# The DECIDE Study:

# Delirium and Cognitive Impact in Dementia

A nested, prospective, longitudinal cohort study exploring the impact of delirium on cognitive outcomes

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## Abstract

*Background:* Delirium is a severe neuropsychiatric syndrome of brain dysfunction precipitated by acute illness and characterised by acute and fluctuating inattention and other cognitive and perceptual deficits. Delirium is common, distressing and associated with poor outcomes. Previous studies examining the impact of delirium on cognitive trajectories have been limited by incomplete ascertainment of baseline cognition or a lack of prospective delirium assessments.

The DECIDE study aimed to explore the association between delirium and cognitive function over time in participants in an existing population-based cohort aged 65 years and older with known baseline cognition.

*Methods:* Over a 12-month period, surviving participants from the Cognitive Function and Ageing Study II-Newcastle were screened for delirium on admission to hospital. Baseline characteristics along with disease relevant clinical parameters were recorded. The progression/resolution of delirium was monitored. In those with and without delirium, cognitive decline and dementia was assessed at one-year follow-up. The effect of delirium on cognitive function over time was evaluated, independent of baseline cognition and illness severity, along with the predictive value of clinical parameters.

*Results:* 82 of 205 participants developed delirium in hospital during the study period (40%). 18 of the 135 participants completing one-year follow-up interviews received a new diagnosis of dementia. Delirium was associated with an increased risk of new dementia diagnosis at follow up, independent of illness severity and baseline cognition (OR 8.76 [CI: 1.85 – 41.37], p=0.006). More than 5 days of delirium and more severe delirium were independently associated with worse cognitive outcomes.

*Conclusions:* An episode of delirium whilst in hospital significantly increases risk of future cognitive decline and dementia, independent of illness severity and baseline cognition. Given that delirium has been shown to be preventable in around a third of cases, it can be proposed that delirium is a potentially modifiable risk factor for dementia.

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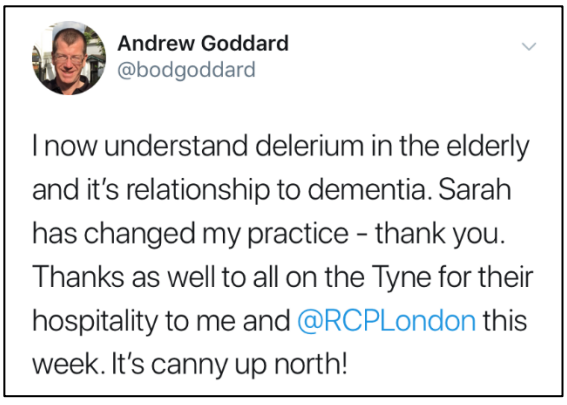
Presentation entitled ‘Does delirium increase the risk of dementia?’ at RCP Conference in Manchester, April 2019.


Photograph taken with president of Royal College of Physicans, Professor Andrew Goddard, following regional presentation at RCP Update in Medicine in Newcastle upon Tyne, November 2018 (above).




Tweet by Professor Andrew Goddard, president of the RCP, following my Quincentennial lecture in Newcastle upon Tyne, November 2018.

*Best Presentation Prize*

Presentation entitled ‘Perceptual disturbances in a population of older people in hospital: prevalence, content and association with delirium’ at Annual Conference of European Delirium Association, Oslo, November 2017.

Photograph taken accepting prize from President of European Delirium Association, Professor Alessandro Morandi.

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# Publications

## Papers arising directly from the thesis

RICHARDSON, S. J., DAVIS, D. H. J., STEPHAN, B., ROBINSON, L., BRAYNE, C., BARNES, L., PARKER, S. & ALLAN, L. M. 2017. Protocol for the Delirium and Cognitive Impact in Dementia (DECIDE) study: A nested prospective longitudinal cohort study. BMC Geriatrics, 17, 98.

## Other papers published during the thesis regarding delirium

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## List of abbreviations

| | |
|---|---|
| 4AT | 4 A's test (screening tool for delirium and cognitive impairment) |
| APACHE II | Acute Physiology and Chronic Health Evaluation II |
| AUROC | Area Under Receiver Operating Characteristic curve |
| BMI | Body Mass Index |
| CAMCOG | Cambridge Cognitive Examination |
| CAM-S | Confusion Assessment Method - severity |
| CFAS II – Newcastle | Cognitive Function and Ageing Study II Newcastle cohort |
| CFAS | Cognitive Function and Ageing Study II |
| CI | Confidence Interval |
| CIRS-G | Cumulative Illness Rating Scale – Geriatrics |
| DECIDE | Delirium and Cognitive Impact in Dementia |
| DMSS | Delirium Motor Subtype Scale |
| DSD | Delirium Superimposed on Dementia |
| DSM 5 | Diagnostic and Statistical Manual of Mental Disorders 5th edition |
| GCS | Glasgow Coma Scale |
| GMS-AGECAT | Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy |
| GP | General Practitioner |
| HABAM | Hierarchical Assessment of Balance and Mobility |
| HR | Hazard Ratio |
| I-AGeD | Informant Assessment of Geriatric Delirium Scale |
| MDAS | Memorial Delirium Assessment Scale |
| MMSE | Mini Mental State Examination |
| m-RASS | modified Richmond Agitation and Sedation Scale |
| MUST | Malnutrition Universal Screening Tool |
| OSLA | Observational Scale of Level of Arousal |
| PI | Principal Investigator |
| RAPA | Recurring Admission Patient Alert |
| RASS | Richmond Agitation and Sedation Scale |
| SAPS II | Simplified Acute Physiology Score II |
| SD | Standard Deviation |
| SOFA | Sepsis-related Organ Failure Assessment |

**Contents**

## List of tables

## List of figures

# Chapter 1: Introduction

## 1.1 Introduction

Delirium is a sudden onset cognitive impairment characterised by fluctuating inattention and deranged level of arousal precipitated by acute illness. Delirium is common, affecting at least one in five adults in hospital (Ryan et al., 2013). As well as causing considerable patient and carer distress (Partridge et al., 2013), delirium results in excess treatment costs of an additional £13,000 per hospitalisation (Akunne et al., 2012) and is independently associated with poor outcomes including mortality (Witlox et al., 2010).

Despite the considerable patient and population impact of delirium, it remains under-researched, with few high-quality studies published, and the impact of delirium on cognitive outcomes is relatively unknown. This chapter outlines how we define and diagnose delirium and provides an overview of the epidemiology of delirium, with a focus on cognitive outcomes after delirium. The limitations of current literature and the challenges involved with case ascertainment will be discussed and the potential for an observational longitudinal study to address key questions on the population impact of delirium will be introduced.

## 1.2 Case study

Mrs Smith is an 85-year-old lady who lives alone in a two-storey house in the centre of Newcastle. She has lived in the city all of her life and has lots of family and friends who live nearby and visit regularly. One Thursday afternoon, she trips and falls in Marks and Spencer. She immediately has pain in her left hip and cannot move. An ambulance transfers her to the accident and emergency department of her local hospital. Her X-rays reveal that she has broken her hip and will require an operation to replace the hip. She is admitted to the orthopaedic ward and has her operation the following day.

The night following her operation, she is found trying to climb out of bed on the orthopaedic ward by one of the nurses. She is trying to get out of bed as she believes that she is late for her train. She starts to shout when the nurse tells her repeatedly to get back into bed. Why do they not understand that she needs to get to the station to catch her train? She becomes increasingly agitated and tries to push the nurse away when she attempts to manoeuvre her back into bed. She has an aching in her hip, she feels thirsty and she just doesn't understand what is going on.

The sun eventually rises just as Mrs Smith has finally fallen asleep after a very disturbed night with lots of shouting and some 'physical aggression' reported by the nursing staff.

The physiotherapist helps Mrs Smith to walk a short distance using a frame. She notes that Mrs Smith is difficult to wake when she first arrives. She also notes that she appears not to follow instructions well and appears distracted. When Mrs Smith's family visit in the afternoon, they are worried, as Mrs Smith seems to be repetitive and somewhat disorientated. She believes that she has been in hospital for many days and tells her family that there was a fight on the ward overnight between a patient and an intruder.

Mrs Smith is diagnosed with delirium by one of the junior doctors on the ward who notes that her cognitive test scores, routinely performed on first admission, have deteriorated significantly. The doctor also acknowledges the family's concerns that this behaviour is completely out of character. They are very concerned about the sudden change they have seen in their relative. They ask the doctor on the ward:

"Will she get dementia?"

## 1.3 Definition

Delirium is a sudden onset cognitive impairment, associated with acute illness, which tends to fluctuate, often being worse at night. Delirium specifically impairs attention, with difficultly focusing, sustaining and shifting attention on a particular task, and causes derangements in level of arousal. This results in a spectrum of presentations with some people being unusually sleepy and withdrawn, known as hypoactive delirium, and others appearing agitated and restless, known as hyperactive delirium.

Delirium has been described for thousands of years. Hippocrates is thought to have recorded some of the earliest descriptions of the syndrome, using multiple terms to describe the mental abnormalities caused by fever, poisoning or head trauma including ‘phrenitis’ (a state of frenzy) and ‘lethargus’ (inertia and dulling of senses) (Adamis et al., 2007). The word delirium itself is derived from the Latin “de-lira”, meaning to go out of the furrow, and was recorded by Celsus as early as the first century AD (Adamis et al., 2007).

The first formal classification did not emerge until the third edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980. This definition has subsequently evolved and the most recent edition, DSM 5 (American Psychiatric Association, 2013), is shown in Table 1. In order to fulfil the criteria for delirium, patients must demonstrate each of the criteria A to E. Without a biological marker for delirium, these criteria are the agreed gold standard for clinical diagnosis.

| |
|---|
| A. Disturbance in **attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment). |
| B. The disturbance **develops over a short period of time** (usually hours to a few days), represents a **change from baseline** attention and awareness, and tends to **fluctuate** in severity during the course of a day. |
| C. An additional disturbance in **cognition** (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). |
| D. The disturbances in criteria A and C are **not explained by another pre-existing, established, or evolving neurocognitive disorder** and do not occur in the context of a severely reduced level of arousal, such as coma. |
| E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a **direct physiologic consequence of another medical condition**, substance intoxication or withdrawal (i.e., because of a drug of abuse or to a medication), or exposure to a toxin or is because of multiple aetiologies. |

*Table 1: American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders Version 5 definition of delirium (American Psychiatric Association, 2013)*

## 1.4 Prevalence, Incidence and Occurrence Rates

Delirium is a common complication associated with hospitalisation and has become synonymous with admission for many older people and their families.

### *1.4.1 Hospital*

The point prevalence of delirium in all adult inpatients was found to be 19.6% in a study from a 400-bed district general hospital in Ireland (Ryan et al., 2013). Importantly, the prevalence increased with age (4.7% if <50 years and 34.8% if >80 years) and varied according to setting, with the highest rates seen in geriatric medicine wards (53.3%) (Ryan et al., 2013).

These findings were replicated in a multi-centre point prevalence study from Italy with overall prevalence of delirium of 22.9% (Bellelli et al., 2016). This study included only those over 65 years of age.

When examining older patients on admission to a general medical unit in Australia, the proportion with prevalent delirium, those with delirium on admission, was found to be 18% (Iseli et al., 2007). The prevalence of delirium was slightly higher (24.6% of all admissions) in a study of routinely collected data from patients over the age of 65 admitted acutely to a hospital in Scotland (Reynish et al., 2017). Other studies of consecutive admissions to general medical or elderly care units report delirium prevalence from 10 to 31% (Siddiqi et al., 2006).

In a study from South Wales, 37% of the 278 medical patients aged 75 years and older admitted acutely to a district general hospital were found to have delirium during their admission (Eeles et al., 2010). These figures are echoed by systematic reviews which found occurrence rates per admission between 11 and 42% (Siddiqi et al., 2006) and 29 to 64% (Inouye et al., 2014) in general medical and old age medicine wards. When focusing only on new episodes of delirium during admission, or incident delirium, rates per admission ranged from 3 to 29% (Siddiqi et al., 2006).

Other areas of the hospital that see high rates of delirium are intensive care units, with between 45% and 87% of patients found to have delirium (Ely et al., 2001, Jackson and Khan, 2015) and palliative care wards, with incidence rates of 47% (Inouye et al., 2014).

The prevalence of delirium in general surgical wards was found to be comparatively low at 7.2% when examining people of all ages (Ryan et al., 2013), but incidence

rates of 26.5% were found when focusing on surgical patients over 75 years (M.M. de Castro et al., 2014) and as high as 28.6% (Ryan et al., 2013) to 41% (Albrecht et al., 2015) in orthopaedic older patients.

Although the exact figures vary considerably depending on the precise age and location of the populations studied and the time over which patients are examined, delirium remains the most common hospital acquired complication (Richardson et al., 2016b).

