median follow-up; years (IQR)	4.3	*(2.0-7.1)*	4.7	*(2.5-7.8)*	
Median number of assessments in last six years[2] (IQR)	2	*(1-3)*	3	*(2-4)*	
Study; N (%)					
Vantaa 85+	232	*(80)*	58	*(20)*	
CC75C	142	*(59)*	99	*(41)*	
CFAS	334	*(73)*	122	*(27)*	
Age at death; mean (SD)	89	*(6.7)*	90	*(5.8)*	0.03
Sex; female (%)	472	*(66)*	210	*(75)*	<0.01
Years of education; median (IQR)	9	*(6-13)*	9	*(8-14)*	<0.01
Pathology[3]; N (%)					
Braak stage	346	*(50)*	166	*(59)*	<0.01
Neocortical amyloid plaques	344	*(50)*	138	*(42)*	0.62
Vascular (infarcts, lacunes or haemorrhages)	358	*(56)*	139	*(57)*	0.54
Lewy bodies in substantia nigra	67	*(10)*	27	*(10)*	0.99
Pathology burden score[4]					0.10
0	136	*(19)*	41	*(15)*	
1	207	*(29)*	72	*(26)*	
2	220	*(31)*	107	*(38)*	
3/4	149	*(21)*	60	*(21)*	
Any moderate-severe pathology[5]	576	*(70)*	239	*(76)*	0.20

[1] 'Delirium' means evidence of delirium at any time, compared to those with no history of delirium
[2] Six years is the chosen intercept for this model describing final trajectory of cognitive decline
[3] Pathology measures are dichotomised, numbers shown here are for the higher category:
   Braak stage ranges 0 to 6; figures are those scoring 4/5/6.
   Neocortical amyloid plaques scored none/mild/moderate/severe; figures are those scoring moderate-severe
   Vascular indicates the presence (yes/no) of: infarcts in arteries >10mm, lacunar lesions or haemorrhage.
   Lewy bodies scored none/mild/moderate/severe; figures are those scoring moderate-severe
   Full details are given in supplementary appendix.
[4] Pathology burden score refers to the number of pathological measures in a higher category for an individual
[5] Any moderate-severe pathology = pathology burden score ≥ 1
P values for differences in means/medians (continuous measures) and proportions tested using t or Wilcoxon and χ^2 tests, respectively

Results from the random-effects models describing delirium and cognitive decline are presented in

Table 6-2. 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 pathology burden), the start point was estimated at 24.7 MMSE points. The start point should be interpreted as the estimated MMSE score six years before death in persons where 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 = all covariates in reference category, e.g., no delirium, lowest pathology score). There was no significant influence of study source (Vantaa 85+, CC75C or CFAS) on the model estimates.

Table 6-2. Quantifying trajectories of MMSE change in relation to delirium and dementia pathology

		Clinical[1]			Clinical + Delirium[2]			Clinical + Pathology[3]			Clinical + delirium + pathology[4]		
		β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p
	N participants	877			877			872			872		
	Observations†	2570			2570			2558			2558		
	Intercept[5]	21.73	(19.98,23.48)	<0.01	22.18	(20.51,23.85)	<0.01	24.76	(22.84,26.67)	<0.01	24.65	(22.77,26.53)	<0.01
	Slope[5]	-0.86	(-0.93,-0.78)	<0.01	-0.66	(-0.74,-0.58)	<0.01	-0.45	(-0.60,-0.31)	<0.01	-0.35	(-0.51,-0.20)	<0.01
Clinical	Age[6]	-0.27	(-0.33,-0.20)	<0.01	-0.25	(-0.31,-0.19)	<0.01	-0.23	(-0.29,-0.16)	<0.01	-0.21	(-0.27,-0.15)	<0.01
	Age (slope)[7]	-0.02	(-0.03,-0.01)	<0.01	-0.02	(-0.03,-0.00)	<0.01	-0.01	(-0.02,-0.00)	<0.01	-0.01	(-0.02,-0.00)	0.05
	Sex[8]	-2.08	(-2.81,-1.34)	<0.01	-1.96	(-2.69,-1.24)	<0.01	-2.08	(-2.80,-1.35)	<0.01	-1.98	(-2.70,-1.27)	<0.01
	Education (years)												
	0-3	(Ref)			(Ref)			(Ref)			(Ref)		
	4-7	0.99	(-0.94,2.78)	0.33	1.17	(-0.66,2.88)	0.22	0.88	(-0.91,2.66)	0.34	1.06	(-0.66,2.77)	0.23
	8-11	1.93	(-0.91,4.77)	0.12	1.22	(-1.51,3.95)	0.24	1.49	(-1.24,4.22)	0.20	0.73	(-1.90,3.37)	0.57
	12 or more	5.55	(2.68,8.43)	<0.01	4.56	(1.79,7.33)	<0.01	5.18	(2.41,7.94)	<0.01	4.16	(1.49,6.83)	<0.01
Delirium	Delirium[9]				-3.84	(-4.62,-3.06)	<0.01				-2.75	(-4.49,-1.01)	<0.01
	Delirium (slope)[10]				-0.62	(-0.77,-0.48)	<0.01				-0.37	(-0.60,-0.13)	<0.01
Pathology	Pathology burden score[11]												
	0							(Ref)			(Ref)		
	1							-1.30	(-2.33,-0.26)	0.04	-0.67	(-1.79,0.45)	0.24
	2							-2.83	(-3.86,-1.79)	<0.01	-2.22	(-3.34,-1.09)	<0.01
	3 or 4							-4.81	(-6.04,-3.58)	<0.01	-4.40	(-5.71,-3.10)	<0.01
	Pathology (slope)[12]							-0.51	(-0.68,-0.35)	<0.01	-0.39	(-0.57,-0.22)	<0.01
Interactions	Delirium x pathology intercept[13]										-0.86	(-2.75,1.03)	0.37
	Delirium x pathology (slope)										-0.16	(-0.29,-0.03)	0.01

*The term 'dementia pathology' refers to those classical dementia pathologies known to contribute to cognitive impairment, i.e. Braak stage, amyloid plaques, infarcts and Lewy bodies.

† Observations refers to the total number of longitudinal outcomes in the model

Abbreviations: MMSE: Mini-mental state examination

Orientation: Each of the four columns represents a model of cognitive trajectories, adjusted by study source.
    [1] Model based on only clinical variables: age, sex, education (not including delirium).
    [2] Clinical model with the addition of delirium variables
    [3] Clinical model with the addition of pathology variables
    [4] Model fully adjusted for delirium, pathology and their interactions on intercept and slope

[5] The intercept and slope are given for each model. These indicate the estimated MMSE six years before death (intercept) and the rate of decline per year (slope). The intercept from six years before death was chosen because the mean time before death was 5.2 years, and the model is centred 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 (see below: Interpretation). All models are adjusted for baseline difference in MMSE.

Clinical variables

[6] Age: the effect of age on the intercept, per year older than centred age at death (90 years)
[7] Age (slope): the effect of age on the rate of MMSE change, per additional year older than centred age at death (90 years)
[8] Sex: women compared to men

Delirium

[9] Delirium: the effect of a history of delirium at any point on the intercept
[10] Delirium (slope): the effect of delirium on rate of MMSE change, per additional year from six years before death

Pathology

[11] Pathology burden score: effect of score on the intercept, per instance of being in a higher pathology category (0 to 4).
[12] Pathology (slope): the effect of being in a higher pathology category on rate of MMSE change, per additional year from six years before death.

Interaction

[13] The effect of a pathology-delirium interaction on the intercept (six years before death)
[14] The effect of a pathology-delirium interaction on the rate of MMSE change (slope), per additional year from six years before death.

Interpretation:

Each coefficient can be interpreted additively from the baseline intercept[5] and slope[5]. For example, a woman in the clinical model[1] aged 91 (1 year older than mean) with 12 years of education would have an estimated intercept of 22.7 (base intercept) + -0.26 (due to age) + -2.11 (due to being a woman) + +2.16 (due to education) = 22.5 MMSE points six years before death. Expected decline per year estimated at -0.84 (base slope) + -0.02 (due to age) = -0.86 MMSE points per year.

[1] **Clinical model**: Age, sex and education are significantly associated with trajectories of MMSE. As new terms are added to the model (below), the estimated coefficients generally become smaller as the additional terms explain more of the model variance.
[2] **Clinical model + delirium:** Delirium also significantly affects intercept and slope.
[3] **Clinical model + pathology:** Pathology is significantly associated with intercept and slope
[4] **Clinical model + delirium + pathology**: delirium and pathology remain significant predictors of MMSE decline. An interaction between delirium and pathology is not significantly associated with the intercept, but does influence rate of MMSE change (additional -0.16 MMSE point per year over and above the contribution of delirium and pathology separately. The effect of this can be visualised in Figure 6-1.

6.4.1 Effect of delirium on start point and rate of change

On average, delirium was associated with a 2.8 point lower MMSE score (p<0.01) six years before death. For these persons, the rate of change was an additional 0.37 points per year (p<0.01). These coefficients are additive. Therefore, for the typical individual aged 90 years at death with delirium, the estimated MMSE is 24.7 points (baseline) and -2.8 points = 21.9 MMSE points, declining at 0.35 points (base rate) and -0.37 (due to delirium) = 0.72 points per year.

6.4.2 Effect of pathology on start point and rate of change

Increasing pathology burden score was associated with lower MMSE score (-0.7 for 1 instance of high dementia pathological marker; -2.2 point for 2 markers, -4.4 for 3 or more markers, p<0.01 for trend). Pathology burden conferred an additional 0.39 point decline in MMSE score over and above the effects of age and delirium (p<0.01).

6.4.3 Interaction between delirium and pathology

A significant interaction between delirium and pathology estimated an additional decline of 0.16 MMSE points per year (p=0.01). Therefore, individuals with both delirium and high dementia pathology had an estimated rate of decline of: -0.35 points (base rate) and -0.37 (due to delirium) and -0.39 points (due to pathology) and -0.16 points (due to interaction) = 1.27 points per year. By way of comparison, the independent effect of age alone on rate of MMSE change was 0.01 points per year (i.e., 0.05 MMSE difference between ages 85 to 90 years).

Figure 6-1 shows how rate of cognitive decline varies by delirium and pathology status. The slowest decline was seen in persons with no history of delirium and least dementia pathology. The fastest decline was seen in persons with both a history of delirium and most dementia pathology. Intermediate rates of decline were observed in individuals with delirium but least dementia pathology and in those with no delirium history but most dementia pathology.
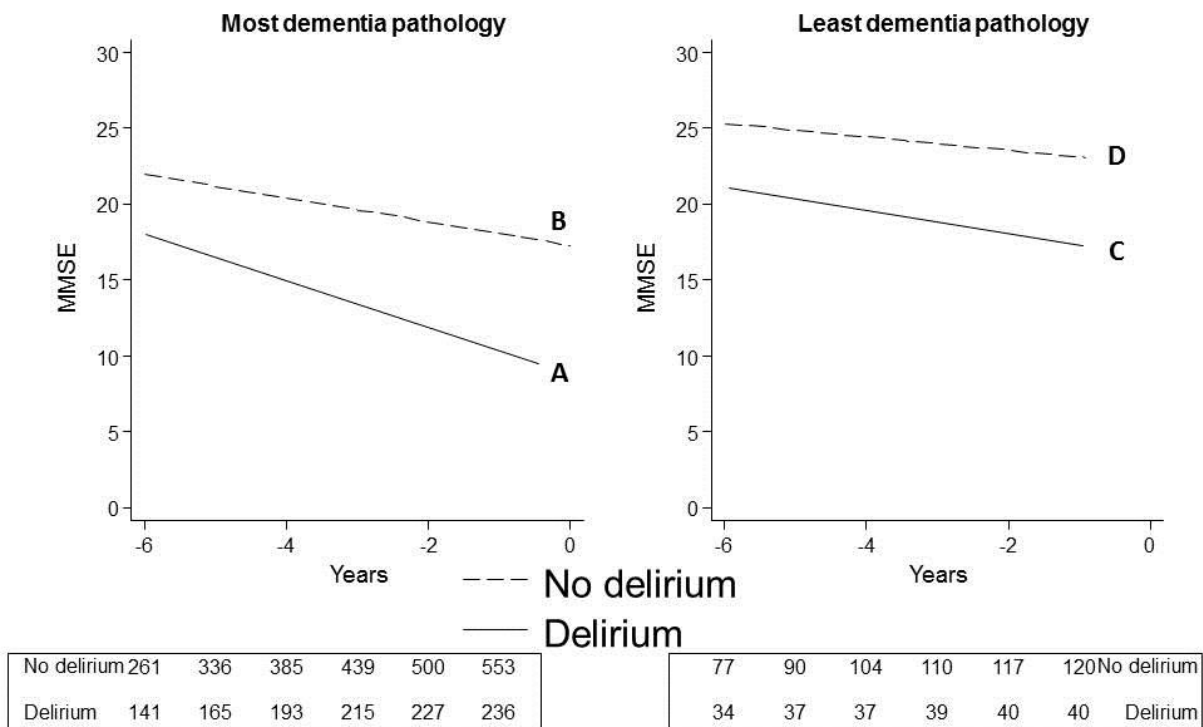
Figure 6-1. Trajectory of cognitive decline in relation to delirium and dementia pathology at autopsy.

Boxes underneath the figures show the number of persons alive at each year before death, according to whether they had experienced delirium.

Left panel: trajectories of cognitive decline in individuals with most dementia pathology (higher dichotomised category for any of Braak stage, cortical amyloid plaques, infarcts, Lewy bodies), according to delirium status. P value A versus B <0.01

Right panel: trajectories of cognitive decline in individuals with least dementia pathology (lower dichotomised category for all of Braak stage, cortical amyloid plaques, infarcts, Lewy bodies), according to delirium status. P value C versus D <0.01

All models are adjusted by age, sex, education, baseline MMSE.

Interpretation: Individuals with delirium and more dementia pathology have the fastest decline (Line A); individuals with no delirium and little dementia pathology have slowest decline (D). For some individuals, cognitive decline is driven by dementia pathology (no delirium, high pathology, B). For other individuals, cognitive decline is associated with delirium (delirium, little pathology, C), and this is distinct from, but contributory to, classical dementia pathology (p value A versus C = 0.01).

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6.5 Discussion

This is the first demonstration that people with both delirium and higher levels of classical dementia pathology show the greatest cognitive decline. Delirium, in the presence of dementia-related neuropathology, was associated with cognitive decline beyond that expected for delirium or the neuropathology itself. This means that delirium may be associated with pathological processes driving cognitive decline which have independent components and are different from classical dementia pathology. These findings suggest new possibilities regarding the pathological correlates of cognitive impairment, positioning delirium and/or its precipitants as a critically inter-related mechanism. Showing this in three unselected samples further attests to the broad significance of these findings and their applicability to the wider population.

These results are in keeping with other studies identified in Section 2.3., demonstrating that delirium is associated with faster trajectories of cognitive decline (Davis 2013). Chapter 5 raised the possibility that classical dementia pathologies might not mediate the observed relationship between delirium and dementia, though the analysis was underpowered (Davis et al. 2012). Here, the larger sample size, and the more precise determination of cognitive change in the six years before death, allows us to be more conclusive about the inter-related effect of delirium on clinico-pathological correlations in dementia.

This analysis has a number of strengths. Firstly, it focuses on a major and previously unaddressed question arising from the prevalence of cognitive impairment and aging. In terms of study design, the three cohorts have high generalisability for the oldest-old, populations that are under-represented in dementia research despite having the highest prevalence of dementia (Schoenmaker et al. 2004). This is also the first analysis to examine delirium and the pathological 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 (Wilson et al. 2012b). Modelling change in cognitive outcomes as continua, rather than simply the presence or absence of dementia, allows for an exploration of the impact of delirium across the whole spectrum of cognitive function, i.e. from no baseline impairment, through mild cognitive impairment to more severe dementia severity. The power to assess such effects, as interactions between delirium and neuropathology, is unique.

A number of limitations should be taken into account. Delirium was retrospectively ascertained, and by slightly different methods. In Vantaa 85+, assessments for history of delirium occurred at each visit, using information from participants, informants and medical records. Ascertainment in CFAS and CC75C relied on diagnostic interviews at each study visit but is likely to underestimate delirium in the intervening period. The diagnostic classification criteria also varied, though the different diagnostic schedules for delirium have been shown to have very good agreement with DSM-III-R (Treloar et al. 1997). 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 — represents an adverse state for subsequent cognitive trajectories, regardless of the exact methods for operationalising the syndrome. As with other prospective cohort data, there remains the possibility that residual confounding contributes to these observed associations. Though the overall sample size is large, the number of brains is a small proportion of the overall study denominator (4.8%). The autopsies from CFAS over-sampled participants with cognitive impairment, though they remain representative on other clinical parameters. Another consideration is that only a limited range of pathological markers and comorbidities could be examined in this harmonised dataset. Finally, though recent research based on neuroimaging and neuropathology suggests that insults in earlier life can also be malignant (Janz et al. 2010; Gunther et al. 2012; Morandi et al. 2012b), this could not be examined within this study.

In conclusion, these results indicate that delirium interacts with underlying classical dementia pathology and so represents a potential independent, but inter-related, pathological pathway to chronic cognitive impairment and dementia. If delirium prevention could lead to consequent prevention of dementia (Inouye 2006; MacLullich et al. 2011), it will be essential to understand if certain dimensions of the delirium syndrome might have a greater impact on cognitive trajectories than others. For example, duration, severity and/or aetiology (e.g. medications versus acute illness, surgery versus sepsis) may be differently important. Animal studies modelling different aetiologies 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, both during acute episodes and in follow-up across all settings, and therefore support wider implementation of best practice in delirium prevention.

7 A new technique for deriving a retrospective diagnosis of delirium from medical records

7.1 Summary

Delirium is increasingly recognised as an important potential contributor to trajectories of cognitive decline. Therefore, analyses of existing cohort studies measuring cognitive outcomes could benefit from methods to ascertain a retrospective delirium diagnosis. This study aimed to develop and validate such a method for delirium detection using medical records in UK and Ireland.

A point prevalence study of delirium served as the reference-standard for delirium diagnosis. Blinded to study results, short clinical vignettes were compiled from participants' medical records in a standardised manner, describing any relevant delirium symptoms recorded in the whole case record for the period leading up to case-ascertainment. An expert panel independently rated each vignette as unlikely, possible, or probable delirium and disagreements were resolved by consensus.

From 95 case records, 424 independent vignettes were abstracted. Median age of subjects was 77 years (interquartile range 55 to 83). Against the original study DSM-IV diagnosis, the chart abstraction method diagnosed delirium with sensitivity 0.88 and specificity 0.75; area under the curve 0.86 (95% CI 0.80 to 0.89).

This chart abstraction method can retrospectively diagnose delirium in hospitalised patients with good accuracy. This has potential for identifying incident delirium in cohort studies where routine medical records are available.

7.2 Introduction

Delirium is an extensive and serious problem in acute hospitals (Siddiqi et al. 2006). It is characterised by an acute and fluctuating failure of attention and cognitive and/or perceptual disturbance precipitated by medical illness. It is associated with high levels of personal and family distress (Partridge et al. 2013), as well as greater healthcare costs (Akunne et al. 2012).

Delirium during hospitalisation is well recognised to be associated with poor cognitive outcomes (Witlox et al. 2010). Indeed, because delirium is partly preventable (Inouye et al. 1999; Marcantonio et al. 2001), delirium interventions might even prevent dementia (MacLullich et al. 2011). However, around half of dementia presenting to hospital is undiagnosed (Sampson et al. 2009), and there is often uncertainty about an individual's premorbid cognitive function. Accordingly, hospital series may overestimate the association between delirium and any subsequent cognitive impairment.

The prospective relationship between delirium and dementia is more reliably assessed by ascertaining incident delirium in the context of a cohort study measuring cognitive outcomes. However, such studies are extremely rare. Only one prospective study has specifically examined cognitive outcomes after delirium in the general population (Davis et al. 2012; Davis 2013). Given the wider importance of delirium's association with dementia, attempts to identify delirium in other cohort studies would be highly informative, even if the delirium measures were retrospectively derived.

Delirium is under-diagnosed and under-reported such that medical records are known to be unreliable sources for delirium (Johnson et al. 1992). Despite this, a chart-based method for retrospectively identifying delirium has been validated against trained interviewers using the Confusion Assessment Method (CAM) as a reference standard (Inouye et al. 1990; Inouye et al. 2005). This instrument has been important in identifying incident delirium in community-based

persons with dementia being followed up with regular cognitive assessments, showing an association with more rapid trajectories of decline (Fong et al. 2009). However, this abstraction tool was developed in the US healthcare system and there are differences in how medical records are kept in UK and Ireland. Accordingly, there is a need for a complementary tool for use outside the USA.

The aim of the present study is to develop and validate a retrospective measure of delirium based on routine medical records used in the general hospital setting in the UK and Ireland. From the medical records of participants in an independent study of delirium prevalence (Ryan et al. 2013), two separate processes were employed: (i) abstraction of symptoms relevant to the DSM-IV criteria for delirium to produce a short clinical vignette; (ii) an expert panel assigning diagnoses by consensus (index test). These diagnoses could then be validated against the DSM-IV diagnosis of delirium (reference standard) applied as part of the delirium prevalence study.

7.3   Methods

The protocol followed the Standards for the Reporting of Diagnostic accuracy studies guidelines (Bossuyt et al. 2003). Ethics approval was given by the Research Ethics Committee, University College Cork (ECM4(e)12/06/12).