### *1.4.2 Community*

The number of older people living in the community with delirium is estimated to be low, with an overall prevalence around 1-2% (Inouye et al., 2014) and an estimated point-prevalence of 7.2 per 1,000 persons in those aged 55 years and older (Davis et al., 2013).

The highest rates are seen in those with dementia (79.5 per 1,000 persons) (Davis et al., 2013) and the oldest old, with 100 per 1000 persons aged over 85 years experiencing delirium over a three year period in the Vantaa 85+ study (Davis et al, 2012). A similar prevalence in those aged over 85 years (10.1%) was obtained from the Cognitive Function and Ageing Study (CFAS) although the delirium was ascertained retrospectively using an algorithmic definition derived from the Geriatric Mental State examination (Davis et al., 2014).

Higher rates of delirium are seen in care homes with a median point prevalence estimate from a systematic review of 14.2% in the United Kingdom (Siddiqi et al., 2009) and a one month prevalence of 7.1% in one particular area of the UK (Siddiqi et al., 2016). Prevalence rates were generally similar in residential (8.2%) and nursing homes (8.9%) in The Netherlands (Boorsma et al., 2012). Prevalence rates are higher (33%) in those with advanced dementia defined as a MMSE score of less than 10 (McCusker et al., 2011).

## 1.5 Aetiology

The cause of delirium is rarely due to a single factor and is most commonly due to the combination of underlying predisposing factors along with a number of contributing precipitating factors (Table 2) leading to a breach of the threshold for delirium (Figure 1).

| **Predisposing factors for delirium** | **Precipitating factors for delirium** |
|---|---|
| Older age (over 75 years) | Medications (e.g. sedatives, opiates) |
| Cognitive impairment and Dementia | Bladder catheter |
| History of delirium | Physical restraint |
| Functional impairment | Physiological (e.g. electrolyte derangement) |
| Visual impairment | Infection |
| Hearing impairment | Surgery |
| Comorbidity | Trauma |
| Depression | Emergency admission |
| Stroke | |
| Alcohol misuse | |

*Table 2: Predisposing and precipitating factors for delirium (Inouye et al., 2014)*

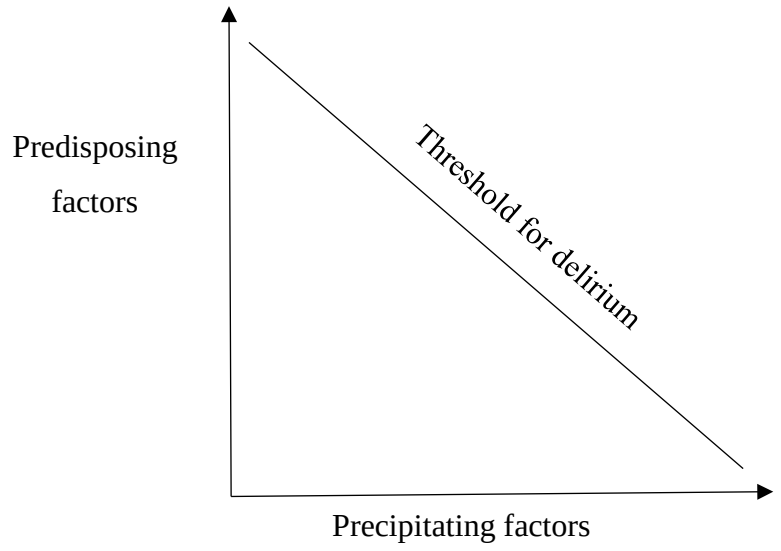



*Figure 1: Graphical representation of the threshold for delirium. The size of the insult necessary to precipitate delirium is inversely proportional to the vulnerability of the individual.*

Figure 1 demonstrates the inverse relationship between predisposing and precipitating factors when examining the threshold for delirium. Consequently, a patient who has no predisposing factors which make them vulnerable would require a very large precipitant to push them over the threshold for developing delirium. An example is a young, fit person who has a trauma, such as a road traffic collision, which results in multiple injuries, surgery and a prolonged stay in intensive care. This hypothesis is supported by the high rates of delirium seen on wards with the most unwell patients (highest precipitant). For example, over half of military personnel in intensive care following trauma (mean age 26 years) had at least one day of delirium (Bullock et al., 2015).

Conversely, in someone who has multiple predisposing factors, for example an older person with cognitive and functional impairment, their high vulnerability to delirium means that even seemingly innocuous precipitants can push them over the threshold of delirium. For example, changes in medication or the insertion of a urinary catheter can trigger delirium in vulnerable people. This hypothesis explains why high rates of delirium are also seen on wards where people often have multiple predisposing factors (highest vulnerability) such as geriatric medicine and orthopaedic wards.

## 1.6 Outcomes

Delirium was previously thought to be a relatively benign and transient condition. We now know that this is not the case and evidence suggests that delirium is associated with a range of adverse outcomes.

### *1.6.1 Distress*

Delirium is highly unpleasant and frightening for patients, their families and the staff caring for them. As well as causing considerable distress at the time, delirium has been shown to be associated with long term psychological sequelae.

Figures vary hugely in terms of the proportion of patients who recall their delirium, ranging from very few to almost all (Partridge et al., 2013). A study of 101 inpatients with cancer, carried out following full resolution of their delirium, found that 53.5% of participants recalled their delirium (Breitbart et al., 2002). They found that patients with more severe short term memory impairment at the time of their delirium, more severe delirium and patients with more severe perceptual disturbances were all significantly less likely to recall their delirium. Other studies have shown that lower pre-delirium cognitive test scores are also associated with lower rates of delirium recall (Partridge et al., 2013). However, a study specifically examining the experience of delirium in those with dementia found that of the 20 participants who were followed up 1 month after their episode of delirium, 13 recalled their delirium (65%) and the most frequently remembered symptoms were deficits in attention, apathy, psycho-motor retardation and anxiety/fear (Morandi et al., 2015).

Breitbart et al retrospectively recorded distress associated with delirium using a validated tool and found that 80% of those who recalled their delirium reported severe distress, with the presence of delusions found to be the most significant predictor of patient distress (Breitbart et al., 2002). Levels of distress were not affected by delirium motor subtype. They also found that delirium was a highly distressing experience for relatives and staff looking after patients, with the distress of observing delirium in a relative sometimes being greater than the distress experienced by the patient themselves (Breitbart et al., 2002). High levels of distress amongst relatives and carers has also been found in studies focusing on palliative care patients (Finucane et al., 2017).

The majority of studies on the longer-term psychological impact of delirium are in intensive care unit survivors. These studies suggest a link between delirium and

post-traumatic stress disorder, with a median point prevalence of between 19% and 22%, along with anxiety and depression (Partridge et al., 2013). However, existing data is limited by small sample sizes and inconsistent and varying methods for diagnosing delirium.

### *1.6.2 Mortality*

It has been widely shown that delirium is associated with an increased risk of death (HR 1.95 [CI: 1.51 – 2.52] after a mean follow up of 22.7 months) (Witlox et al., 2010). In this analysis, the authors controlled for the potentially confounding effects of age, comorbidities or illness severity and baseline cognition. In practice, this means that a patient with delirium in hospital is twice as likely to die as an identical patient, in terms of age, comorbidities or illness severity and baseline cognition, without delirium (Witlox et al., 2010).

The relationship between delirium and increased inpatient mortality has been shown in a number of settings including general intensive care (Salluh et al., 2015) and cardiac intensive care (Pauley et al., 2015). This relationship has also been shown to persist for 3 months, 6 months or a year following discharge from a number of settings including acute hospital (McCusker et al., 2002, Buurman et al., 2011), general medical and trauma wards (González et al., 2005), post-acute care facilities (Marcantonio et al., 2005), the emergency department (Israni et al., 2018, Han et al., 2010a), palliative care wards (Lawlor et al., 2000), general medical wards (Rockwood et al., 1999) and following hip surgery (Kat et al., 2008). In a study from London, 81% of the participants with delirium had died within 3 years as opposed to 49% of those without delirium (Dani et al., 2018). The impact of delirium on mortality has been shown to persist for up to 5 years after discharge (Eeles et al., 2010).

This relationship has also been shown in community populations (Davis et al., 2014, Davis et al., 2012) including a study of community dwelling older people in Canada, which showed that delirium was associated with a very poor 5 year survival, similar to that of people with severe dementia (Andrew et al., 2006).

Only one study has shown no link between delirium and mortality, although the results were limited by the small sample size in this study (Adamis et al., 2007).

### *1.6.3 Inpatient complications*

People who have delirium during their hospitalisation have increased lengths of stay (Holmes and House, 2000, Siddiqi et al., 2006, Salluh et al., 2015) and have more

hospital-acquired complications, such as falls (Sillner et al., 2019) and pressure sores (Fong et al., 2015).

### *1.6.4 Readmission*

Patients with delirium have been shown to be at increased risk of readmission, within 30 days (LaHue et al., 2019, Marcantonio et al., 2005) and within the first year following discharge (Reynish et al., 2017).

### *1.6.5 Financial*

An inpatient stay complicated by delirium leads to additional healthcare costs estimated at an extra £13,200 per admission (Akunne et al., 2012). This figure comes from detailed cost-benefit analysis, which showed that multi-component interventions for delirium prevention in emergency admissions to general medicine were cost effective.

### *1.6.6 Institutionalisation*

Delirium is associated with an increased risk of institutionalisation, or discharge to a care home, even when controlling for relevant confounders (OR 2.41 [CI: 1.77 – 3.29]) (Witlox et al., 2010). This was true on discharge from acute hospitals (Siddiqi et al., 2006) and post-acute care facilities (Marcantonio et al., 2005). In fact, even when initially discharged home following an inpatient stay complicated by delirium, institutionalisation was higher in the first year following delirium (Eeles et al., 2010).

### *1.6.7 Frailty*

Frailty is a state of increased vulnerability to minor stressors and reduced physiological reserve (Clegg et al., 2013). There is a lack of a standardised working criteria for frailty and a lack of consensus regarding how best to measure it. Although age has long since been identified as a significant risk factor for poor outcome, chronological age is highly heterogeneous. It has been argued that frailty provides a more nuanced measure of function and may help to further risk stratify older persons (Bellelli et al., 2017).

The relationship between frailty and delirium is complex and overlapping with delirium and frailty sharing many common features. For example, both conditions are multifactorial, associated with increased mortality and generally negative outcomes and similar underlying pathophysiology has been proposed (Rockwood, 2004).

Frailty is an independent risk factor for delirium (Persico et al., 2018) and delirium in itself has been shown to be associated with functional decline and general poor

outcome (Buurman et al., 2011). Previous studies have shown that mortality rates following delirium are higher in those who are frail (Eeles et al., 2012). Traditionally, it was thought that delirium was more dangerous in those who were more frail at baseline. However, a recent study has shown that mortality rates following delirium were in fact highest in the least frail group (Dani et al., 2018). Delirium and frailty, according to a 31-item frailty index, were both examined as exposures in this cohort of acutely admitted patients over 70 years in London: both were shown to independently predict the primary outcome of mortality up to 3 years after the index admission. Given the predisposing and precipitating factors hypothesis and the threshold for delirium (Figure 1), the authors attempt to explain this perhaps unexpected finding by suggesting that in less frail individuals, the precipitant for delirium must be greater and therefore more likely to result in mortality (Dani et al., 2018).

Studies regarding the relationship between delirium and frailty are lacking and contradictory results are common (Bellelli et al., 2017). Previous work is significantly limited by heterogeneity in the definition and measurement of delirium and frailty. Only eight studies qualified for a recent meta-analysis and many of these studies were assessed to be methodologically suboptimal (Persico et al., 2018). A further limitation of previous work is that frailty has often been viewed as a dichotomous variable, either present or absent, using an arbitrary cut off.

### *1.6.8 Predicting poor outcomes*

In a systematic literature review examining predictors of poor outcomes in older hospital patients, delirium related factors including hypoactive motor subtype, more severe delirium and longer delirium duration were all found to predict both mortality and new institutionalisation, along with co-morbid dementia and depression (Jackson et al., 2016b). A number of patient related factors and biomarkers were also found to be associated with both mortality and institutionalisation and these are summarised in Table 3.

| Outcome | | Predictors identified, in order of frequency |
|---|---|---|
| Mortality | 1 month | Hypoactive subtype, length of delirium, delirium and depression |
| | 1-6 months | Hypoactive subtype, severity of delirium, dementia, length of delirium, hyperactive subtype, age, lower serum albumin, missed diagnosis |
| | ≥1 year | Length of delirium, hypoactive subtype, dementia, no dementia, illness severity, age, hospital length of stay |
| | Reduced survival time | Length of delirium, frailty, age, raised cerebrospinal fluid 5-hydroxyindoleacetic acid, raised CSF acetylcholinesterase activity |
| New institutionalisation | | Persistent delirium, delirium and depression, delirium severity, hyperactive subtype |

*Table 3: Predictors of mortality and new institutionalisation identified by a literature review on predictors of outcome after delirium (Jackson et al., 2016b) (table taken directly from paper)*

A missed diagnosis of delirium in the emergency department was also associated with significantly increased mortality at 6 months (Kakuma et al., 2003), although this was a relatively small study.