7.3.1   Delirium point prevalence study

The reference standard for delirium was derived from the medical records of participants in the Cork Delirium Point Prevalence Study (Ryan et al. 2013). Briefly, the entire adult inpatient population of a general hospital (excluding ICU and moribund patients) was examined for delirium over a single day. Participants were assessed in two stages. Firstly, participants were screened for inattention using the spatial span forwards and months backwards. Participants

were additionally screened for subjective and objective confusion by asking: "Have you felt muddled in your thinking, or confused, since you came into hospital?" Further information was derived from nurse informants and hospital records. Participants screening positive on any of these components, and a random sample of screen negative participants were assessed in more detail. This second stage consisted of two independent delirium assessments: the CAM (Inouye et al. 1990) and the Delirium Rating Scale – Revised-98 (DRS-R98) (Trzepacz et al. 2001). These were conducted by trained registrars or consultants in geriatric medicine and experienced psychiatrists, respectively. Ultimately, the diagnosis of delirium was based on DSM-IV criteria, applied by consensus using all available psychometric, clinical and informant data. Accordingly, all persons in the prevalence study could be assigned a diagnosis of delirium, subsyndromal delirium, or no delirium for a specific day. In addition to the assessments for delirium, pre-morbid cognitive status was assessed using the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm 1994). This was done for all participants with delirium (n=55) as well as a random subsample of those aged ≥65 years without delirium (n=40).

7.3.2   Chart abstraction technique

A random selection of case notes was identified using the RAND() function in Excel. The sample was designed to maintain the underlying prevalence of delirium (that is, 20% of the identified hospital records were delirium cases). The case notes were then requested from the medical records department on a convenience basis, in batches. All clinical information was used for abstraction, from the date of admission, up until the date of the point-prevalence study (15/05/2010). If the inpatient stay had been longer than two weeks, only clinical information from these two weeks leading up to the index date was used. This included verbatim reports from the entirety of the medical, nursing and allied health professional records. Symptoms deemed relevant to any criterion in the DSM classification were abstracted (Table 7-1), resulting in a clinical vignette. The Charlson co-morbidities index (Charlson et al. 1987), metabolic and

physiological parameters were recorded closest to the date the reference standard was assessed. Abstractors were specialist trainees in geriatric medicine, and were also blind to the study diagnosis. Case notes were abstracted multiple times to assess the influence of abstracting author on the consensus process.

Table 7-1. Abstracted symptoms in relation to DSM-IV criteria

DSM-IV criterion	Abstracted symptoms
A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.	Agitation; drowsiness; any formal rating e.g. AVPU or GCS Any verbatim comment, e.g. 'drowsy', 'slept poorly', 'agitated'
B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.	Any formal cognitive assessment (AMT; MMSE) Any formal specialty assessment, e.g. neurology, geriatric medicine, liaison psychiatry Any verbatim comment, e.g. 'more confused', 'disorientated'
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day	Observations at least three times daily (nursing) Any verbatim comment indicating change in mental state
D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.	General clinical vignette, including metabolic and laboratory parameters taken closest to date of prevalence study: AVPU score; systolic blood pressure; pulse; respiratory rate; oxygen saturation; temperature; C-reactive protein; urea; creatinine

AVPU = assessment of arousal where categories are Alert, Verbally-responsive, Pain-responsive, Unresponsive
GCS = Glasgow Coma Scale
AMT = Abbreviated Mental Test
MMSE = Mini-Mental State Examination

7.3.3 Consensus diagnosis

The consensus diagnosis process was the basis of the index test. The consensus panel comprised three geriatricians and an old age psychiatrist, all of whom provide specialist clinical services for

delirium patients.[7] Assessors only had access to the abstracted vignettes, and were therefore blind to the underlying diagnosis. Each vignette was rated independently as: unlikely, possible, probable delirium. Assessors were asked to use each criterion from the DSM-IV classification to support their assigned diagnoses. Cases where the initial diagnoses were not unanimous were re-examined together until consensus was reached.

7.3.4   Statistical methods

All analyses were conducted in Stata, version 12.1 (Stata Corps, Texas, USA). Sensitivities, specificities, positive and negative predictive values were calculated from 2 x 2 tables, with confidence intervals testing significance at 95%. ROC curves were derived from estimates of sensitivity and specificity. For each individual with multiple vignettes (one vignette per abstractor), Fisher's exact test was used to assess if differences in the initially-assigned diagnostic categories varied according to abstractor.

7.4   Results

Case records from 95 individuals were retrieved (Figure 7-1). Two or more abstractors[8] separately extracted 424 independent vignettes. The characteristics of participants is summarised in Table 2. Median age was 77 years (interquartile range 55 to 83 years), 49% were women (n=47), and median co-morbidity score was 3 (interquartile range 1 to 5). Dementia status was ascertained in 31 persons (target subsample of 65 and older + all delirium cases), with a prevalence of 9/31 (29%). Table 2 describes physiological (level of consciousness, heart rate, respiratory rate, systolic blood pressure, temperature, oxygen saturation, inspired oxygen) and metabolic (C-reactive protein, urea : creatinine ratio) characteristics in those with and without

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[7] Dr Louise Allan and Dr Andrew Teodorczuk, Newcastle University, Dr Dan Wilson, King's College Hospital, Prof Alasdair MacLullich, University of Edinburgh.
[8] Dr Elvira Kuhn, Dr Keith McGrath, Dr Sarah Coveney, Dr Niamh O'Regan, St Finbarr's Hospital, Cork.

delirium. No significant differences were apparent, except that all non-delirious participants were 'alert' on the AVPU scale (arousal scale where categories are 'alert', 'verbally responsive', 'pain responsive' and 'unresponsive'), compared with 3 participants with delirium being less than alert (p=0.03).
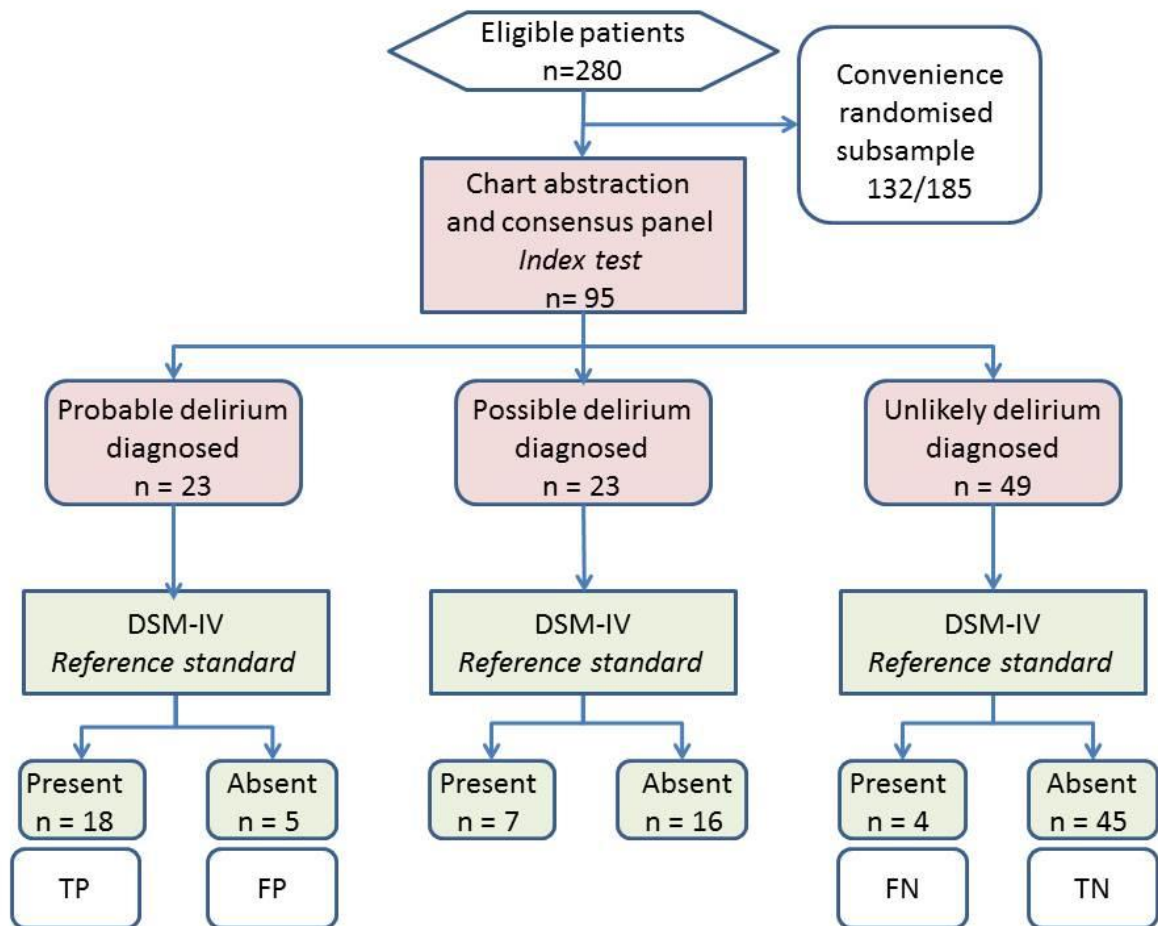

Figure 7-1. STARD flow diagram showing performance of index test relative to reference standard. 'Convenience randomised subsample' refers to the randomised identification of medical notes, which were accessed on a convenience basis.

Table 7-2. Characteristics of participants, by delirium diagnosis.

	DSM delirium (n=29)		No DSM delirium (n=66)		P value*
Age, median (IQR)	80.6	(74.9-88.6)	68.2	(54.5 – 80.2)	0.07
Sex, male	14	(50%)	33	(50%)	1.00
Dementia (y)	6/9		3/22		0.01
Co-morbidity score, median (IQR)	4	(2-6)	2	(0 – 4)	0.44
CRP (mg/L), median (IQR)	57.3	(13 – 121)	37.0	(0 – 120)	0.49
Median Urea:creatinine	0.11	(0.09 – 0.14)	0.08	(0.06 – 0.10)	0.45
ViEWS*					
AVPU	A = 26/29 V/P/U = 3/29		A = 66/66		0.03
HR	82.0		82.3		0.99
RR	19.5		18.7		0.31
BP	125		124		0.99
Temp	36.2		36.6		0.10
SaO_2	96		96		0.99
FiO_2	Y = 6 N = 23		Y = 9 N = 57		0.38

DSM delirium = reference standard delirium

IQR = interquartile range

Dementia ascertained through IQCODE

Co-morbidity score = Charlson co-morbidity index

CRP C-reactive protein

AVPU = assessment of arousal where categories are Alert, Verbally-responsive, Pain-responsive, Unresponsive

HR heart rate; RR = respiratory rate; BP = systolic blood pressure in mm Hg; Temp = temperature in $^{\circ}$C; SaO_2 = pulse oxymetry (%); FiO_2 = supplemental oxygen (y/n).

FiO_2 is scored as Y = supplemental oxygen; N = room air

* Aggregate information derived from multiple vignettes, therefore the standard errors (not shown) are not robust to the clustered nature of the data. However, the p values *are* derived from estimates with robust standard errors.

Table 7-3 gives the diagnostic test accuracy of the expert rater for each vignette. Using a cut-point for 'possible delirium', initial independent ratings prior differences submitted to consensus panel, demonstrated sensitivity of 0.84 and specificity of 0.77. At a higher threshold for 'probable delirium', sensitivity was 0.63 and specificity 0.92 (AUC 0.84, 95% confidence interval (CI) 0.80 to 0.89). Furthermore, the individual DSM-IV criteria perform less well than the raters' overall impression (Table 7-3). Insofar as these could be evidenced in the clinical record, the order of

test accuracy for each criterion (highest to lowest) was: change in cognition (B), demonstration of an acute change (C), documentation of inattention (A), physiological precipitant (D).

After a consensus diagnosis was applied, there was a small improvement in diagnostic test accuracy. For 'possible delirium', sensitivity was 0.88 and specificity 0.75; 'probable delirium' showed sensitivity 0.58 and specificity 0.93 (AUC 0.86, 95% CI 0.82 to 0.89). Vignette abstractor was not significantly associated with the eventual consensus diagnosis.

Table 7-3. The diagnostic test accuracy of the consensus method for delirium diagnosis.

	Sensitivity (%)	Specificity (%)	LR+	LR-	AUROC
DSM-IV Criteria					
Inattention (y/n)	67.5	86.0	4.83	0.38	0.77
Change in cognition (y/n)	71.1	92.2	9.14	0.31	0.82
Acute and fluctuating (y/n)	70.2	88.6	6.16	0.34	0.79
Physiological precipitant (y/n)	67.5	82.4	3.83	0.39	0.75
Possible delirium					
Before consensus	84.3	76.7	3.62	0.21	0.84
Final consensus	88.5	75.0	3.54	0.15	0.86
Subgroup aged ≥70 years	88.1	67.8	2.74	0.18	0.82
Subgroup with dementia	88.2	57.1	2.06	0.21	0.69
Probable delirium					
Before consensus	63.0	92.1	7.97	0.40	0.84
Final consensus	57.6	92.6	7.80	0.46	0.86
Subgroup aged ≥70 years	54.2	89.8	5.33	0.51	0.82
Subgroup with dementia	70.6	57.1	1.65	0.51	0.69

LR likelihood ratio
AUROC area under the receiver operating characteristic curve

Table 7-3 also shows that sensitivity for 'possible delirium' remains high (0.88) in the subgroup of persons aged ≥70 years (n= 57) (AUC 0.82, 95% CI 0.77 to 0.87). In the ten persons with prior cognitive impairment identified from previously documented dementia or by IQCODE score (≥3.5), sensitivity for 'possible delirium' and 'probable delirium' was 0.88 and 0.71

respectively. Specificity in this group was 0.57 for both 'possible delirium' and 'probable delirium' (AUC 0.69, 95% CI 0.44 to 0.94).

Ten cases (11%) were retrieved for which no usable vignette could be abstracted, i.e. insufficient clinical records in the period leading up to the day the reference standard was applied. Whether a vignette could yield sufficient information was decided by consensus.

7.5 Discussion

Here a new technique for retrospectively ascertaining delirium from health care record is presented. Diagnoses assigned by consensus panel based on abstracted clinical vignettes (index test) were sensitive to 'possible delirium' and more specific to 'probable delirium' when compared to DSM-IV diagnoses applied during assessment by a psychiatrist (reference standard). The diagnostic test accuracy remains similar in the subgroup of persons aged ≥70 years, though performed less well in the group with prior cognitive impairment.

The strengths of this study lie in the use of routine clinical records of participants against which expert delirium was assessed. The consensus panel builds on a standard approach to case-ascertainment in psychiatric epidemiology. Use of multiple vignettes showed that the two-stage process was robust, as variations between abstractors recorded in the vignette did not ultimately influence the diagnosis reached at consensus. Certain limitations must also be acknowledged. Diagnoses could not be assigned in 11% of cases, entirely because there were insufficient data from routine clinical records. The process was also relatively time consuming, though multiple abstractions do not seem necessary. It is also possible that hypoactive delirium is under-recognised by this method, and depression may also complicate the diagnosis of delirium.

7.5.1 Findings in context

One other approach has pioneered the use of medical records to derive a retrospective measure (Inouye et al. 2005). Developed in the US healthcare system, it has been useful in leveraging information from dementia cohorts. That study was much larger, and used slightly different methods. Firstly, a one-stage approach was used for abstraction and diagnosis (with variation in agreement assessed by kappa). Secondly, the CAM was used as a reference standard and in the Cork Delirium Prevalence Study, CAM applied by trained geriatricians had a sensitivity of 0.83 and specificity of 0.71 for DSM-IV delirium. As with our findings, diagnostic test accuracy was lower in the group with dementia. The overall accuracy of the US chart technique reported sensitivity 0.74 and specificity 0.83. Our findings are comparable, though the outcome from the consensus panel offered 'possible' (when sensitivity is more important, and 'probable' (when specificity is more important) diagnostic categories.

Overall, the technique can said to perform well, and allowing an intermediate category ('possible delirium') depending on if it is more relevant to identify true positives (sensitivity) or true negatives (specificity). As might be expected, the diagnostic test accuracy is lower in patients with existing dementia and the optimum method for delineating delirium with or without dementia remains uncertain.

7.5.2 Implications

The general implications of the present results are that routine clinical data can be used to systematically gather information on delirium. There is the potential to use a consensus approach to establish evidence of incident delirium during hospitalisation, though this is time consuming. Linking this to information from prospective studies with cognitive outcomes has research utility, thereby leveraging information from existing cohorts with linkage to medical records. In addition, a standardised consensus technique might also have a place in clinical governance and

audit. Future work should establish whether the delirium status could be ascertained with fewer people. The outcomes from apparent false negative delirium diagnoses could also be of interest. More generally, this technique could be useful in existing and on-going studies where the relationship between delirium and trajectories of cognitive decline is of interest.

8 General discussion

This thesis has explored the relationship between delirium and cognitive decline. Chapter 1 discussed the clinical dimensions of delirium, and outlined the wider context to delirium research. Chapter 2 framed the specific questions for this thesis in terms of epidemiological principles. Chapter 3 detailed the cohorts used to address these questions. This concluding chapter will summarise the findings, discuss the strengths and limitations, and then describe how these results make a contribution to knowledge. The final section suggests future directions for research.

Chapter outline

- Main findings
- Strengths and limitations
- Context and wider impact of findings
- Conclusions

8.1 Main findings

8.1.1 Algorithmic definition of delirium

In the absence of a systematic description of delirium in CFAS and CC75C, it was necessary to attempt a definition from the existing standardised interviews. From the GMS data, including the informant data documented in the HAS, an algorithm was constructed based on the clinical principles of the DSM-IV criteria. It was possible to test the criterion validity of this definition against death and future dementia diagnosis in this sub-sample enriched for cognitive outcomes.

This algorithmic definition of delirium was associated with increased mortality, even after adjusting for the usual delirium predisposing factors (dementia) and precipitating factors (illness

severity) (HR 1.28, 95% CI 1.03 to 1.60). The risk of incident dementia at two-year follow-up was also strongly associated with the algorithmic definition (OR 8.82, 95% CI 2.76 to 28.2). These estimates are very similar to those ascertained in the only population cohort to have measured delirium (Vantaa 85+). Taken together, these findings suggest that a valid study-diagnosis of delirium can be operationalised from psychiatric interview schedules.

8.1.2 The clinical impact of delirium in Vantaa 85+

Vantaa 85+ was the only population cohort to have specifically assessed a history of delirium at each interview. The definition was based on clinical interview of patient and informant, together with medical records to minimise recall bias (in either direction, that is, over- or under-recall). Clinical outcomes were explored in relation to this variable.

Dichotomous outcomes investigated were: mortality (HR 1.6, 95% CI 1.2 to 2.1); odds of dementia at follow-up (OR 8.7, 96% CI 2.1 to 35); odds of worsening dementia severity score (OR 3.1, 95% CI 1.5 to 6.3); worse functional decline (OR 2.8, 95% CI 1.4 to 5.5, measured by a Likert global function score). In addition, trajectory of MMSE change was assessed in a random-effects longitudinal model, showing that delirium adversely affected both the intercept (β = -2.95, 95% CI -4.47 to -1.43 points) and slope (β -1.00, 95% CI -1.89 to -0.11 points per year).

Some preliminary analyses of the interaction between delirium, dementia and neuropathology were possible in the Vantaa 85+ dataset. It investigated the observed associations between various pathology or genetic markers known to be related to dementia (neurofibrillary tau, amyloid, ApoE, infarcts, Lewy-bodies and neuronal loss in substantia nigra). The analysis found that when stratifying by history of delirium, associations with these markers remained effectively the same in the pure dementia group, but weaker when delirium was part of dementia. Though underpowered to definitively conclude there was an underlying interaction, the suggestion was

that when dementia follows delirium, the pathological substrates were not fully accounted for by these conventional dementia markers.

8.1.3 Delirium modified the relationship between dementia and pathology

A more detailed analysis of the relationship between delirium, trajectories of cognitive decline and dementia pathology was possible in the harmonised EClipSE database. Here, the outcome was rate of cognitive decline in the last years of life (intercept centred at 6 years before death) and the exposures were delirium (never/ever) and pathology burden (where 'pathology' was a composite measure of conventional dementia pathology, specifically: neurofibrillary tangles, neocortical amyloid, vascular lesions, Lewy bodies in substantia nigra). Interactions were tested between delirium and pathology on the model intercept and slope.

The analysis found that delirium and classical dementia-related pathology were both negatively associated with rate of cognitive decline. An interaction between delirium and dementia pathology was evident such that individuals with fastest rate of decline had both these, with a multiplicative effect beyond that expected for each variable alone. This suggests that delirium accelerates cognitive decline in late life, over and above the decline contributed to by dementia. The pathophysiological substrate(s) of this interaction is unclear and not captured by the current paradigm for the pathological correlates of cognitive impairment in this population.

8.1.4 A validated method for extracting information from clinical records

There are many more longitudinal studies with cognitive outcomes than those which record delirium exposures. Therefore, there is a possibility of leveraging information from existing cohort studies with respect to a method for deriving a delirium diagnosis.

The opportunity to develop this came from use of routine medical records of participants in a point-prevalence study of delirium in an acute adult inpatient population. Symptoms reported in

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the healthcare record pertaining to each DSM-IV criterion for delirium extracted by multiple abstractors, resulting in a clinical vignette. This vignette was then submitted to a consensus panel expert in clinical delirium diagnosis and their decision tested against the diagnosis in the original study.