When the systematic review by Jackson et al was published (Jackson et al., 2016b), there were no studies found which specifically examined predictors of cognitive outcome. Subsequently, a study has shown that patients with the highest delirium severity, rated according to the Confusion Assessment Method-Severity (CAM-S), experienced the greatest rate of cognitive decline up to 36 months after surgery and higher mortality (Vasunilashorn et al., 2018). The cohort studied was 70 years and over and all undergoing major elective non-cardiac surgery. A significant limitation of the study, along with the lack of generalizability of the cohort, was the fact that baseline cognition was not accounted for in the analysis. The following section will discuss why this is problematic.

## 1.7 Delirium and dementia

### *1.7.1 Delirium superimposed on dementia*

Dementia is a major risk factor for delirium (Inouye et al., 2014, Fong et al., 2015) and the two frequently co-exist, with prevalence rates between 22% and 89% (Fick et al., 2002). Delirium superimposed on dementia (DSD) is associated with considerable distress (Morandi et al., 2015) and worse outcomes, in terms of mortality, functional dependence, institutionalisation and length of stay, when compared to either delirium or dementia alone (Bellelli et al., 2007, Morandi et al., 2014, Reynish et al., 2017). Prevalence of delirium appears to vary according to dementia subtype, with the highest prevalence of delirium amongst those with Dementia with Lewy Bodies (DLB) (Vardy et al., 2014) and vascular dementia (Hasegawa et al., 2013).

### *1.7.2 Delirium as a risk factor for dementia*

“Is delirium simply a marker of vulnerability to dementia, or does delirium itself lead to dementia?” (Inouye et al., 2014)

The relationship between delirium and dementia is complex. Dementia is a major risk factor for delirium but emerging literature indicates that delirium is a strong predictor of new-onset dementia as well as acceleration of existing cognitive decline (Jackson et al., 2004, MacLullich et al., 2009, Fong et al., 2015). 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 (Bickel et al., 2008, Lingehall et al., 2017, Saczynski et al., 2012); after critical care (Pandharipande et al., 2013); and in community populations (Davis et al., 2012, Tsui et al., 2018, Davis et al., 2014). Cognitive decline has also been shown to be significantly greater following an episode of sub-syndromal delirium (Cole et al., 2003a), defined as having one or more features of delirium, without having the full syndrome.

In terms of quantifying the size of the impact of delirium on cognitive decline and risk of dementia, a population-based study of over 85 year olds showed an 8 fold increased risk of cognitive decline following an episode of delirium (OR 8.7 [CI: 2.1-35.0]) (Davis et al., 2012). A similar risk of cognitive decline was seen in a younger, population-based cohort from the UK (OR 8.8 [CI: 2.8-28.0]) (Davis et al., 2014) and an elective cardiac surgery cohort (OR 7.57 [CI: 2.15-26.65]) (Lingehall et al., 2017). An almost 2 point reduction on the Addenbrooke's Cognitive Examination was

associated with self-reported symptoms of delirium over the seventh decade (-1.7 points [CI: -3.2 - -0.1]) (Tsui et al., 2018). In people with dementia, delirium was associated with twice the rate of cognitive decline than in those without delirium over 5 or more years (Gross et al., 2012). A biphasic decline in cognition was seen after surgery with an acute decline and then recovery by 2 months, followed by gradual decline over 36 months (Inouye et al., 2016). This may explain why no association was found between delirium and cognitive decline measured at just 6 months post aortic valve surgery (Eide et al., 2016).

There are very few studies which have examined cognitive outcomes after delirium whilst controlling adequately for baseline cognition. It is vital to adequately and robustly ascertain baseline cognition in order to determine whether any cognitive decline observed following delirium is new or pre-existing but undiagnosed. This is crucial when testing the hypothesis that delirium is not simply a marker of vulnerability but is, in fact, leading to cognitive decline.

The few studies that do attempt to control for baseline cognition are summarised in Table 4 along with the limitations of each study, which will be discussed in more detail below.

Very few of these studies have accounted for the confounding effect of illness severity. Acute hospitalisation itself has been shown to adversely affect trajectories of cognitive decline, even when delirium has not been specifically ascertained (Ehlenbach et al., 2010, Wilson et al., 2012, Mathews et al., 2014). This implies that delirium and/or its acute causes can contribute to the overall burden of dementia. Pulling apart the attributable components of cognitive decline is crucial to our understanding of the consequences of delirium.

| Study | Sample | Sample size | Delirium measure | Cognitive outcome | Control for illness severity | Mean age at baseline | Patients with delirium | Adjusted effect size (95% CI) | Limitations |
|---|---|---|---|---|---|---|---|---|---|
| Tsui et al, 2018 (Tsui et al., 2018) | MRC National Survey for Health and Development (British birth cohort) | 2090 | Self-reported delirium symptoms between ages 60 and 69 years at follow up aged 69 years | Addenbrooke's Cognitive Examination version III at age 69 years | None | 69 | Ten year period prevalence: 4% | -1.7 points (-3.2 - -0.1) | Non-validated and retrospective delirium ascertainment |
| Lingehall et al, 2017 (Lingehall et al., 2017) | Patients ≥70 years without dementia having elective cardiac surgery with cardiopulmonary bypass | 114 | Retrospective diagnosis by nurse and physician specialized in geriatric medicine based on MMSE and Organic Brain Syndrome scale recorded on Days 1 and 4 after extubation | MMSE at 5 years | None | 76.5 | 56.1% | OR 7.57 (2.15-26.65) | Retrospective delirium ascertainment based on non-validated scales, non-generalisable, highly selected population |
| Eide et al, 2016 (Eide et al., 2016) | Individuals aged 80 and older undergoing elective surgical aortic valve replacement or transcatheter aortic valve implantation (TAVI) | 136 | CAM for 5 days post operatively | MMSE at 6 months | None | 84 | 66% of participants in the SAVR group and 44% of those in the TAVI group | No association between cognition at 6 months and presence/absence of delirium | Short follow up, non-generalisable, highly selected population |
| Inouye et al, 2016 (Inouye et al., 2016) | Patients ≥70 years without dementia having elective major surgery | 560 | CAM | General Cognitive Performance and IQCODE | None | 77 | 24% | Significant decline in cognition in delirium compared to non-delirium group | Non-generalisable surgical cohort, excluded participants with dementia |

| Study | Sample | Sample size | Delirium measure | Cognitive outcome | Control for illness severity | Mean age at baseline | Patients with delirium | Adjusted effect size (95% CI) | Limitations |
|---|---|---|---|---|---|---|---|---|---|
| Krogseth et al 2016 (Krogseth et al., 2016) | Hip fracture patients with pre-fracture cognitive impairment defined using IQCODE-SF | 287 | CAM daily during admission | IQCODE-SF at mean follow up of 5.2 months | None | 85 | 70% | Delirium was a significant and independent predictor of cognitive decline at follow up measured using IQCODE-SF | Reliance largely on retrospective measure of cognitive impairment as primary outcome measure |
| Cognitive function and ageing study (Davis et al., 2014) | Population-based sample; multicentre sampling from health authority lists | 2197 | Algorithmic operationalisation of DSM-IV based on Geriatric Mental State examination | AGECAT-defined dementia at 2 years | Interviewer's rating of any current acute illness (none, mild, moderate, or severe). | 77 | 6% | OR 8·8 (2·8–28·0) | Retrospective delirium ascertainment, subjective and non-validated assessment of illness severity |
| BRAIN-ICU (Pandharipande et al., 2013) | Multicentre ICU admissions | 821 | CAM-ICU | Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score at 1 year | SOFA daily | 61 | 74% | −5·6 points per day of delirium (−9·5 to −1·8) | Young cohort, non-generalisable as ICU population, excluded participants with severe dementia |
| Gross et al, 2012 (Gross et al., 2012) | Memory clinic patients with clinically diagnosed Alzheimer's dementia | 263 | Retrospective diagnosis of delirium from case notes (validated algorithm) | Worsening of Blessed IMC test score over 5 or more years | None | 78 | 56% | Additional 1·2 points per year (0·5–1·8) | Retrospective delirium ascertainment |

| Study | Sample | Sample size | Delirium measure | Cognitive outcome | Control for illness severity | Mean age at baseline | Patients with delirium | Adjusted effect size (95% CI) | Limitations |
|---|---|---|---|---|---|---|---|---|---|
| Saczynski et al, 2012 (Saczynski et al., 2012) | Patients aged ≥60 years undergoing elective CABG or valve surgery | 225 | CAM daily | Trajectory of MMSE change over 1 year | None | 73 | 46% | Prolonged impairment in recovery. Mean MMSE scores at 6 and 12 months after surgery did not differ significantly between delirium and no delirium groups (p=0.06) | Non-generalisable surgical cohort |
| Davis et al, 2012 (Davis et al., 2012) | Population-based sample of all residents aged ≥85 years | 553 | Participant and informant interview, along with medical record review | Dementia (DSM-IIIR; individual clinician) at 2·5 years | None | 89 | 13% | OR 8·7 (2·1–35·0) | Retrospective delirium ascertainment |
| Fong et al, 2009 (Fong et al., 2009) | Memory clinic patients with clinically diagnosed Alzheimer's disease | 408 | Retrospective diagnosis of delirium from case notes (validated algorithm) | Worsening of Blessed IMC test score over 0·7 years | None | 74 | 18% | Additional 2·4 points (1·0–3·8) | Retrospective delirium ascertainment |
| Bickel et al, 2008 (Bickel et al., 2008) | Patients aged ≥60 years undergoing elective hip surgery | 200 | CAM | Cognitive impairment or dementia, or both | None | 74 | 21% | OR 41·0 (4·3–396·0) | Non-generalisable surgical cohort |
| Lundstrom et al, 2003 (Lundstrom et al., 2003) | Dementia-free patients aged ≥65 years with acute hip fracture | 78 | DSM-IV | Consensus diagnosis of dementia at 5 years | None | 79 | 38% | OR 5·7 (1·3–24·0) | Excluded people with dementia, non-generalisable surgical cohort |

*Table 4: Summary of studies which examine cognitive outcomes after delirium whilst controlling for baseline cognition. Headline results and limitations included. Table adapted from Inouye et al, 2015.*

### *1.7.3 Persistent delirium*

Most delirium tends to resolve over several days to a few weeks. However, delirium can persist for several months, which is known as persistent delirium. Persistent delirium is poorly researched with no widely accepted definition. In a review of the topic (Cole et al., 2008), persistent delirium was defined as delirium which persisted throughout hospital admission and was present at follow up. The prevalence of persistent delirium at 1, 3 and 6 months after discharge was found to be 32.8%, 25.6% and 21% respectively (Cole et al., 2008). In a study from Birmingham which reviewed people with delirium at 3 months, 6% had persistent delirium (Jackson et al., 2016a). A major limitation in these studies is that it was not possible to determine whether the patient had the same episode of delirium, which had persisted throughout the follow up period, or whether a new delirium had developed following the resolution of the previous episode.

It is usually not possible to make a diagnosis of dementia in the presence of delirium as it is unclear whether the cognitive deficits demonstrated will resolve. The diagnosis of dementia is based upon the demonstration of progressive cognitive impairment over a period of at least 6 months which significantly impacts upon activities of daily living (American Psychiatric Association, 2013). However, if delirium truly persists beyond 6 months, the margins between the definitions of delirium and dementia become blurred and it can be very difficult to know whether the patient will ever recover or whether their current state is their new baseline.

## 1.8 Limitations of current literature

Delirium was previously thought to be a benign and transient condition and, consequently, is under-researched, well out of proportion to its prevalence and impact. The studies that do exist have a number of crucial limitations.

### *1.8.1 Variations in diagnostic criteria*

Current delirium research is limited by huge variations in the methods used to ascertain delirium. This is apparent when comparing the varied figures quoted for prevalence, incidence and occurrence rates across different studies.

In the absence of a biomarker, clinical criteria provide the gold standard for delirium diagnosis. The most widely used of these is the Diagnostic and Statistical Manual criteria, now in its 5th edition (Table 1) (American Psychiatric Association, 2013). Over time, there have been several revisions of the DSM criteria, with subtle differences in the criteria. An alternative classification is produced by the World Health Organisation and first appeared in the 10th edition of the International Classification of Diseases (ICD) (World Health Organization, 1992).

Although there is considerable overlap between the various iterations of the DSM criteria and the ICD criteria, studies have shown that these subtle differences impact on the rates of delirium reported in both hospital and care home settings, with only a small proportion of patients meeting all criteria (Laurila et al., 2003, Adamis et al., 2015, Cole et al., 2003b, Voyer et al., 2009, Meagher et al., 2014b). The classification system used for delirium has also been shown to identify populations with differing outcomes in terms of mortality, length of stay and institutionalisation (Adamis et al., 2018).