This method yielded a sensitivity of 0.88 and specificity 0.75 for 'possible delirium', with lower sensitivity (0.58) and higher specificity (0.93) for 'probable delirium' (AUC 0.86, 95% CI 0.82 to 0.89). In the subgroup of individuals aged ≥70 years, sensitivity for 'possible delirium' remained high (0.88). Sensitivity for 'possible delirium' was also 0.88 in the group with prior cognitive impairment, though specificity was much poorer (0.57). Collectively, these findings suggest that the method is a feasible approach for ascertaining delirium in cohort studies with linkage to hospital records (at least in this population and healthcare setting).

8.2   Strengths and limitations

8.2.1   Strengths

This thesis focuses on a common exposure (delirium) and a common outcome (cognitive impairment). Therefore, its strengths lie in its attempt to address as series of important questions in the epidemiology of ageing: What is the optimum way of studying delirium in whole populations? What are the clinical consequences of delirium? How does delirium relate to the pathological determinants of cognitive decline?

Another major strength of these analyses derives from their basis as population samples. As a result, the findings have high external generalisability for the oldest-old, a population widely under-represented in the literature (Schoenmaker et al. 2004).

8.2.2 Limitations

8.2.2.1 *Systematic reviews*

There are limitations that apply to the systematic reviews in Chapter 2. These may relate to the search strategy, data extraction and synthesis (both quantitative and narrative). Though the searches were performed in three databases (Medline, Embase, Science Citation Index), there is a possibility that some studies were not identified. To some extent, errors in study selection and data extraction were mitigated by having had a second reader.

8.2.2.2 *Prospective studies*

The data from cohort studies are limited by the sampling, response, measurement, attrition and analytical issues. These were mainly explored in Chapter 3. However, there are specific limitations that principally relate to the lack of direct correlation of the delirium variable with clinical assessment (except in Chapter 7). Delirium was ascertained by different methods and different sources (retrospective clinical interview; information from medical records, standardised psychiatric interview). Interestingly, there was great consistency across the cohort studies despite these differences, suggesting that the core features of delirium – acute cognitive change precipitated by acute illness – is a harbinger for adverse events regardless of the exact operational definition used. Nonetheless, there is uncertainty as to the degree and direction of any misclassification bias. Moreover, the associations presented here will be subject to residual confounding, especially given the limited number of other covariates accounted for.

8.3 Context and wider impact of findings

The purpose of this section is to show how the results from this thesis have made a contribution to our understanding of delirium, providing answers to the questions posed in the introductory

chapters. This thesis provides a narrative that can be summarised in three areas: descriptive epidemiology, analytic epidemiology, and biological underpinnings.

8.3.1   Descriptive epidemiology

8.3.1.1   *Previous state of knowledge*

The vast majority of descriptive epidemiology studies in delirium had been undertaken in selected samples, mainly hospitalised cohorts (Siddiqi et al. 2006). As summarised in Section 2.2, three studies reported point-prevalence in whole populations and two described period-prevalence. There was an understanding that point-prevalence at any time might have been low, though this may have been limited by survey response rates being lower during intercurrent illness / delirium. Therefore period prevalence might have been more informative, and one study, GERDA, showed the one-month period prevalence of 27% in 503 individuals aged ≥85.

8.3.1.2   *Specific contribution to knowledge*

Chapter 4 offers another report on the age-specific period prevalence of delirium in the general population. With 122 cases identified in a denominator of 2197 (representative of 13004), it is the largest analysis of its kind. Chapter 4 also describes the period prevalence of subsyndromal delirium, the first report in a population sample.

In this subsample enriched for cognitive impairment, the estimates show that period prevalence of delirium increases with age. In confirming this, the study also proposes an efficient approach to investigating delirium in population-samples, that is, by using a stratified sample at higher-risk for cognitive dysfunction.

Complementary to the delirium algorithm, the validation of a delirium diagnosis through case notes review offers a new method to ascertain the descriptive epidemiology of delirium in hospital samples.

8.3.2 Analytic epidemiology

8.3.2.1 *Previous state of knowledge*

The cognitive and functional sequelae of delirium had never been tested in whole populations. In addition, the outcome data from hospital cohorts were usually limited by the inability to account for both precipitating and predisposing factors (Siddiqi et al. 2006; Witlox et al. 2010). Two prospective studies demonstrated worsened cognition after hospitalisation (from any cause) (Ehlenbach et al. 2010; Wilson et al. 2012a) and after severe sepsis (Iwashyna et al. 2010). However, none could examine delirium.

One study had described the cognitive outcomes after incident delirium (retrospectively determined). This was in a community-based cohort of 402 persons already diagnosed with dementia (Fong et al. 2009). This reported that delirium was associated with worsening in dementia severity, confirmed in a subset (n=263) with longer follow-up (median 3.2 years) (Gross et al. 2012).

In unselected populations, Vantaa 85+ had published preliminary data on cross-sectional associations between delirium and dementia (Rahkonen et al. 2001).

8.3.2.2 *Specific contribution to knowledge*

Constructing an algorithmic diagnosis using data from a standardised psychiatric interview was novel. In testing its construct validity, it added to the findings from Vantaa 85+ (described below) that showed that delirium, and its symptom clusters, were separately and independently

associated with mortality and dementia risk. This was also the first analysis in an unselected population to account for both illness severity as well as baseline dementia.

Vantaa 85+ extended these findings. The analyses showing an association with greater dementia severity scores corroborated the conclusions from the Fong study, but in a larger and unselected sample. The random-effects models of the longitudinal trajectories had also not previously been attempted. Altogether, the Vantaa 85+ study could be regarded as the largest and most comprehensive assessment of cognitive outcomes after delirium, and the first in an unselected population.

8.3.3   Biological underpinnings

8.3.3.1   *Previous state of knowledge*

Substantial work has been done in clinical and animal models of delirium, and the putative pathophysiology of delirium was described in Section 1.4. However, none have been able to take a whole-population perspective, and none had related findings to clinical neuropathology.

8.3.3.2   *Specific contribution to knowledge*

The neuropathology analyses in Vantaa 85+ alone suggested a possible interaction between delirium, dementia and neuropathology. EClipSE was powered to test these interactions more conclusively. The EClipSE study adds data from two further population cohort studies and therefore reports the largest analysis to date of the relationship between delirium and trajectories of cognitive decline. As such, it is also the first study sufficiently powered to show that this decline is beyond that expected for conventional dementia-related neuropathology. Delirium, and/or its precipitants, appear to act through unmeasured neuropathological processes, and should be considered as an independent and additive mechanism for cognitive impairment in late life. As such, these findings challenge the current paradigm for the biopathological basis of

dementia, arguing for a broader understanding of the pathophysiology of cognitive impairment in late life.

8.4 Conclusions

This thesis has sought to understand the impact of delirium on cognitive outcomes in population samples, adding to the emerging evidence that delirium can be a critical event in cognitive decline. This work has shown that after an episode of delirium, there are implications for dementia prognosis. Prospectively linking delirium with permanent decrements in cognitive function challenges the construct of dementia because it suggests that dementia pathophysiology may be affected by processes outside the brain, e.g. peripheral infection. This appears to act over and above mechanisms already known to be pathological in dementia, such as tau phosphorylation or amyloid cleavage, opening up novel areas of research.

This final section examines how the conclusions of this thesis, in the context of previous work, might contribute to an understanding of the nature of the association between delirium and dementia. Firstly, the methodological difficulties of investigating the inter-relationship itself are outlined. Understanding these challenges allows for a more nuanced understanding of the research possibilities. Secondly, the strength of the wider evidence is summarised, along with a description of the clinical and research implications. Finally, future directions for the field are considered.

8.4.1 Methodological challenges for studying delirium and dementia

Three particular difficulties apply to research in delirium with respect to dementia: (1) the phenomenological constructs around delirium superimposed on dementia; (2) identifying apparently new cognitive deficits after an episode of delirium may be confounded by

undiagnosed dementia; (3) predisposing and precipitating factors accounting for cognitive decline and these factors must be adequately adjusted for when examining the independent effect of delirium on cognitive outcomes.

8.4.1.1 Phenomenology of delirium and dementia

The prevailing view is often that delirium and dementia are phenomenologically distinct. As dementia is the major risk factor for delirium, delirium superimposed on dementia is very common. However, there is likely to be widespread under-diagnosis of superimposed delirium, under an assumption that observed cognitive deficits are due to dementia. Delirium symptoms can persist for months or even years, and therefore potentially related conditions of 'persistent delirium' and 'reversible dementia' blur the boundaries between these syndromes of cognitive dysfunction (Inouye 2006; Cole et al. 2009) (Section 2.1.2.2.). More detailed characterisation of the neuropsychology when delirium and dementia co-exist is required, both for clinical diagnostic purposes as well as for research standardisation.

8.4.1.2 Temporal sequence and undiagnosed dementia

In hospital series, when cognitive deficits are described after an episode of delirium (or delirium itself it persistent), it is difficult to be certain to what degree these deficits are new. That is, to what extent can residual impairments be attributed to delirium, or were such impairments actually pre-existing, yet unrecognised, dementia? Some studies following hospitalised patients have sought to derive retrospective measures of pre-delirium cognition (e.g. IQCODE), though this is probably imperfect (Rockwood et al. 1999; Gruber-Baldini et al. 2003; Wacker et al. 2006; Furlaneto et al. 2007; Kat et al. 2008). This inferential limitation is a principal justification for the epidemiological work in prospective studies and the general work of this thesis.

8.4.1.3 Adjusting for precipitating and predisposing factors

Theoretically, any apparent association between delirium and dementia should adjusted for predisposing and precipitating factors in order to assess the independent effect of delirium. How

these constructs are measured and operationalised is not straightforward (Section 2.1.2.4.). Few have been validated in relevant populations and others need revision in light of secular trends (e.g. Charlson co-morbidity score, originally described in 1986). In addition, given that causal pathways in delirium pathophysiology are yet to be fully elaborated, careful choice of covariates is essential to avoid the possibility of over-adjustment. In this respect, there may be merit in considering the marginal structural models that have a role in causal inference, though to date, these have not been used in delirium research (Robins et al. 2000; Moore et al. 2012). At the very least, it should be acknowledged that attention to the measurement of both predisposing and precipitating factors should be an integral component of delirium studies. Broader agreement on how to measure and standardise these variables in clinical epidemiological studies would greatly facilitate progress in the field.

8.4.2   Evidence for delirium leading to dementia

8.4.2.1   *Epidemiological evidence*

As outlined in Section 2.3, prospective studies more reliably establish the temporal sequence between baseline cognitive function, incident delirium and subsequent cognitive impairment. This approach has shown that cognition can decline after hospitalisation (from any cause) (Ehlenbach et al. 2010; Wilson et al. 2012a), and after severe sepsis (Iwashyna et al. 2010). However, as above, none of these cohort studies specifically considered delirium. On the other hand, it is possible that systemic inflammation may lead to accelerated rates of cognitive decline in dementia, even in the absence of delirium (Holmes et al. 2009). Ascertaining delirium in the context of an epidemiological survey is challenging, and efforts to date have relied on retrospective measures. Nonetheless, incident delirium has consistently shown to adversely affect cognitive decline (Section 2.3, Chapters 5 and 6).

Together, these epidemiological cohorts show that delirium may be a determinant of cognitive trajectories. Moreover, the pathological substrates may be different to conventional dementia

pathology. The possible mechanisms underlying this relationship are discussed below (Section 8.4.2.3. Experimental evidence). Though further research is necessary, at the very least it could be argued that the pathological paradigm for dementia must include some concept of how acute changes in mental status can signal more permanent underlying neuronal damage.

8.4.2.2 Clinical populations

Though studies in clinical populations have less external generalisability, prospective studies in this group have the advantage over community studies in that there are usually better opportunities to characterise the delirium episode. Two studies identified by systematic review (Section 2.3.) suggested that long-term cognition could be adversely affected by peri-operative delirium in elective surgery (Bickel et al. 2008; Saczynski et al. 2012).

In critically unwell patients, finding persistent cognitive impairments in previously young healthy persons after an ICU admission has led to a new paradigm as far as brain care during critical illness. Diffusion tensor imaging and cortical volumetric analyses found that longer duration of delirium was associated with more white matter disruption and smaller brain volume respectively and, both these correlated with worse cognitive scores 12 months later (Gunther et al. 2012; Morandi et al. 2012b) (Section 1.4.2.2.). These findings have been confirmed in a much more comprehensive multi-centre study of 821 ICU admissions with a median age of 61 years, assessing the independent effects of delirium duration and sedative exposure, adjusting for a wide range of confounders (Pandharipande et al. 2013). At follow-up, global cognitive scores were found to be between 1 and 2 standard deviations below what might be expected for the general population, i.e. a significant proportion of participants had scores in the range of individuals with mild cognitive impairment or frank dementia. Longer duration of delirium was associated with worse cognitive scores at both 3 and 12 month follow-up. Taken together, these findings in ICU populations indicate that duration of delirium exposure is progressively

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associated with long-term cognitive impairment, independent of burden of illness severity and pre-morbid co-morbidities.

8.4.2.3 *Experimental models*

8.4.2.3.1   Animal models

Though delirium is clinical complex and heterogeneous, experimental models provide an opportunity to explore specific pathophysiological pathways in delirium and dementia (Section 1.4.1.)(Cunningham et al. 2013). As highlighted above, any clinically relevant experimental approach to delirium must capture both predisposing and precipitating dimensions. Murine models for this have specifically been developed using various methods of mimicking predisposing dementia (prior pathology) with a superimposed inflammatory challenge to simulate bacterial or viral infection (e.g. lipopolysaccharide and poly I:C respectively) (Field et al. 2010; Murray et al. 2012b). In these models, prior pathology has been induced by either neurodegeneration associated with prion infection (Cunningham et al. 2005; Murray et al. 2012b), or through selective and partial lesioning of the cholinergic projections of the basal forebrain (Field et al. 2012). In these mice, acute peripheral inflammation leads to acute deficits cognition and motor function, and these behavioural effects are consistent regardless of the underlying prior pathology.

Where neurodegeneration has led to microglial priming, it has been shown that these microglia elaborate a more aggressive inflammatory cytokine response during peripheral inflammation (Cunningham et al. 2005). This cytokine response may be responsible for the acute and transient cognitive deficits observed during T-maze testing, but in themselves lead to further neurodegeneration (Cunningham et al. 2009). However, microglial priming was not essential for the same deficits reproduced in cholinergically deficient mice, which could be blocked by donepezil (Field et al. 2012). Therefore, the interplay between acetylcholine deficiency and

microglial priming requires better definition. Nonetheless, these models have begun to explore pathophysiological pathways that may identify future targets for intervention. In the progressive neurodegeneration model, microglia express cyclo-oxygenase (COX) 1 and synthesise prostaglandins. Inhibition of this using COX-1 selective inhibition or indeed ibuprofen is protective against systemic LPS or IL-1 induced cognitive deficits (Griffin 2013). There is not yet direct evidence that the delirium *per se* and the concurrent neuronal death actually occur by the same mechanisms. However, it has been shown in other murine models that lipopolysaccharide in itself can result in generation of nitric oxide, inducing neuronal apoptosis and persistent cognitive deficits (Semmler et al. 2005; Weberpals et al. 2009).

8.4.2.3.2 Clinical models

Investigations into biomarkers for delirium are still in their infancy, though some have focused on putative pathophysiological links between delirium and dementia in clinical populations (Hall et al. 2011; Khan et al. 2011). Insofar as the biological mediators of delirium may result in permanent neuronal damage, four systems have come to attention: specific Alzheimer's pathology, S100B, cortisol, and inflammatory cytokines.

In a cohort of individuals with hip fracture, postoperative delirium was strongly associated with premorbid cognitive decline, though this was not associated with CSF Aβ1-42, tau, and phosphorylated-tau levels (Witlox et al. 2011), This was underpowered to detect mediating pathways between premorbid cognitive impairment, biomarkers of Alzheimer's pathology and subsequent delirium. Nonetheless, consistent with the Vantaa study of epidemiological pathology, postoperative delirium might be taken to arise through pathophysiological pathways distinct from Alzheimer's disease.

S100B, a marker of astrocyte damage, has been shown to be elevated in delirium, both in plasma and in CSF (Van Munster et al. 2010b; Hall et al. 2013).

The hypothalamus-pituitary-adrenal (HPA) axis may be dysregulated in delirium and dementia. Chronic hypercortisolaemia is directly cytotoxic (e.g. cognitive impairment in Cushing's disease) and aberrant stress responses may be a core feature of delirium (Seckl et al. 1995; MacLullich et al. 2008). Moreover, neurodegeneration in the limbic system may lead to inappropriately sustained cortisol after a stress response, and delirium itself is associated with elevated CSF cortisol (Pearson et al. 2010; van Munster et al. 2010a; Bisschop et al. 2011; Colkesen et al. 2012).

Though these studies are small and require cautious interpretation, this accumulating evidence lends support for the impact of delirium itself contributing to and/or being a mediator of permanent cognitive impairment. Future human studies with careful baseline characterisation of cognitive function, control for confounding factors, and long-term follow-up, including neuropsychological testing and neuroimaging, will be helpful to address this important area.

8.4.2.4   *Implications of viewing delirium and dementia as being inter-related*

8.4.2.4.1   Clinical

The prompt diagnosis and management of delirium is manifestly clinically important. However, additional urgency should arise from the recognition that 'brain care' for delirium could contribute to the secondary prevention of dementia and chronic cognitive impairment. Moves in England and Wales to link hospital remuneration to delirium and dementia screening in inpatients aged ≥75 (Commissioning for Quality and Innovation payment framework) will lead to better detection. Persons with delirium diagnosed in hospital should be routinely seen at outpatient follow-up, and this should be integrated with appropriately resourced memory services.

Delirium prevention has been most successful with multicomponent interventions in both medical and surgical series (Inouye et al. 1999; Marcantonio et al. 2001). In particular care,

should focus on an enabling environment such that cognitive, but also functional preservation should be prioritised.

8.4.2.4.2   Research

Delirium may serve as an important model system for research, offering a unique approach to advance our understanding of cognitive disorders and dementias more generally. The frequency and acuity of delirium and its associated serious adverse outcomes make it a promising area for investigation. The development of delirium may help to identify persons who are vulnerable to cognitive decline through genetic predisposition or through the presence of unrecognised dementia. Indeed, if the magnitude of illness precipitants could be quantified, then this could offer a measurement of remaining cognitive reserve.

Investigation of delirium also provides a window to observe the link between brain pathophysiology and behavioural manifestations, which may hold broader implications for other neurologic and psychiatric disorders. Moreover, advancing the understanding of the pathogenesis of delirium will be critical to identify preventable factors which can lead directly to neuronal injury, and thus, permanent cognitive sequelae. Finally, though most dementia intervention trials have chosen to recruit persons with mild cognitive impairment, the group of individuals post-delirium, cognitively-recovered might be a better a population in whom to detect treatment differences. Indeed, targeting delirium for new therapeutic approaches may offer the sought-after opportunity for early intervention, preservation of cognitive reserve capacity and prevention of permanent cognitive damage, which may potentially delay or halt the progression to dementia.

8.4.3   Future recommendations for epidemiological study designs

This section ties together the overall findings from this thesis to suggest directions for future work in delirium epidemiology. A program of work such as this would have the following aims:

(1) To characterise more precisely the temporal relationship between delirium and trajectories of cognitive decline.

(2) To understand which clinical aspects of delirium (e.g. duration, severity or aetiology) most strongly determine cognitive outcomes.

(3) To use the infrastructure from epidemiological cohorts as a platform for investigating biological underpinnings, e.g. delirium biomarkers.

(4) The scope of this research should be broad (in whole populations), perhaps adopting a life-course perspective.

8.4.3.1 Population

The conclusions from both systematic reviews (Sections 2.2 and 2.3) indicate that there are very few population-based studies assessing delirium prevalence. However, it is probable that point-prevalence of delirium in the community is low. Nonetheless, the value of these studies is that they describe an approach to characterising a base population, with the possibility of enriching it with groups likely to eventually yield more incident delirium cases (older, persons with pre-existing cognitive impairment). Therefore, though the point-prevalence at any given moment may be low, in persons aged ≥85 years, the one-month period-prevalence may be as high as 25%. More intensive follow-up of higher risk subsamples – randomly selected to maintain external generalisability – has been successfully employed in CFAS and CC75C for dementia ascertainment and delirium could be usefully considered in conjunction.

Though issues of consent and capacity were not detailed in this thesis, these must be addressed in the recruitment of representative populations. The ethical framework for approaching this has been reviewed elsewhere, and this highlights the need to protect vulnerable participants while also asserting the equal moral status for persons with delirium to have their condition researched in a valid way (Holt et al. 2008; Sweet et al. 2013). Other studies have also demonstrated that methods used to assess capacity, including individuals with fluctuating capacity, had an effect on the research conclusions, depending on whether persons were included or excluded according to

capacity status (Adamis et al. 2010). In some circumstances, the use of proxy consent, especially for low-risk studies, may be a practical option.

8.4.3.2   Case-ascertainment

From systematic review in Section 2.3, the next steps would be to establish a system whereby acute changes in mental status can be identified (e.g. via GPs). As in the OXVASC study (Section 2.1.1.1), this requires excellent links between hospital and community services. Use of GPs to notify study personnel of acute changes is likely to need dedicated resources to be effective. A brief screening instrument would be the first step for case-ascertainment. It is not known if delirium can be optimally diagnosed, investigated and treated in the community, and the study should have access to clinical personnel able to determine the need for hospitalisation.