The water is further muddied by studies which diagnose delirium using tools such as the Confusion Assessment Method (CAM) (Inouye et al., 1990). Designed primarily as a screening tool rather than a diagnostic tool, the CAM does operationalise aspects of the diagnostic criteria it was based upon (DSM-III-R) but remains subjective, time consuming and requires considerable training to obtain the sensitivity and specificity quoted in the original studies (Green et al., 2019).

### *1.8.2 Operationalising the criteria*

The diagnostic criteria state the features that must be demonstrated in order for a diagnosis of delirium to be made but offer only limited guidance on how best to do this. This leaves the diagnostic criteria open to individual interpretation and the diagnosis subjective. There is significant variability in the reference standard methods used for delirium diagnosis in published delirium research studies (Neufeld et al., 2014). This makes the comparison of studies challenging and the heterogeneity of case ascertainment is sited as a significant limitation in the majority of delirium literature reviews and meta-analyses. Clinically, this may have contributed to the considerable uncertainty amongst clinicians regarding how to diagnose delirium (Jenkin et al., 2016) and the extensive heterogeneity in clinical practice, particularly with respect to delirium superimposed on dementia (Richardson et al., 2016a).

There is no guidance regarding how to test for key features of the DSM 5 criteria including inattention and cognitive impairment, and very little research specifically evaluates tests for these in the context of delirium. There are also features of the delirium itself that make the diagnosis particularly challenging to make. One such situation is the assessment of delirium in the context of severely deranged level of consciousness or alertness. Patients can either be too drowsy or too hyperactive to engage with formal testing, rendering them 'untestable'. As such, arousal and attention are hierarchically related whereby level of consciousness must be sufficient in order to demonstrate disorders of attention (Figure 2). 15% of delirium research studies excluded these patients (Neufeld et al., 2014) but this clearly introduces significant bias, particularly as hypoactive delirium has been associated with worse outcomes (Jackson et al., 2016b).

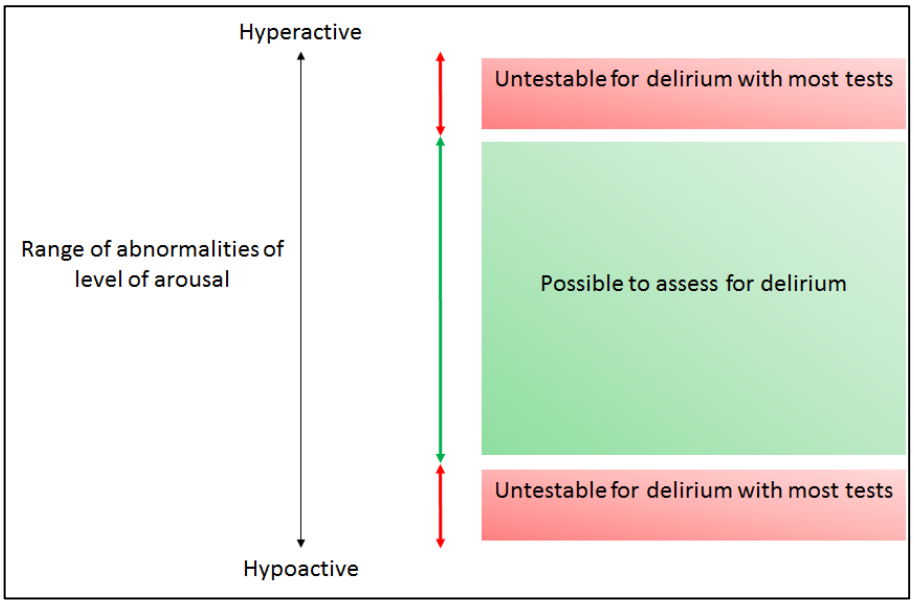



*Figure 2: Diagrammatic representation of the hierarchical relationship between level of arousal and attention in delirium. Patients with very deranged level of arousal are unable to complete most of the tests used to assess for delirium*

DSM-5 only offers brief guidance on this but an approach has been proposed which recommends that the inability to engage in cognitive testing or interview is considered severe inattention for the purposes of delirium diagnosis (European Delirium Association and American Delirium Society, 2014). This "relaxed" interpretation of the DSM 5 criteria has been shown to be more inclusive (Meagher et al., 2014b).

Standardising a clear definition of delirium is essential to ensure consistent case ascertainment in future delirium research and ensure results of studies are comparable. The optimal operationalisation of DSM 5 criteria is currently elusive but will require reliable and valid tests of inattention, cognition and neuropsychiatric symptoms with clear guidance regarding what to do when people are unable to complete the tests due to advanced dementia or very deranged level of arousal. Until this time, greater transparency amongst delirium researchers regarding the methodology used for delirium diagnosis, in the form of a table showing how each component of DSM 5 was operationalised, would facilitate better comparisons between studies and more consistency in delirium research. Authors should also be encouraged to publish the processes they used to capture information from patients unable to participate in formal testing. One approach to determine whether delirium is present or absent in research studies is to use a consensus panel to review

vignettes for each participant containing data collected prospectively regarding each of the components of DSM 5 criteria.

### *1.8.3 Delirium Superimposed on Dementia*

The clinical phenotypes of delirium and dementia show considerable overlap, which makes diagnosing delirium in the context of dementia challenging. In the absence of specific tools or guidance for the application of diagnostic criteria in the context of pre-existing dementia, delirium superimposed on dementia (DSD) is currently evaluated with instruments used for diagnosing delirium alone (Morandi et al., 2012). This is problematic given that many of these tools rely on cognitive tests, which may be abnormal in both dementia and delirium (Meagher et al., 2010, Tieges et al., 2014). Therefore, in order to differentiate the two conditions, the diagnosis of delirium relies upon the demonstration that there has been an acute change from the patient's baseline (Criterion D from Table 1). This depends upon the availability of a reliable informant who can provide an accurate collateral history of an acute change, which is often problematic in the acute setting. This may delay diagnosis or result in delirium being missed, along with its potentially treatable cause, as people commonly assume that the abnormalities detected on cognitive testing are due to underlying dementia rather than delirium. This emphasises the need for robust knowledge of baseline cognitive status in delirium research studies.

### *1.8.4 Poor recognition and documentation of delirium*

Despite its high prevalence and poor outcomes, the diagnosis of delirium is frequently missed. A study of 710 acute elderly medical admissions found that 72% of the 110 cases of delirium were not detected by the clinical teams (Collins et al., 2010). These findings have been replicated throughout the hospital (Ryan et al., 2013) including the emergency department where it is estimated that 57% to 83% of cases are missed (Han et al., 2010b). Delirium is also poorly documented and under-recorded (Milisen et al., 2002). Unfortunately, missing the diagnosis of delirium is associated with worse outcomes, including mortality (Kakuma et al., 2003).

The reasons for the poor recognition of delirium are complex. A lack of knowledge about delirium (Davis and MacLullich, 2009), particularly the diagnostic criteria (Jenkin et al., 2016), and uncertainty regarding differentiating delirium from dementia have been demonstrated (Steis and Fick, 2011). However, beyond gaps in knowledge, there remain significant attitudinal barriers to improving delirium care, with a lack of ownership and a general lack of awareness of its importance (Teodorczuk et al., 2013). Hospitals are not currently designed for frail older people (Richardson et al., 2016b) and time constraints have been listed as a reason for not routinely screening people for cognitive impairment (Kennelly et al., 2013). There is also significant uncertainty regarding patients with delirium who are ‘untestable’, as discussed previously, with screening tools often left incomplete for these patients, which may in itself be a sign of adverse outcomes (Eeles et al., 2009).

The poor recognition and documentation of delirium has important implications for research studies that rely on the retrospective ascertainment of delirium from case notes.

### *1.8.5 Methodological issues in cohort studies*

#### *1.8.5.1 Selection bias*

In existing delirium research, there is a lack of good quality, large epidemiological studies in unselected populations. A number of studies simply exclude participants with dementia, despite the fact it is a major risk factor for delirium, probably resulting in an underestimation of the true incidence of delirium. Due to the association between illness and delirium, many of the studies sample inpatient populations. Even within this setting, highly selected participants are often studied such as surgical patients, a particularly appealing cohort to study due to the ease of case finding, baseline assessment and the clear timing of a precipitant i.e. surgery. However, this selection bias towards a population fit enough for major surgery, renders these studies non-generalisable to the majority of patients seen in hospital who are considerably frailer.

#### *1.8.5.2 Incomplete ascertainment of baseline cognition*

It is likely that previous studies may have been confounded by incomplete ascertainment of cognitive status at baseline (Davis et al., 2012), particularly given that around half of dementia is undiagnosed (Sampson et al., 2009). Other studies have attempted to address the lack of baseline cognitive assessments by using tools such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to assess baseline cognition. A recent study aiming to address the lack of evidence for its use in hospital patients with delirium found that it performed well at a cut-off >3.82 for detecting dementia (sensitivity 0.91 [CI: 0.79–0.97]; specificity 0.93 [CI: 0.76–0.99]) (Jackson et al., 2016a). However, these retrospective measures do not give any quantitative information on pre-delirium cognition, particularly not for specific domains, and it is not possible to subtype any dementia present.

#### *1.8.5.3 Lack of prospective delirium assessments*

A major limitation of the few population studies of cognitive trajectories in delirium that have included extensive baseline cognitive assessments is the fact that delirium could not be prospectively defined (Davis et al., 2012, Tsui et al., 2018, Davis et al., 2014). As well as being susceptible to recall bias, particularly in the context of residual cognitive impairment, and poor documentation, retrospective ascertainment only allows delirium to be viewed as a dichotomous variable, which may be misleading. It is probable that delirium characteristics such as motor subtype, duration and aetiology, may impact upon outcomes (Jackson et al., 2016b).

*1.8.5.4 Controlling for illness severity*

Retrospective ascertainment of delirium is also limited by the fact that it is not possible to control for the potentially confounding effect of simultaneous illness severity. Is it simply the case that those who had delirium were just sicker, and it was this underlying illness that resulted in their cognitive impairment or is delirium itself neurotoxic? These are fundamental questions which can only be answered in a robustly designed population-based cohort study with prospective delirium assessments which adequately control for illness severity.

Two studies have attempted to account for illness severity (Table 4) in the context of a cohort study. Although both studies demonstrated that delirium was associated with cognitive decline even when controlling for illness severity, both had significant methodological limitations. One study used the interviewer's rating (none, mild, moderate, severe) of any current acute illness (Davis et al., 2014). This is non-validated and highly subjective. The other study used the Sequential Organ Failure Assessment (SOFA) (Vincent et al., 1996), a validated tool for the assessment of illness severity, but this study was limited by a young, non-generalisable intensive care population and excluded participants with severe dementia (Pandharipande et al., 2013).

The optimal method of ascertaining illness severity in a hospitalised older population is unknown as there are a lack of validated tools to measure illness severity in older people. Two of the most frequently cited illness severity scores, Acute Physiology and Chronic Health Evaluation II (APACHE-II) (Knaus et al., 1985) and the Simplified Acute Physiology Score II (SAPS-II) (Le Gall et al., 1993), were designed for use on admission to the intensive care unit to predict mortality. These severity rating scales have not been validated for use outside of intensive care and include variables that are not commonly recorded in general medical patients including pH and arterial oxygen concentrations. The SOFA was also designed for use on admission to intensive care and includes these variables. However, unlike APACHE-II and SAPS-II, SOFA was also designed for use every 24 hours until discharge. It records the worst parameters measured over the preceding 24 hours to produce a mortality prediction score based on the degree of dysfunction of six organ systems.

As a compromise, other delirium studies have used a modified version of APACHE II, without the components which are not routinely recorded outside of the intensive care unit (Jackson et al., 2016a).

## 1.9 Moving forward: introduction to the DECIDE study

In a population-based cohort study of men and women aged 65 years and older, the DECIDE study measured the effect on cognition of an episode of delirium, independent of baseline cognitive status and illness severity. The study also explored the predictive value of clinical parameters, including delirium severity, duration and subtype, on cognitive outcomes following an episode of delirium.

The DECIDE study was nested within the MRC Cognitive Function and Ageing Study II (CFAS II). This is a large, population-based cohort of community dwelling individuals aged 65 years and over from five geographical areas in the UK, which aimed to investigate dementia and cognitive decline. The CFAS studies have provided unique data on prevalence, risk factors, service needs and financial implications of dementia within the UK (Matthews et al., 2013).

The nesting of a prospective delirium study within CFAS II provided a unique opportunity to use an existing, well-characterised and representative, population-based cohort to avoid the selection biases associated with much of the current literature based solely on hospitalised samples (Davis et al., 2013, Brayne and Davis, 2012).

The DECIDE study recruited hospital attending CFAS II – Newcastle participants and followed them throughout their hospital stays in order to identify delirium. Those recruited were followed up one year after their discharge to repeat their CFAS interviews. Before and after cognitive test scores were compared in those with and without delirium, whilst controlling for relevant confounding factors including illness severity.