Once in secondary care, longitudinal delirium assessments must try to account for temporal fluctuations. Information on delirium severity and duration in relation to long-term outcomes would be an important and new finding in the general population. The assessment of candidate biomarkers could be incorporated both at this stage, and earlier – as an assessment of delirium vulnerability. The optimum examination schedule will be based on resources and patient tolerability. They may range from several (shorter) assessments several times daily, or in other settings e.g. long-term care, twice-weekly assessments may be sufficient (Cole et al. 2012). In addition, the frequency of assessments minimises the risk of misclassification bias.

8.4.3.3   Attrition and missing data

Procedures for determining outcomes need to be reliable, using data from multiple, overlapping sources. Missing data are to some degree unavoidable and analyses must account for these with appropriate estimations of standard error. The random-effects models used in the cohort studies identified in the systematic review are generally flexible in this regard. However, missing data may well arise when competing outcomes are at play, for example when dementia *or* death might

follow delirium. Here, data on post-delirium cognition is 'missing' because of intervening death between resolution of the delirium and next follow-up in the cohort study. Techniques such as multi-state, or shared parameter models might be considered.

8.4.3.4   Residual confounding

Within the assessments for delirium and serial cognition function, other clinical factors need to be accounted for. Measurement of predisposing factors – e.g. age, sex, education, functional frailty, depression – needs to be embedded in the assessment schedule and standardised with the same degree of precision as the delirium and cognitive variables. Illness severity may be more complex to capture, but basic physiological parameters (such as those that comprise early warning score systems) have the advantage of being brief, reproducible, non-invasive and repeatable. Repeatability is an important dimension as these measures of physiological disturbance can then be tracked alongside fluctuations in delirium state.

8.4.3.5   Final comments

Acknowledging delirium as a determinant of chronic cognitive impairment obliges us to broaden our understanding of dementia. In recognising that otherwise slowly evolving neurodegenerative processes may be accelerated by delirium and/or its precipitants, future work needs to consider the long-term impact of acute illness on the vulnerable brain.

Many questions of direct clinical relevance to the understanding and management of delirium could be addressed by a convincingly designed observational study. Starting with a cognitively characterised, unselected base population, tracking individuals longitudinally in and out of hospital settings, is essential. Case-ascertainment would benefit from a more standardised application, perhaps including a battery of objective tests alongside conventional subjective assessments, in consensus conferences and/or algorithmic operationalisation. Fluctuating symptoms are a core feature of delirium, and this will not be reliably captured without specific

attention to how this is to contribute to case-ascertainment. Despite these challenges, efforts will be rewarded by generating methodologically rigorous clinical data applicable to the broad generality of patients with delirium.

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10 Appendix

10.1 Search strategies for systematic review 1

Search strategy for identification studies of descriptive epidemiology of delirium in community populations

MEDLINE (Ovid SP) search strategy
1. exp Delirium/ep [Epidemiology]
2. delirium.mp or "acute confusion".mp or "metabolic encephalopathy".mp
3. 1 and 2
4. community or population

10.2 Search strategies for systematic review 2

Search strategy for identification of cohort studies of dementia which include delirium

MEDLINE (Ovid SP) search strategy
1. exp Cohort Studies/
2. cohort.ti,ab.
3. longitudinal.ti,ab.
4. follow-up.ti,ab.
5. "*year risk".ti,ab.
6. (prospective adj2 (study or analysis or evaluation)).ti,ab.
7. epidemiologic studies/
8. "observational study".ti,ab.
9. "preclinical detection".ti,ab. OR predict*.ti.
10. Disease Progression/
11. or/1-10
12. (dement* OR "cognit* impair*").ti.
13. (alzheimer* or AD).ti.
14. exp Dementia/di [Diagnosis]
15. exp Dementia/ep [Epidemiology]
16. *Cognition Disorders/di [diagnosis]
17. ((endpoint* or outcome*) adj6 (dement* or alzheimer* or AD)).ab.
18. (conversion adj4 (dement* or alzheimer*)).ti,ab.
19. (convert* adj4 (dement* or alzheimer* or AD)).ti,ab.
20. (predict* adj6 (dement* or alzheimer* or AD)).ti,ab.
21. (progress* adj4 ("to dement*" or "to alzheimer*" or "to AD")).ti,ab.
22. or/12-21
23. "Predictive Value of Tests"/
24. (dement* or alzheimer* or AD).ti,ab.
25. 23 and 24
26. Neuropsychological Tests/
27. (dement* or alzheimer* or AD or "cognit* impair").ti,ab.
28. 26 and 27
29. or/22,25,28
30. 11 and 29
31. (animals not (humans and animals)).sh.
34. 32 not 33
35. exp Delirium/
36. delirium.mp or "acute confusion".mp or "metabolic encephalopathy".mp
37. 35 and 36
38. 37 and 34

10.3 Delirium questions

10.3.1 CC75C

Test	Source	Question
CAMDEX	Examination	20 to 1
	Examination	Serial 7s
	Informant	Drowsiness / clouding
	Informant	Impaired ability to focus, sustain and shift attention
	Informant	Has there been a sudden worsening in mental confusion in recent weeks or months, which has continued to the present time?
	Informant	Are there episodes lasting days or weeks when his/her thinking seems quite clear and then becomes muddled?
	Informant	Are there brief episodes during 24 hours when he/she seems much worse and then times when quite clear?
	Informant	Is the confusion worse towards dusk or the evening?
	Informant	How long have these changes been present (months)?
	Judgement	Primary psychiatric diagnosis of present condition
	Judgement	Recent acute physical illness (i.e. weeks or rarely months duration)
RInI	Informant	Did his/her thinking seem muddled?
	Informant	Were there episodes lasting days or weeks when his/her thinking seemed quite clear and then became muddled?
	Informant	Were there brief episodes during the 24 hours when he/she seemed much worse and then times when quite clear?
	Informant	Was the confusion worse towards dusk/evening?
	Informant	Did he/she suffer confusion or delirium during his/her final illness

10.3.2 CFAS

Test	Source	Question
Prevalence screen	Judgement	Errors made in clouded consciousness, i.e. subject was falling asleep, under the influence of alcohol, drugs or delirium due to acute physical illness. The individual will be very distractible, unfocussed and may drift in and out of consciousness. Often worse in the evening and afternoon
Incidence (re-)screen	Judgement	Errors made in clouded consciousness, i.e. subject was falling asleep, under the influence of alcohol, drugs or delirium due to acute physical illness. The individual will be very distractible, unfocussed and may drift in and out of consciousness. Often worse in the evening and afternoon
	Examination	Serial 7s
Assessment	Examination	20 to 1
	Examination	Serial 7s
	Judgement	Impaired ability to focus sustain and shift attention
	Judgement	Errors made in clouded consciousness
Combined	Judgement	Errors in clouded consciousness
	Examination	20 to 1
	Examination	Serial 7s
	Judgement	Repeatedly falls asleep
	Judgement	Sleepy, but not asleep
	Judgement	Attention impairment
HAS	Informant	Has there been sudden worsening in mental confusion in recent weeks or months, which has continued to the present time?
	Informant	Are there episodes lasting days or weeks when his/her thinking seems quite clear and then becomes muddled?
	Informant	Has s/he been troubled by voices or visions not experienced by others?
	Informant	Are there long periods during the day when s/he is lucid and not confused (that is, knows where s/he is and knows what s/he is doing and saying)?
	Informant	Does s/he get confused at night, wander about or talk nonsense?
	Informant	Or at any other time? What about during the day time?
	Informant	How long has this difficulty been present (months)?
	Judgement	Could a physical illness (not drugs or alcohol intoxication) be sufficient explanation for the subject's mental or psychiatric symptoms (e.g. delirious due to acute infection)?
	Informant	Disturbance of consciousness, that is either being sleepy, or awake but unaware of their surroundings
	Informant	Or drowsy now?
	Informant	Is s/he physically ill at present?
	Judgement	Rate if actively physically ill.

(continued)

RInI	Informant	Had there been an abrupt change towards mental confusion in the period before the final illness?
	Informant	Were there periods lasting days or weeks when his/her thinking still seemed quite clear?
	Informant	Were there brief episodes during the 24 hours when s/he seemed much worse and then times when quite clear?
	Informant	Did s/he become completely normal when the confusion cleared?
	Informant	Was the confusion worse towards dusk or evening?
	Informant	Were there marked fluctuations in his/her level of attention or alertness?
	Informant	How long had the confusion been present (months)?
	Informant	Do you think there was anything specific that caused these changes?

10.4 Neuropathology methods

10.4.1 Vantaa 85+

Paraffin-embedded tissue samples were assessed for neuropathology. All specimens were performed by one pathologist using exactly the same dissection and examination protocol, blinded to all clinical data. The protocols for assessing Alzheimer-type (Polvikoski et al. 2006), vascular (Rastas et al. 2007; Ahtiluoto et al. 2010), and Lewy body (Oinas et al. 2009) pathologies have been described previously. After fixation (phosphate-buffered 4% formaldehyde for at least two weeks), samples were obtained from the middle frontal, superior temporal and middle temporal gyri, and inferior parietal lobule, according to the standard Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (Mirra et al. 1991).

10.4.1.1 Alzheimer pathology

10μm sections were stained with a modified Bielschowsky method for neuritic pathology (Mirra et al. 1991). For scoring, the maximum density of the neuritic plaques was evaluated in the cortical sections. Tissue blocks were embedded in polyethylene glycol 1,000 and then cut (80μm) for free-floating staining with the Gallyas silver method for neurofibrillary pathology (Kondoh et al. 1993). Apolipoprotein E (ApoE) genotyping was performed using a combination of polymerase chain reaction and solid-phase minisequencing technique (Syvanen et al. 1993). Braak

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stage is a semi-quantitative measure of neurofibrillary tangle load (Braak et al. 1991), and was performed without knowledge of clinical diagnosis, neuritic plaque score or ApoE genotype.

10.4.1.2 *Vascular pathology*

Cavitary lesions or solid cerebral infarcts visible to the naked eye were identified by examination of the intact brain and from 1-cm-thick coronal slices of the cerebral hemispheres, from 5-mm-thick transverse slices of the brain stem and sagittal slices of the cerebellum. These lesions were histologically ascertained to be infarcts ($\geq$10mm diameter), lacunes (<10mm) or haemorrhages.