This was an exceptional opportunity to answer questions of major clinical significance and to guide clinicians, patients, families and researchers as well as making full use of, and adding value to an existing cohort study. The prospective nature of the delirium assessments, and the data to be collected, will increase understanding of the natural history of delirium. As such, this study could address many unanswered questions of clinical significance in delirium. This will facilitate accurate and realistic conversations with families and will have important implications for healthcare planning and resource allocation.

If delirium is robustly associated with trajectories of cognitive decline, it is reasonable to hypothesise that delirium is a potentially modifiable risk factor for dementia. Given

that delirium is preventable in around one third of cases (Inouye et al., 1999), this paves the way for future dementia prevention trials that focus on delirium intervention. Given the current lack of treatments for dementia, and the ageing population, prevention is becoming increasingly relevant and appealing.

## 1.10 Summary

Despite being first described more than 2000 years ago, “delirium remains hard to define and difficult to study” (Adamis et al., 2007). Much of the existing research is limited by inconsistencies with case ascertainment and highly selected populations. The nesting of a prospective delirium study that prospectively tracks cognitive change before, during and after delirium within a well-characterised, representative cohort with known baseline cognition will provide a unique opportunity to answer questions of major significance to patients, their family and the population as a whole.

# Chapter 2: Methods

## 2.1 Design

The Delirium and Cognitive Impact in Dementia (DECIDE) study is a nested prospective longitudinal cohort study. The protocol for the study has been published (Richardson et al., 2017) (Appendix A).

## 2.2 Aims

To explore the association between delirium and cognitive decline, independent of baseline cognition and illness severity.

## 2.3 Objectives

In a population-based cohort study of men and women aged 65 years and older:

- To measure the effect on cognition of an episode of delirium, independent of baseline cognition and illness severity
- To explore the predictive value of clinical parameters (including delirium severity, subtype and duration) on cognitive outcomes following an episode of delirium

## 2.4 Population

The DECIDE study was embedded within the Cognitive Function and Ageing Study II-Newcastle centre (CFAS II-Newcastle). This is a large, population-based cohort of individuals from five geographical areas in the UK. The protocol for this study is published online (http://www.cfas.ac.uk/cfas-ii/cfasii-study-design/) but the details are as follows.

### *2.4.1 CFAS II-Newcastle baseline assessments*

At baseline (2008-2011), 2500 participants aged ≥65 years were recruited using primary care registration, which included care settings, to CFAS II-Newcastle. The UK system of primary care registration provides the “most robust population base for sampling by age group for epidemiological studies in the UK” (Matthews et al., 2013). Sampling was stratified by age to ensure that there were 1,250 individuals aged 65-

74 and 1,250 individuals aged 75 years and over. Interviews were undertaken over a two-year period. Participants were re-seen two years later, again over a two-year period.

The interviews were carried out and entered directly onto a laptop computer. The interview collected information regarding demographics such as age at time of interview, gender, place of residence and years of education, lifestyle variables, health status, functional limitations, social support, measures of hearing and visual impairment, and receipt of health services. Social class according to the main occupation of the participant and their partner, where applicable, was calculated from this data and divided according to the categories in Figure 3 based upon the Standard Occupational Classification (SOC) developed by the UK Office for National Statistics.

| | |
|---|---|
| I - | Professional occupations |
| II - | Managerial and technical occupations |
| IIIN - | Skilled non-manual occupations |
| IIIM - | Skilled manual occupations |
| IV - | Partly-skilled occupations |
| V - | Unskilled occupations |

*Figure 3: Social class categories based on occupation*

The Modified Townsend Disability Scale was also calculated based on the data collected at the interviews. This scale rates functional incapacity and consists of 9 activities which are rated as follows: 2 if help needed; 1 if some difficulty or used aids in order to complete the activity; and 0 if no difficulty and did not need any aids. The activities are: cutting own toenails, washing all over or bathing, getting on a bus, going up and down stairs, heavy housework, shopping and carrying heavy bags, preparing and cooking a hot meal, reaching an overhead shelf and tying a good knot in string. The scores from these activities are added up to form a score from 0 – 18 where 0 is no functional incapacity and 18 is very severe functional incapacity. The total scores were dichotomized where a score of 1 was given if the total score was 11-18, and 0 if the total score was 0-10.

### *2.4.2 CFAS II-Newcastle cognitive function assessments*

Global as well as domain specific cognitive function was assessed at baseline and two years follow-up using the Geriatric Mental State (GMS), the Cambridge Cognitive Examination (CAMCOG) and the Mini Mental State Examination (MMSE). An algorithmic approach to the diagnosis of dementia, depression and anxiety was also possible within the interview using the AGECAT (Automated Geriatric Examination for Computer Assisted Taxonomy), drawing on respondent and observer ratings. This method has previously been validated and shown to be reliable (Copeland et al., 1986). In 20%, an informant interview was also conducted for the refinement of study diagnosis and to provide essential proxy information where respondents were unable to answer questions. The full content of the interviews is available on the CFAS website (http://www.cfas.ac.uk/).

If participants were unable to complete the full interview, often due to severe cognitive impairment, resulting in missing data and preventing an algorithm diagnosis, a review of all available information was completed by a diagnostician, applying DSM-IIIR criteria (Matthews et al., 2013).

## 2.5 Recruitment

### *2.5.1 Contacting General Practitioners of potential participants*

At the start of the DECIDE study, the General Practitioners (GPs) of all of the participants in CFAS II-Newcastle were contacted in order to confirm the appropriateness of re-contact with surviving members. They were asked to notify the CFAS team if they felt there was any reason why participants should not be approached, including patients no longer being registered with the surgery or if there was a medical reason such as end stage terminal illness. As one of the main focuses of the study was cognition and ageing, surgeries were requested not to exclude participants because they had dementia or were living in institutions.

### *2.5.2 Contacting potential participants via CFAS*

In those surviving members of CFAS II-Newcastle whom the GPs felt it acceptable to re-contact, an introductory letter and participant information sheet was sent by the CFAS team detailing the proposed DECIDE study. Participants were invited to contact the CFAS team if they did not want their NHS number to be shared with the

DECIDE study team. All surviving CFAS II-Newcastle participants were eligible to participate in DECIDE.

### *2.5.3 Recruiting participants into the DECIDE study during an admission to hospital*

All participants sampled in CFAS II-Newcastle live within the catchment area of the Newcastle-upon-Tyne Hospitals NHS Foundation Trust.

During a one-year period from 5th January 2016 to 5th January 2017, participants of CFAS II-Newcastle were approached on emergency or elective admission to hospital. In order to identify participants admitted to hospital, a Recurring Admission Patient Alert (RAPA) was set up on the Newcastle upon Tyne hospitals electronic records system. This flagged up participants on admission to the two acute hospitals in the Newcastle Hospitals NHS Foundation Trust (Royal Victoria Infirmary and Freeman Hospital). They were then approached as soon as possible following admission and invited to take part in the DECIDE study. Once recruited, they were seen on each subsequent hospital admission if agreeable verbally. As such, they were not asked to provide written consent on each subsequent hospital admission during the study period.

## 2.6 Inclusion criteria

Any participant in CFAS II-Newcastle admitted to hospital during the recruitment period from 5th January 2016 to 5th January 2017 was invited to take part. If the participant themselves lacked capacity, according to a capacity assessment performed by the lead researcher (SR), an appropriate personal consultee was sought and invited to provide written confirmation of willingness to participate.

## 2.7 Exclusion criteria

Patients were excluded from the study if they lacked capacity to consent and the study team were unable to identify or contact an appropriate personal consultee. Participants were also excluded if they were receiving end of life care. If the patient was being isolated for infection control reasons, invitation to participate was delayed until they were no longer being isolated. Participants who were expected to be in hospital for less than 24 hours were not invited to participate.

## 2.8 Consent

Potential participants were approached as soon as possible on admission to hospital. This did not interfere with clinical care. They were approached by the chief investigator (SR) or the research nurse and provided with another copy of the participant information sheet. Participants were given a maximum of 24 hours to decide whether they would like to take part in the study. However, given the low risk and largely observational nature of the study, along with the fact that all participants had previously been notified of the study by post and provided with a participant information sheet, many participants and their personal consultees were willing to consent before this.

### *2.8.1 Capacity*

The inclusion of some participants lacking capacity was inevitable as the study aimed to look at the effect of delirium on cognition and both delirium and dementia can impair a person's capacity. A formal capacity assessment based on the Mental Capacity Act was performed by a trained member of the research team, mainly the chief investigator (SR). Participants were asked to give consent appropriate to their level of understanding, ranging from written informed consent to account being taken of verbal and non-verbal communication in determining willingness to participate. In those individuals found to be without capacity to give full written informed consent, a personal consultee was identified, and their advice sought regarding participation as per Section 32 of the Mental Capacity Act (Great Britain, 2005). As per this guidance, the personal consultee was not a paid carer.

The advantage of re-evaluating CFAS II participants, as opposed to other study populations, is that they have already expressed an interest in research by virtue of their willingness to participate in CFAS II. This made conversations with the personal consultee easier as they were familiar with research and aware of the wishes and feelings of the participant about taking part in research studies.

### *2.8.2 Continued consent process*

Verbal reconfirmation of the study participant’s willingness to continue with the study was sought at each point of contact. Participants who were very distressed or refused to engage (whether due to delirium or having the capacity to refuse assessment on that occasion) were not assessed by the research team on that

occasion but a record of the outcome of the interaction was documented. Due to the fluctuating nature of delirium, further contact was attempted later. Any patient appearing consistently distressed by participation or withdrawing consent whilst having capacity were excluded from the study without prejudice to clinical care. As such, every effort was made to respect the wishes of the person, both previously made and at the time the research was undertaken.

If they recovered capacity, participants admitted to the study via a personal consultee were given the opportunity to consider whether they would like to continue to be part of the study and if so, written consent was obtained.

### 2.9 Data collection

Following recruitment to the DECIDE study, data was collected as per the example flowcharts below (Figure 4 and Figure 5) and detailed in this section and Appendix B. Each participant had demographic information collected on just one occasion regardless of the number of admissions during the study period. Admission information was collected once on each admission. Daily review documentation was completed each time the participant was reviewed during their admission. Participants were invited to the study on every admission during the one-year study period.

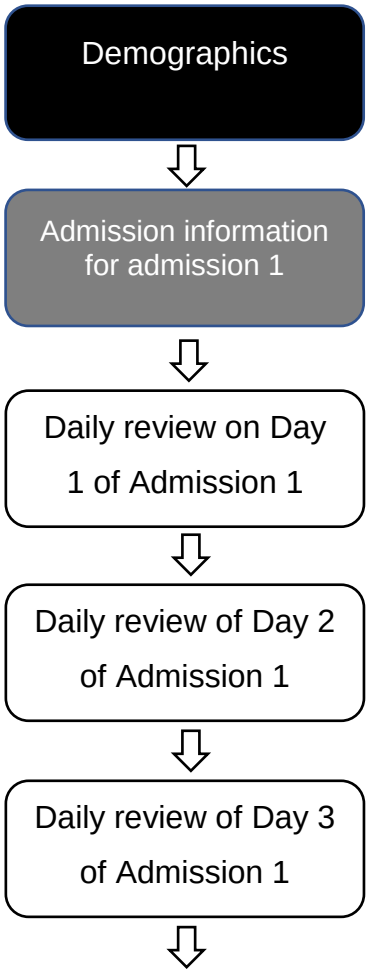



*Figure 4: Flowchart to demonstrate the structure of data collection for a participant admitted on one occasion during the study period for 3 days*