10.4.1.3 *Lewy body pathology*

For the assessment of Lewy body pathology, brain samples were obtained following recommendations of the First DLB Consortium International Workshop (McKeith et al. 1996) and assessed for changes in α-synuclein pathology (McKeith et al. 2005). Sections of the substantia nigra were stained with the haematoxylin and eosin (H&E) method and with antibodies against α-synuclein. If any Lewy bodies were detected in the screened areas, the immunohistochemistry for α-synuclein was performed on cortical samples. The type of α-synuclein pathology (none, brainstem-predominant, limbic, diffuse neocortical) was determined for every participant (Oinas et al. 2009). A semiquantitative grading of the cell loss/atrophy in the ventrolateral tier of SN pars compacta was determined from none (0) to severe (3), as reported earlier (Oinas et al. 2009).

10.4.2 Cambridge City over-75s Cohort

After death, the brains were removed as soon as feasible in the local mortuary. The brains were cut in the sagittal plane. One hemisphere was dissected coronally into approximately one cm slices, macroscopically examined, and snap frozen at −80∘C. All assessments were performed blind to clinical status by neuropathologists at Addenbrooke's Hospital, Cambridge, UK.

10.4.2.1 Alzheimer pathology

The CERAD protocol was followed. Typical Alzheimer's lesions were considered by taking the CERAD ratings for neuritic plaques, diffuse plaques, and neurofibrillary tangles in the following areas: entorhinal, hippocampal, frontal, temporal, parietal, and occipital. Ratings for tau reactive tangles were estimated according to Braak stage and ratings for neuritic amyloid-β-reactive plaques were estimated according to the age dependent CERAD protocol for all areas.

Tau and amyloid-β protein were assessed on immunohistochemical preparations using antibodies obtained from the Cambridge Brain Bank Laboratory. Anti-tau antibody (mAb 11.57) was used to immunostain neurofibrillary tangles, neuritic plaques, and dystrophic neurites. Plaques were assessed using anti-amyloid-β antibody (DAKO (M872) Clone 6F/3D). Diffuse amyloid-β-reactive plaques were distinguished from neuritic plaques by the presence or absence of dystrophic neurites. All sections were counterstained with Ehrlich's haematoxylin with 3,3'-diaminobenzidine as the chromagen.

10.4.2.2 Vascular pathology

Microinfarcts, irrespective of age of infarct, were assessed by their presence or absence in the following areas: entorhinal, hippocampal, frontal, temporal, parietal, occipital, deep grey, and other neocortical and subcortical areas. White matter pallor was assessed as present or absent in the occipital, parietal, frontal, temporal cortices, and as pallor in the deep white matter or internal capsule in slides containing the basal ganglia.

Macroscopic vascular burden was assessed by the number, size, and location of visible macrovascular lesions in any area. The age of the infarct or whether they were present in grey or white matter was not noted. The arterial distribution for the largest infarct involved was recorded. Number of lacunes was recorded in categories of 0, 1–4, 5–9, or 10 or more in each of the following locations: basal ganglia, thalamus, cerebral white matter, brainstem, and other. For

diagnostic purposes, blocks for paraffin embedding were taken from: the hippocampus (at the level of the lateral geniculate body), entorhinal cortex (at the level of the mammillary body), frontal, temporal, parietal, and occipital lobes, the basal ganglia, thalamus, pons, medulla, cerebellum, and from two levels of the midbrain. The tissue blocks included subcortical white matter, deep cerebral white matter, and the internal capsule.

Ten micrometre thick sections were stained with haematoxylin and eosin to qualitatively assess white matter pallor, perivascular gliosis, presence of microinfarcts, and microvascular changes in each area sampled. Separate scores were recorded in white and grey matter for V-R space expansion, perivascular gliosis, and microinfarcts. Small-vessel disease was defined as presence of white matter pallor, perivascular gliosis or 'other' microscopic vascular disease.

10.4.2.3 Lewy body pathology

Lewy bodies were assessed by their presence or absence in entorhinal, hippocampal, frontal, or temporal areas and, in addition, in the substantia nigra, nucleus basalis, dorsal raphe nucleus, locus coeruleus, and dorsal vagal nucleus. Sections were either immunolabelled with anti-ubiquitin antibody (pAb BR 251 DAKO Z0458, early cases) or anti-α-synuclein antibody (Biomol International SA3400, later cases), or stained with haematoxylin and eosin to visualise Lewy bodies.

10.4.3 MRC Cognitive Function and Ageing Study

At necropsy, frozen samples of brain tissue were removed for storage. The remainder of the brain was fixed for standardised assessment on paraffin-embedded tissues, following the CERAD protocol with minor modifications (see the MRC CFAS website: www.cfas.ac.uk). Neuropathological examination was carried out without knowledge of clinical or interview data, with semiquantitative rating of specific lesions and a prediction of clinicopathological preliminary diagnosis, according to likely importance. To ensure consistency between the centres, inter-rater

reliability was addressed at the start of the study, including circulation of macroscopic brain photographs and microscopic slides.

10.4.3.1 Alzheimer pathology

Amyloid protein pathology and neurofibrillary tangles (NFTs) were assessed in the hippocampus (CA1), entorhinal cortex and in the frontal (Brodman Area 8/9), temporal (BA21), occipital (BA17/18) and parietal (BA7) lobes. Severity of pathology was scored as none, mild, moderate, or severe. Plaque pathology was assessed with Congo red, silver stains (including Bielschowsky, Palmgren and Gallyas), or immunohistochemistry. NFTs were assessed with immunohistochemistry (mAb AT8 or mAb 11/57). All slides were counterstained with Ehrlich's haematoxylin and visualised with 3,3'-diaminobenzidine. For this analysis, burden of classical AD features was taken from the CERAD ratings in the entorhinal and hippocampal regions combined and in the neocortex. Each variable was defined as the maximum score in each region.

10.4.3.2 Vascular pathology

Vascular pathologies were assessed for each area examined using haematoxylin-eosin slides. Cerebrovascular pathology measures included the presence or absence of haemorrhages, infarcts (parenchymal ischemic lesions >10 mm), lacunes (parenchymal ischemic lesions <10 mm) and small vessel disease (diffuse pallor of myelin staining in white matter associated with hyaline degeneration of subcortical arteries and arterioles, micro-infarcts or a combination of these features).

10.4.3.3 Lewy body pathology

Lewy bodies (LB) were identified using hematoxylin-eosin and ubiquitin immunohistochemistry in the cortices, locus coeruleus, substantia nigra, nucleus basalis of Meynert, raphe nuclei, and dorsal efferent nucleus of vagus nerve.

10.5 Pilot study – notes abstraction

10.5.1 Methods

30 participants in CC75C with at least five study visits were selected from 34 eligible participants. All components of the case records (medical, nursing, physiotherapy, etc.) were comprehensively reviewed. Any reference to cognitive or higher neurological symptoms were recorded, along with the time, date and clinical experience of the commentator. In this way, it was possible to build a summary of clinical reports of cognition during the admission. Information on medications, co-morbidities, and physiological parameters (heart rate, blood pressure, oxygen saturation, urea / creatinine, CRP) were also recorded. All assessments of case notes were performed blind to study data. A typical extract is reproduced below:

18/06. 13:00	NS	"appears increasingly confused during morning"
18/06. 21:40	Med	"confused at times"
19/06. a.m.	NS	"Disorientated to place"
19/06. 20:00	Med	"well, orientated"
20/06. 07:00	NS	"appears orientated to ward"
21/06. 03:00	NS	"one episode of confusion noted earlier in evening"
21/06. 21:00	NS	"seems confused at times"
24/06. 04:30	NS	"disorientated early evening, but settled well"

10.5.1.1 Exposure

These symptoms were mapped to items in DSM-IV. For the purposes of the pilot project, DSM-IV criteria were applied by a single assessor (DD), however it is envisaged that this process will eventually be subject to assessment at a consensus conference. Delirium was recorded as total

days spent in hospital with evidence of delirium. At each analysis of hospital records, delirium was coded as:

- Probable delirium, where the total record suggested symptoms sufficient to satisfy the CAM algorithm of DSM-IV criteria

- Possible delirium, where the total record suggested symptoms of altered cognition, but not sufficient to meet DSM-IV criteria

This analysis only considered those with probable delirium. Probable and possible delirium were regarded as mutually exclusive.

10.5.1.2 Outcomes

Dementia diagnosis in CC75C is based on a consensus according to DSM-IV criteria, though this is not currently available in the whole cohort. For this pilot, the working definition for cognitive impairment / dementia was taken as MMSE 0—20 (n=13). There were insufficient participants to use a more specific cut-off: MMSE<18 (n=6). While this classification was not decided *a priori*, it was deemed acceptable for the purposes of a pilot study.

10.5.1.3 Statistical Analyses

Associations between delirium and dementia were modelled using logistic regression, adjusting for age, sex and education. Analyses were restricted to delirium events occurring prior to follow-up in CC75C. Power calculations for the wider PhD project are based on estimates from this pilot study and those Vantaa 85+, assuming $\alpha=0.05$ and $\beta=0.8$. To allow for misclassification bias, the upper 90% CI for controls were compared to lower 90% CI for cases (two tailed test), and sample size calculated by the Kelsey method (Kelsey et al. 1996).

After receiving specific training in the chart abstraction, this pilot study has been repeated by a medical student. The level of agreement between the data awaits full assessment.

10.5.2 Results

The mean age of participants at study entry and death was 78 years (SD 2.2) and 96 years (SD 3.0) respectively. The total number of admissions reviewed over an average of 18 years follow-up was 143, with mean of 4.8 admissions per participant over the entire adult medical record.

From age 65 years, 85 admissions showed no evidence of delirium, 31 admissions had evidence of probable delirium (duration ranging from 1 to 71 days) with a further 18 admissions with evidence of possible delirium.

Because the cognitive outcomes are derived from the measures at the study interview, the participants are limited to those in whom hospitalisation was followed by at least one study visit (n=7). Those participants who never had delirium can also be included in the denominator (further n=11). The association between delirium and subsequent dementia was strong (age-adjusted OR = 21 (95% CI 1.3 to 300)).

The two estimates of delirium prevalence in controls (pilot 0.15; Vantaa 0.22) and cases (pilot 0.8; Vantaa 0.7) yielded an estimated total sample size of 150, where cases and controls are matched 1:1.

10.5.3 Discussion

The estimated prevalence of delirium at any given hospital admission is 23% (31 probable cases in 134 admissions). This is in keeping with hospital point-prevalence studies of delirium (Siddiqi et al. 2006). The OR for history of delirium in those with dementia is consistent with the Vantaa study, though the confidence intervals are very wide due to the small sample size. However,

power calculations suggest that there are sufficient participants available in the EClipSE studies to investigate the relationship in more detail.

Abstraction of information from hospital records is feasible in terms of: (i) consent to access notes; (ii) retrieval (if deceased within last ten years); (iii) deriving information on altered mental status due to acute conditions. Clinical information can be assessed (by consensus) to determine if sufficient evidence for a retrospective diagnosis of delirium (based on CAM operationalisation of DSV-IV criteria) can be made. The derived exposure can be demonstrated in cases (dementia) and controls, in proportions consistent with delirium measures in Vantaa.