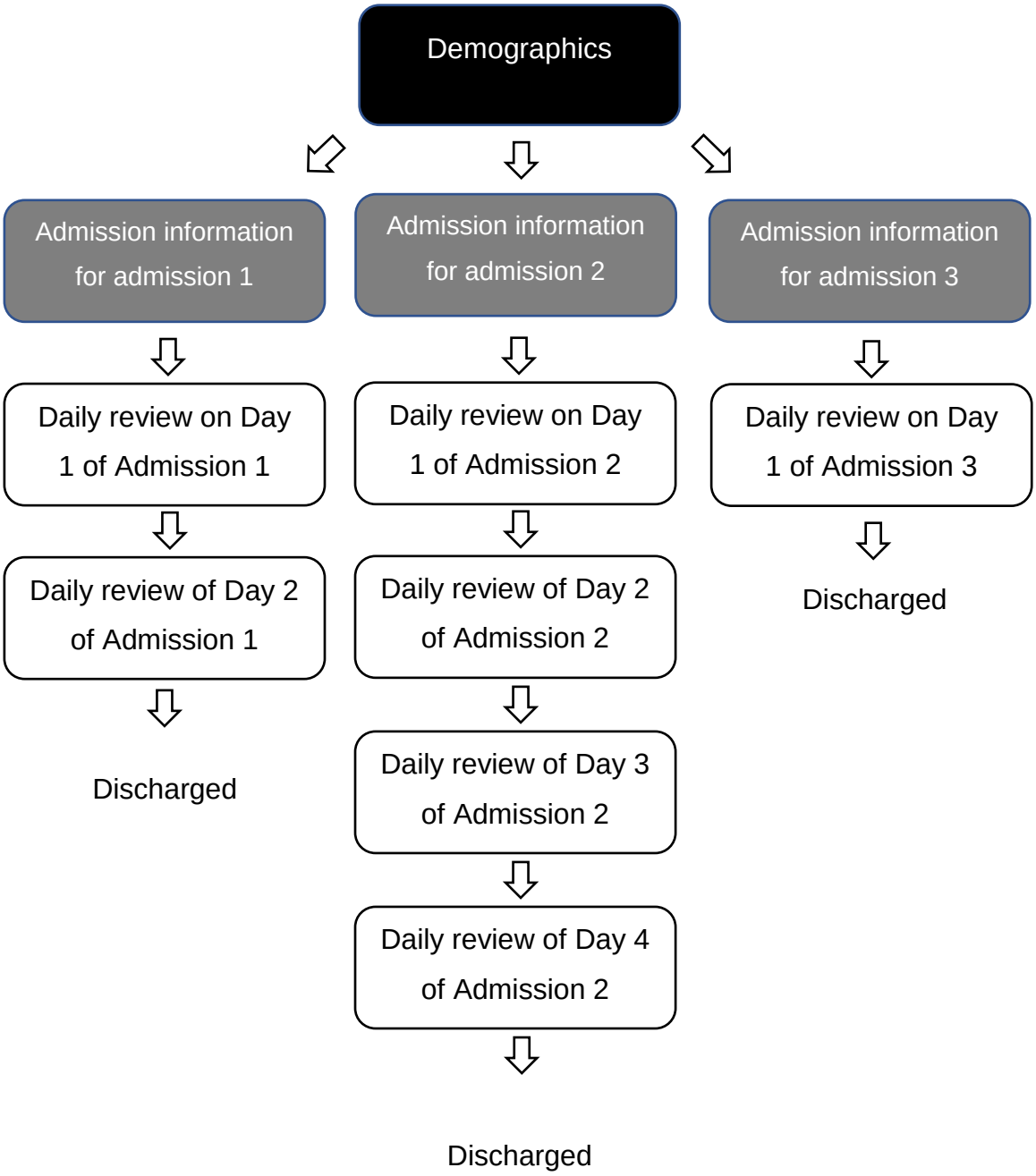



*Figure 5: Flowchart to demonstrate the structure of data collection for a participant admitted on three occasions during the study period for 2 days, 4 days and then 1 day*

### *2.9.1 Demographics*

Demographic data was collected on just one occasion from the participant, their informant, if available, and from the medical records following consent being obtained and not repeated on subsequent admissions. The data collected included age, gender, co-morbidity, whether there was a history of delirium prior to the study period documented in the clinical records and whether there was a history of delirium from the patient or their informant. Previous episodes of delirium are a recognised predisposing factor for further episodes of delirium (Inouye et al., 2014) but it is notoriously poorly documented (Milisen et al., 2002).

#### *2.9.1.1 Recording co-morbidity*

The previous medical history of the participants was recorded in a structured way according to the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992). It was then possible to score patients in each of fourteen categories representing clinically relevant body systems according to severity, rated from 0 to 4, as per the 1991 manual (Figure 6). The information for the completion of the CIRS-G was obtained mostly from medical records with come clarification from participants or their consultee.

#### *2.9.1.2 Choice of measure of co-morbidity*

The CIRS-G was chosen over other measures of co-morbidity, such as the Charlsson index (Charlson et al., 1987), because it was developed specifically for use in older people. It is derived from the Cumulative Illness Rating Scale (Linn et al., 1968), which, in itself, has been shown to be a valid and reliable measure of co-morbidity for use in clinical research (de Groot et al., 2003). The CIRS-G showed good interrater reliability for total scores and is accompanied by a useful and comprehensive manual (Miller et al., 1992). This outlined specific examples for each of the 14 categories as well as providing overall guidance regarding severity scoring (Figure 6).

0 - No Problem

1 - Current mild problem or past significant problem

2 - Moderate disability or morbidity/ requires "first line" therapy

3 - Severe/constant significant disability/ "uncontrollable" chronic problems

4 - Extremely Severe/immediate treatment required/end organ failure/severe impairment in function

*Figure 6: Guidance for severity scoring for the CIRS-G* (Miller et al., 1992)

### *2.9.2 Admission information*

On each admission, data was collected on one occasion regarding where the participant was admitted from and the level of support they were receiving along with the date and reason for admission. The weight (kg), height (cm) and Malnutrition Universal Screening Tool (MUST) score were recorded if documented by the clinical team. Recognised predisposing factors for delirium (Inouye et al., 2014) such as presence of visual or hearing impairment and whether they had a urinary catheter in situ prior to admission were documented along with whether patients were screened for delirium on admission.

The Rockwood Clinical Frailty Score (Rockwood et al., 2005) and the Barthel Index of Activities of Daily Living were completed based on the history from the participant or their consultee in order to assess frailty and dependence in the weeks preceding hospital admission, prior to their current illness. Although similar data was collected as part of the CFAS interview, these were performed up to 6 years prior to recruitment to DECIDE and so this data was collected to provide an up to date assessment of their level of independence.

#### *2.9.2.1 Frailty*

The Clinical Frailty Score (Rockwood et al., 2005) was selected as the measure of frailty to be used in this study due to the fact that it is quick and relatively simple to complete. It consists of 9 descriptions ranging from “very fit” to “terminally ill” and is scored based on clinical judgement having spoken with the patient. It does not require measurements of multiple domains like some of the more unwieldy frailty scores based on deficit counts but has been shown to be highly correlated with the Frailty Index (r=0.8) (Rockwood et al., 2005).

#### *2.9.2.2 Anti-cholinergic burden*

All regular medications taken by participants prior to admission were recorded. These were later rated based on the total number prescribed, indicating the degree of polypharmacy, and the anticholinergic burden, according to the Anticholinergic Burden Scale (Boustani et al., 2008).

### *2.9.3 Daily review*

Participants were assessed daily, as far as possible, for the first five days by SR or a clinical research nurse. From day 6, those with delirium continued to be seen daily until delirium resolution. In the absence of delirium from day 6, or following resolution of delirium, participants were screened for delirium twice per week using a semi-structured interview including a modified version of the Delirium Observation and Screening Scale (Schuurmans et al., 2003). If participants displayed any signs of delirium according to this, the full assessment described in Appendix B was performed to determine whether DSM-5 delirium was present (Figure 7).

#### *2.9.3.1 Delirium*

The primary exposure was delirium during hospital admission, ascertained prospectively using a standardised procedure based on DSM-5 criteria (American Psychiatric Association, 2013) (Table 5). This assessment combined objective testing of the participant, lasting approximately ten minutes, with information gained from informants (usually nurses, next of kin and clinical records) and assessor's judgement regarding subjective features. Along with determining whether delirium was present according to DSM-5, these assessments enabled the recording of features of the delirium along with the development of new delirium. It was possible to follow the natural history of the delirium in terms of any fluctuations, potential resolution and therefore estimate duration. The subsequent development of delirium in previously non-delirious participants was also captured. Delirium duration was recorded as the total number of days on which delirium was captured prospectively.

The assessment was designed to combine multiple validated tools for delirium which enabled scores to be generated for a number of relevant variables. The detailed recording of the phenomenological details of delirium provides unique information not previously collected at a population level. All of the data collected contributed to the assessor's overall judgement as to whether delirium was present or absent (Figure 8).

As well as detailed recording of the delirium itself, a number of other variables were recorded on a daily basis. These are detailed below and were delirium severity, delirium motor subtype, level of alertness, attention, mobility and illness severity. Other factors that were also recorded on a daily basis were medication changes, ward moves, pain score, presence of glasses or hearing aids if required, last bowel

movement as a proxy for constipation, fluid chart completion and fluid input as a proxy for dehydration, food chart completion, recent surgery, presence of a urinary catheter, physiotherapy input and whether delirium had been recognised and documented by the clinical team looking after the patient. Completion of a FOCUS chart was also recorded. This is a nursing assessment tool designed to be completed at least every two hours for all patients at risk of falls, pressure damage or delirium or with dementia. It includes sections on footwear, orientation, constipation, whether the patient needs to go to the toilet, pain, whether they would like a drink, and comfort in order to prompt positional changes.

These variables were carefully selected based on literature demonstrating these factors as either affecting the risk of developing delirium (Inouye et al., 2014) or as potential predictors of outcome following delirium (Jackson et al., 2016b). As both reviews demonstrate, there is a lack of good quality studies in this area. Therefore, this study will be uniquely placed to explore more fully the role and effect size of confounding factors. The confounding effect of number of admissions and number of episodes of captured delirium will also be explored in the analysis of the data.

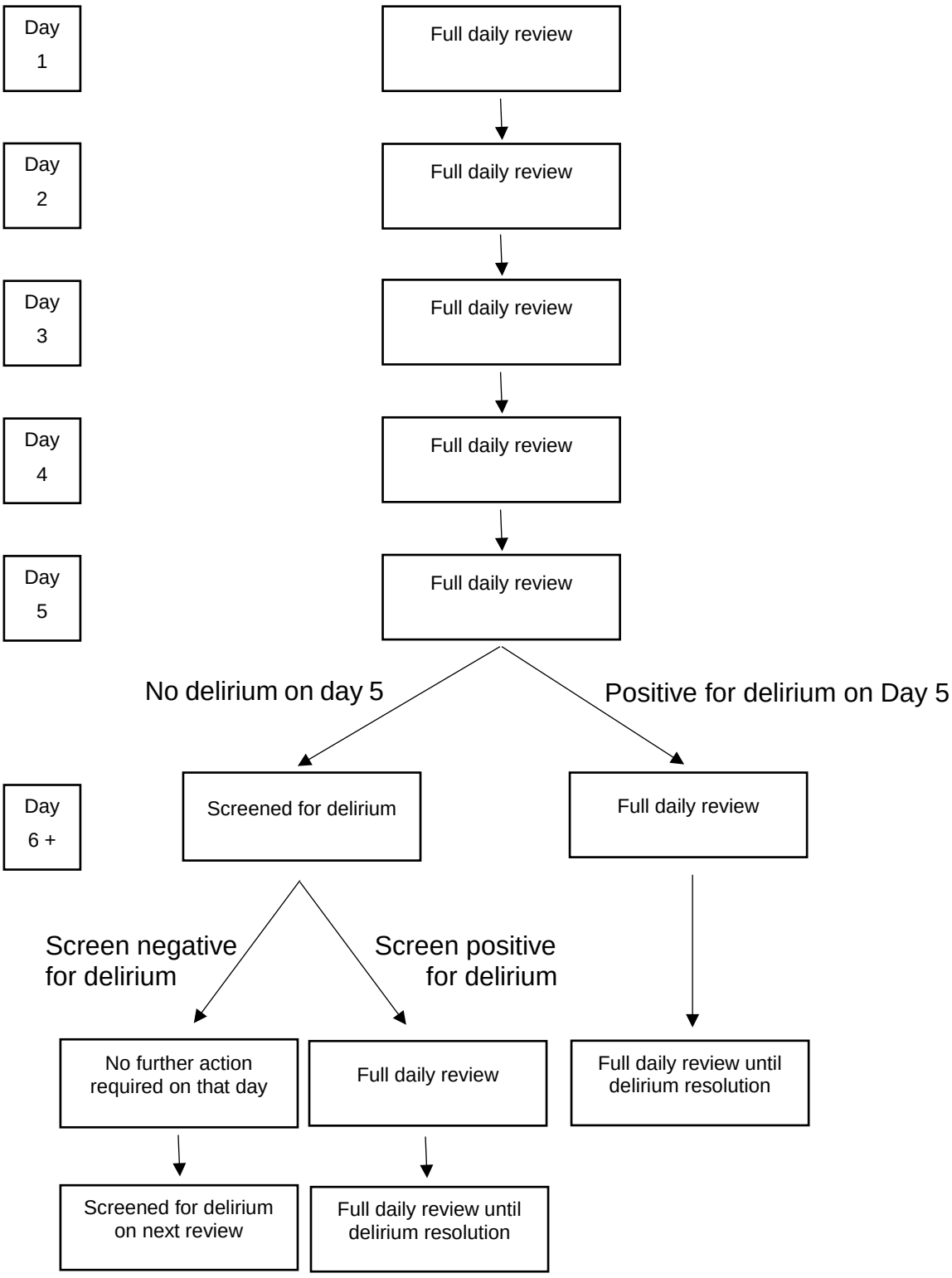
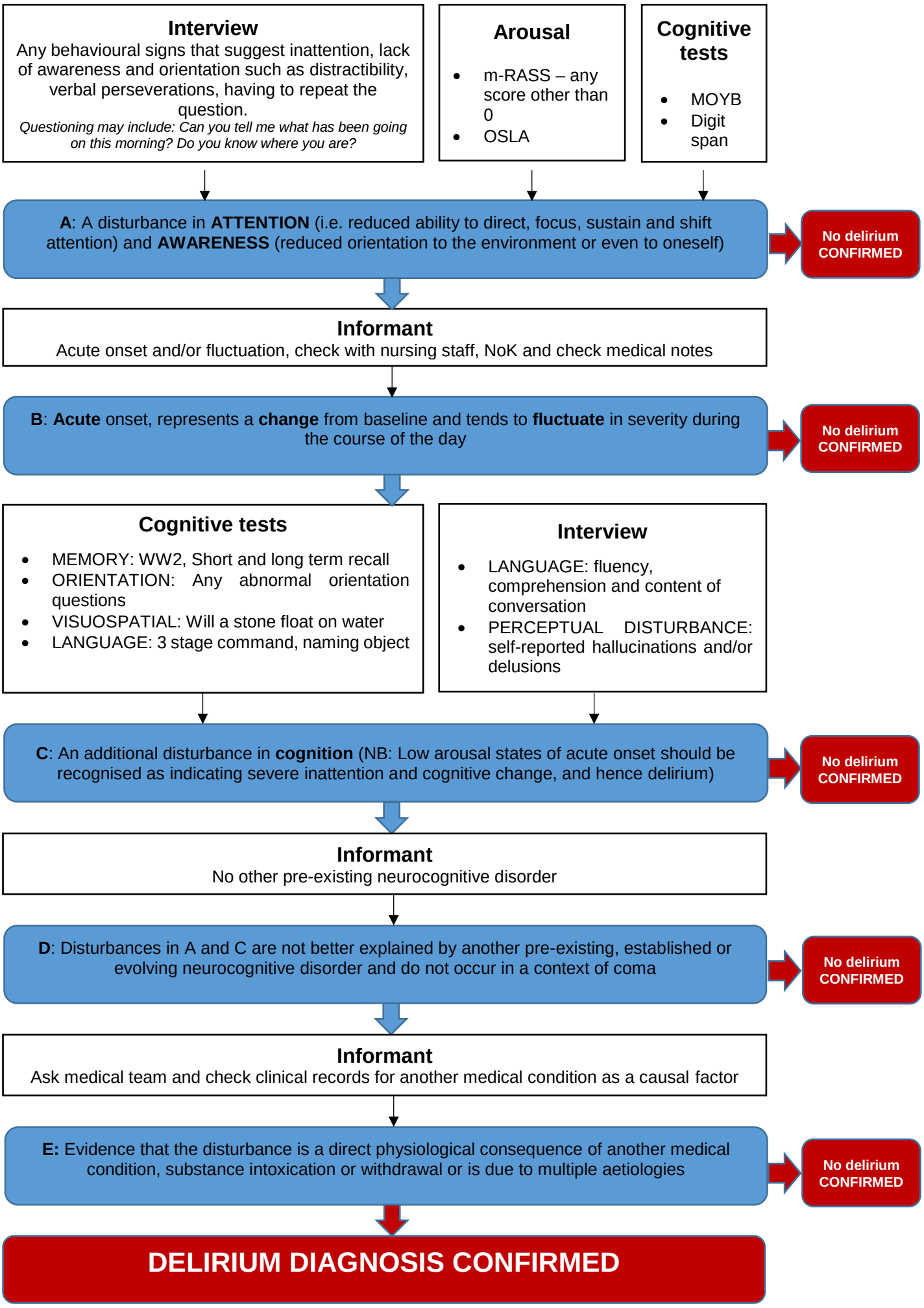



*Figure 7: A flowchart to represent the data collection plan for participants whilst inpatients*

Data collection continued until hospital discharge, the participant declined to participate, or they died.)

*Figure 8: Flowchart to represent the standardised approach used to diagnose delirium based on DSM 5 criteria for delirium (On next page)*


Interview
Any behavioural signs that suggest inattention, lack of awareness and orientation such as distractibility, verbal perseverations, having to repeat the question.
Questioning may include: Can you tell me what has been going on this morning? Do you know where you are?
Arousal
m-RASS – any score other than 0
OSLA
Cognitive tests
MOYB
Digit span
A: A disturbance in ATTENTION (i.e. reduced ability to direct, focus, sustain and shift attention) and AWARENESS (reduced orientation to the environment or even to oneself)
No delirium CONFIRMED
Informant
Acute onset and/or fluctuation, check with nursing staff, NoK and check medical notes
B: Acute onset, represents a change from baseline and tends to fluctuate in severity during the course of the day
No delirium CONFIRMED
Cognitive tests
MEMORY: WW2, Short and long term recall
ORIENTATION: Any abnormal orientation questions
VISUOSPATIAL: Will a stone float on water
LANGUAGE: 3 stage command, naming object
Interview
LANGUAGE: fluency, comprehension and content of conversation
PERCEPTUAL DISTURBANCE: self-reported hallucinations and/or delusions
C: An additional disturbance in cognition (NB: Low arousal states of acute onset should be recognised as indicating severe inattention and cognitive change, and hence delirium)
No delirium CONFIRMED
Informant
No other pre-existing neurocognitive disorder
D: Disturbances in A and C are not better explained by another pre-existing, established or evolving neurocognitive disorder and do not occur in a context of coma
No delirium CONFIRMED
Informant
Ask medical team and check clinical records for another medical condition as a causal factor
E: Evidence that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal or is due to multiple aetiologies
No delirium CONFIRMED
DELIRIUM DIAGNOSIS CONFIRMED

| DSM-5 criteria | Test to be performed or information needed |
|---|---|
| A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). | • Observations by the examiner during the interview (initiated by questioning such as "can you tell me what has been going on today?")<br>• Level of arousal measured using m-RASS and OSLA<br>• Months of the year backwards<br>• Digit span from MDAS |
| B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. | Acute onset and/or fluctuation obtained from informant history from nursing staff, next of kin and clinical notes |
| C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). | Impairment in any of the following domains:<br>SHORT-TERM MEMORY: three item recall at three minutes<br>LONG-TERM MEMORY: when did World War II end?<br>ORIENTATION: 10 orientation questions from MDAS<br>LANGUAGE: 3 stage command, naming an object and explain purpose of object along with fluency, comprehension and content of conversation<br>VISUOSPATIAL: Will a stone float on water?<br>PERCEPTUAL DISTURBANCE: evidence of illusions or hallucinations by collateral or direct observation/questioning |
| D. The disturbances in criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma. | Information from history/chart/clinical examination |
| E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., because of a drug of abuse or to a medication), or exposure to a toxin or is because of multiple aetiologies. | Information from history/chart/clinical examination |

*Table 5: Standardised diagnostic algorithm for DSM-5 delirium (Richardson et al., 2017)*

*2.9.3.2 Delirium severity*

Delirium severity was calculated based upon the Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997). The MDAS is a brief, physician-rated scale designed specifically for quantifying delirium severity among a medically ill population (Breitbart et al., 1997). The ten-items included in the MDAS are based upon the diagnostic criteria for delirium in DSM-IV (American Psychiatric Association, 1994) and are rated by integrating behavioural observations and objective cognitive testing. Each item is rated from 0 to 3 based upon descriptions reflecting the severity or intensity of the symptom.

Although originally designed for use in inpatients with Acquired Immunodeficiency Syndrome (AIDS) and cancer (Breitbart et al., 1997), the MDAS has been successfully validated in people over 65 years (Marcantonio et al., 2002). Validation studies have also demonstrated that, at a cut-off for maximum MDAS score during admission of 9, the MDAS can also successfully identify delirium (sensitivity of 88%, specificity of 91%) (Marcantonio et al., 2002). Despite this, the MDAS was built into the overall assessment of participants and not used as a primary measure of presence or absence of delirium due to the fact that it does not include items for temporal onset or fluctuation of symptoms needed to diagnose delirium according DSM 5 (American Psychiatric Association, 2013).

Unlike other measures of delirium severity such as the Delirium Rating Scale (DRS-R98) (Trzepacz et al., 2001), the MDAS was designed for repeated assessment by clinicians and requires less cognitive testing. This made it advantageous for the purpose of this study whereby we did not want to over-burden participants on a daily basis with too many questions. The MDAS and the DRS-R98 have previously shown substantial agreement in a palliative care setting (O'Sullivan et al., 2015).

*2.9.3.3 Delirium motor subtype*

Motor subtype was defined based upon the Delirium Motor Subtype Scale (Meagher et al., 2014a). Previous work in highly selected populations has shown that hypoactive delirium is associated with worse outcomes in terms of mortality and institutionalisation (Jackson et al., 2016). In order to avoid unnecessary repetition within the data collection proforma, the DMSS was derived from item 9 of the MDAS (Breitbart et al., 1997).

*2.9.3.4 Level of alertness/arousal*

Level of alertness was recorded using the Observational Scale of Level of Arousal (OSLA) (Tieges et al., 2013), the modified Richmond Agitation and Sedation Score (Chester et al., 2012) and the Glasgow Coma Scale (GCS).

The OSLA was designed by geriatricians specifically for use in delirium and provides a structured approach for the detailed recording of the features of deranged level of arousal. It consists of 4 domains: eye opening, eye contact, posture and movement with higher scores indicating an abnormal level of arousal. The OSLA is appealing as it is brief, observational, and does not require formal testing of cognition. Therefore, it was possible to record an OSLA score for all participants, even if they were unable to complete any of the cognitive testing. This inclusivity is relatively unique to the OSLA. In validation studies, abnormal level of arousal, as measured by the OSLA, has been shown to be strongly associated with the presence of delirium (area under the receiver operating characteristic curve was 0.89 [CI: 0.81-0.97), with a sensitivity of 0.87 and a specificity of 0.81) (Tieges et al., 2013).

The Richmond Agitation and Sedation Scale (RASS) is used mainly in mechanically ventilated intensive care patients to measure their agitation or level of alertness to avoid over and under-sedation (Sessler et al., 2002). RASS scores have been shown to be correlated with onset of delirium (Ely et al., 2003). However, a disadvantage of using the RASS is its limited attention assessment. The modified-RASS aimed to build on this limitation by improving the assessment of attention by including a brief, open-ended question to be asked prior to scoring (”Describe how you are feeling today”) (Chester et al., 2012). The modified-RASS was designed for use in a general hospital setting for serial assessments and, with a cut-off of any score other than 0, has demonstrated a sensitivity of 74% and specificity of 92% for delirium (Chester et al., 2012). The m-RASS provides either a positive or a negative score, which is informative of subtype, unlike the OSLA, which is non-directional.

The Glasgow Coma Scale (Teasdale and Jennett, 1974) was recorded due to the fact that it forms part of most of the illness severity measures which will be discussed shortly.

*2.9.3.5 Measures of attention*

A patient's inability to focus, sustain and shift attention toward environmental stimuli is relatively specific to delirium (Brown et al., 2011b, Tieges et al., 2013). Multiple tests of attention have been studied in the context of delirium diagnosis (Meagher et al., 2010, Brown et al., 2011a, Tieges et al., 2014, Tieges et al., 2015). However, the best methods for measuring inattention in delirium are not known. A major problem is that many of the existing tools are not specific for delirium because attentional deficits may already be present if someone has dementia, particularly when it is severe, regardless of whether they have delirium superimposed on their dementia. Many of the tools available currently also test multiple cognitive domains alongside attention and so may also be abnormal in someone with dementia due to their cognitive impairment rather than due to inattention.

In this study, several measures of attention were included. The MDAS uses digit span to test attention along with an overall evaluation of attention based on the assessor's judgement. The months of the year backwards test was also included. The month reached was recorded along with a score: 0 equated to being untestable, 1 equated to participants who started but did not reach June and a score of 2 was given if participants reached June or better. This was in line with the scoring used for the widely validated 4 A's Test (4AT) (Bellelli et al., 2014).

For those unable to complete these tests, 3 other measures of attention were also included. These were days of the week backwards, counting backwards from 20 to 1 and a test of vigilance. To test vigilant attention, participants signalled each time an "A" was heard when the sequence of ten consecutive letters "S-A-V-E-A-H-A-A-R-T" was read out, each letter 3 seconds apart. A failure to complete the test was defined as when a patient failed to signal on the letter "A" or when a patient signalled on any letter other than "A". A test of vigilant attention is appealing as it is simple enough to remain possible even for those with dementia (Leonard et al., 2016). This test is included as the test for attention in the CAM-ICU (Ely et al., 2001), a widely used screening tool for delirium in the intensive care unit.

*2.9.3.6 Illness severity*

A major confounding factor that has not previously been explored is illness severity. Illness severity was recorded during admission using recognised illness severity measures (APACHE II (Knaus et al., 1985)/SOFA (Vincent et al., 1996)/SAPS II (Le Gall et al., 1993)). The data required to complete these measures was collected when participants were seen as part of the 'daily review'. Due to the fact that these scores were designed for use in the intensive care unit, they include variables that are not commonly recorded in general medical patients including pH and arterial oxygen concentrations. Therefore, a modified total score was used which does not include these variables.

Due to the limitations of these illness severity markers previously discussed, the utility of the Hierarchical Assessment of Balance And Mobility (HABAM) (MacKnight and Rockwood, 1995) as a surrogate marker for illness severity and recovery along with delirium development/resolution was also explored.

*2.9.3.7 Hierarchical Assessment of Balance and Mobility*

The HABAM consists of three domains (balance, transfers, and mobility) which are scored based on observation of the patient with items in each domain arranged hierarchically to provide a graphic and rapid assessment. The HABAM overcomes the floor effect associated with other measures such as the Tinetti Gait and Balance Scale (Tinetti, 1986) and Timed Up-and-Go test (Podsiadlo and Richardson, 1991), in those unable to walk, by including clinically relevant changes such as being completely unable to move to being able to roll over.

The HABAM has been shown to be a valid, reliable, and responsive assessment of balance, transfers, and mobility designed to be used by clinicians at the bedside. It was validated in 167 frail older adults in medical and geriatric wards, ambulatory care, emergency department and home visits and showed good inter-rater reliability (0.92) and test-re-test reliability (0.91) (Rockwood et al., 2008).

### *2.9.4 Delirium recognition*

Documentation of the diagnosis of delirium by the clinical team looking after the patient was also recorded. Previous work has shown that delirium is under-recognised and poorly documented (Milisen et al., 2002). Patients in whom their delirium was missed have also been shown to have worse outcomes (Kakuma et al., 2003).

### *2.9.5 Validated tool for retrospective delirium ascertainment*

If it was not possible to review participants prospectively at any particular time point, due to illness, refusal or study capacity, a validated tool was used to retrospectively review the medical records for a diagnosis of delirium (Kuhn et al., 2014).

### *2.9.6 End of data collection*

Recruitment of hospital attendees stopped after 12 months on the 5th January 2017.

In those participants in whom a diagnosis of delirium was not possible or was contentious, vignettes were generated and sent to an expert consensus panel (LA, SP, and DD) consisting of experienced clinicians with considerable familiarity with diagnosing delirium. The vignettes contained a complete copy of the data collection forms for the participant along with a summary of this data following entry onto the study database. It also contained any information collected retrospectively regarding cognition from the medical records as described in section 2.9.5.

Two members of the expert panel (LA, DD) independently reviewed each case and if they disagreed, a third member (SP) reviewed the case and a majority decision was applied. The panel were tasked with determining whether delirium was present or absent. The use of a consensus panel enabled an objective approach. Participants were identified only by their unique study identifier and were therefore anonymised.

## 2.10 Follow up interviews

All participants recruited in hospital, with and without delirium, were invited for follow up 12 months after their most recent hospital discharge. Follow up consisted of a home visit to complete the same interview participants had for CFAS II wave II. This included the Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT) which provides a quantitative measure of cognition, including a CAMCOG and MMSE, along with dementia status and other relevant data such as place of residence and an assessment of physical function. As was the protocol for CFAS II, participants were not informed of their results from the interview.

The Informant Assessment of Geriatric Delirium Scale (I-AGeD) (Rhodius-Meester et al., 2013) was used to explore whether there had been any further episodes of delirium between their discharge from hospital and the follow up interview. This was completed by a next of kin in person at the follow up interview if available or by telephone with the permission of the participant. The I-AGeD was designed to be used on admission to hospital but was modified to request information from "over the past year" in order to cover the study period from 5th January 2016 to 5th January 2017.

A control group of non-hospital attendees during the study period were sampled from the CFAS II-Newcastle cohort on a 1:2 basis. Stratified sampling was used to match 1 control to every 2 participants already recruited to DECIDE by gender, age and years of education. To do this, the recruited participants were divided into 12 groups according to their age, gender and years of education. The eligible control population were then divided into the same 12 groups. 4 to 1 oversampling was used initially. A random number generator was used to assign each of the sampled controls a random number. Participants with an even number were then invited to participate following checking to ensure that they had not been admitted to hospital or died. Once all of these participants had either been approached or excluded due to admission to hospital or death, further controls were selected from the remaining sampled participants by selecting those with the lowest random numbers in the groups still requiring matched controls.

Absence of a history of delirium was ascertained via an interview based on the Informant Assessment of Geriatric Delirium Scale (I-AGeD) (Rhodius-Meester et al., 2013) completed by a next of kin in person at the follow up interview if available or by telephone with the permission of the participant. In order to assess the diagnostic test accuracy of the I-AGeD in this setting, completion was attempted for all participants in the DECIDE study, and not limited to just the controls.

This control group provided a comparator to those admitted to hospital to determine the effect of hospital admission in itself on cognitive decline.

### 2.11 Training of researchers

All data collection was carried out by the chief investigator (SR) and a part time research nurse. The chief investigator is a trainee in Older People's Medicine with experience in the detection of delirium in acute hospitals whilst working as a doctor. The research nurse also had previous experience of working with people with delirium on the intensive care unit where she worked as a nurse prior to starting as a research nurse.

At the start of the study, prior to the commencement of data collection, both completed a comprehensive programme of training in the assessment of delirium in a research setting and familiarisation with the data collection proformas. Educational resources were used, designed by Edinburgh University, to learn about the basics of delirium assessments. A Standard Operating Procedure was also devised for use alongside the data collection proformas.

The chief investigator and the research nurse travelled to Birmingham University to meet with Dr Thomas Jackson to receive training in the assessment of patients with delirium. The day consisted of sessions on how to assess for the core features of delirium including awareness, attention, cognition and onset. The assessment of participants who were difficult to evaluate due to drowsiness, for example, were also discussed. Visits to the wards to observe the assessment of patients with delirium were completed and videos were used to practice scoring patients in a controlled environment.

Following this visit, time was spent watching online videos as well as specially recorded training videos and assessing patients using the data collection forms. These data collection forms were also piloted on the wards in the hospital.

At random time-points throughout the study, joint assessments of a sample of participants were completed to monitor inter-rater reliability and to optimise consistency between assessors.

Training to deliver the standardised computerised interview was identical to that received by staff working on previous waves of the study. A week-long course run by the team based at Cambridge University was completed, with follow-up practice until each interviewer achieved the necessary quality standards. There was also ongoing quality control which involved audio recording interviews with consenting participants for review by the team at Cambridge University (Matthews et al., 2013).

### 2.12 Data Handling and Confidentiality

Data was handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data left the study site. Participants were allocated a unique study identifier which was used on all data stored in order to ensure anonymity. Caldicott approval was granted. Personal data was regarded as strictly confidential. All study records, including the consent forms, and investigator site files were kept in a locked filing cabinet with restricted access.

### 2.13 Ethical approvals

The study design, protocol and paperwork were reviewed and given favourable opinion by the Newcastle and North Tyneside 2 Regional Ethics Committee (REC reference: 15/NE/0353).

### 2.14 Power calculations

We aimed to detect a clinically and statistically significant difference in the annual decrease in the total CAMCOG (total score 107), between 6 points in delirium participants and 3 points in participants without delirium. Assuming that 10% of the cohort (the most conservative end of the range) was a delirium case and that the standard deviation of the decrease in CAMCOG is 2.7 points (Cullum et al., 2000),

then in order to detect the desired difference (2-fold) in the CAMCOG with 90% power, using a two-sided test at the 5% level, 10 participants with delirium at the time of admission to hospital and 90 participants without delirium would be needed, i.e. a total of 100 participants. The analysis would additionally allow for other factors using a regression approach, rather than simply comparing how the change in CAMCOG from admission to follow-up differs between the two groups. Also, whilst the calculation assumes complete data have been collected for all participants, the analysis will explore the possibility of incorporating participants with missing data. The above calculations are based on a very conservative prevalence of delirium of 10%. If, for example, the prevalence was 20%, then a total of 55 participants (11 with delirium, 44 without) would be required, based on the assumptions outlined above.

By applying the expected number of admissions per age group, based on best available data (Blunt et al., 2010), to the number of people within these age groups remaining in the CFAS II-Newcastle cohort, it was possible to estimate that 450 people would be admitted during the year long study period.

## 2.15 Statistical analysis

All statistical analysis was performed on STATA Version 15. All graphs, unless otherwise stated, were created using Microsoft Excel 2013.

### *2.15.1 Recruitment, admission rates and demographics*

All continuous variables were checked for normality by plotting in histograms and assessing the normality of the distribution. These graphs, generated on STATA version 15, are displayed where relevant. Between groups differences for baseline characteristics were checked using an independent t-test, Kruskall-Wallis test or chi-squared test depending on whether the data were continuous or categorical, normal or non-normally distributed. For clarity, the statistical test used is stated in the results tables below the p value obtained. Multiple logistic regression analysis was used to determine which of the variables were independently associated with admission.

### *2.15.2 Delirium incidence*

As above, between groups differences in characteristics were checked using an independent t-test, Kruskall-Wallis test or chi-squared test depending on whether the data were continuous or categorical, normal or non-normally distributed. The

statistical test used is stated in the results table below the p value obtained. Multiple logistic regression analysis was used to determine which of the variables were independently associated with delirium.

In cases of diagnostic uncertainty, the diagnosis of delirium was determined by a consensus panel as described in section 2.9.5. When there was disagreement in the diagnosis between the two expert assessors, a third expect panel member was required to create a majority decision. Sensitivity analysis was performed to explore whether these cases impacted on the results obtained in statistical analysis. This was done by performing all subsequent analysis with these cases and then without these cases. The results of these sensitivity analyses are recorded.

### *2.15.3 Outcomes at 1 year*

The primary aim of the study was to measure the effect on cognition of an episode of delirium, independent of baseline cognition and illness severity.

The CAMCOG was used as the primary measure of global cognitive status when examining the effect of delirium as the exposure. Total MMSE score at follow up was also evaluated as a measure of cognitive status. This is shorter than the CAMCOG and consequently, would be expected to be completed by a greater proportion of participants, even if very cognitively impaired. The binary outcome measure of dementia yes or no at follow up according to the AGECAT was also considered.

In order to evaluate the contribution of delirium to cognitive outcomes at follow up (measured using CAMCOG, MMSE and AGECAT diagnosis), regression analysis was performed. Relevant confounders including age, years of education, gender, illness severity, frailty, baseline cognition, comorbidities and time between wave 2 and follow up interviews were included in the regression analysis alongside delirium status.

Death prior to the follow up interview and new institutionalisation were also considered as outcomes and regression analysis, as described above, was performed to evaluate the independent contribution of delirium.

To avoid the survivor effect associated with evaluating CAMCOG score alone as an outcome, a binary ‘poor outcome’ was considered to be death, institutionalisation or

new dementia at follow up interview. Regression analysis was performed to evaluate the independent contribution of delirium.

The outcome measures explored are summarised in Table 6 along with whether the variable was continuous or binary. Multiple regression analysis was used for continuous outcome measures and logistic regression analysis was used for binary outcome measures.

| **Outcome measure** | **Type of data** |
|---|---|
| Total CAMCOG score at follow up interview | Continuous |
| Total MMSE score at follow up interview | Continuous |
| AGECAT diagnosis of dementia | Binary |
| Death prior to follow up interview | Binary |
| Institutionalisation | Binary |
| Poor outcome – new AGECAT diagnosis of dementia OR death prior to follow up interview OR institutionalisation | Binary |

*Table 6: Outcome measures to be explored in analysis*

The sensitivity of the results to patterns of missing data and methods for accounting for this were also explored. In general, due to the small amount of missing data, participants with missing data were excluded from analysis. Where this occurred, the reasons for the missing data were investigated and any specific patterns were detailed in the discussion.

Sensitivity analysis was performed, as described previously in Section 2.15.2, to explore whether the more challenging diagnostic cases impacted on the results obtained in statistical analysis.

Regression analysis was also used to explore the impact of hospital admission on these outcomes by comparing outcome data in those who were admitted during the

study period with the controls sampled who were not admitted to hospital during the study period.

The diagnostic accuracy of the I-AGeD for ascertaining a retrospective diagnosis of delirium over the preceding year was evaluated using the diagnosis of delirium obtained prospectively for the DECIDE study as a gold standard. A receiver operating characteristic curve was generated for the I-AGeD along with a calculation of the area under the curve (AUROC) and the best cut-off determined.

### *2.15.4 Predictors of poor outcomes*

Using regression analysis as described above, with the outcomes listed in Table 6, it was possible to explore the predictive value of peak delirium severity, delirium motor subtype, delirium duration, number of episodes of delirium and presence or absence of perceptual disturbances whilst controlling for the confounding effects of age, years of education, gender, illness severity, frailty, baseline cognition, comorbidities and time between wave 2 and follow up interviews.

The overall approach is novel because no previous delirium ascertainment studies have been nested within an existing, well-characterised cohort allowing baseline characteristics to be controlled for in the final analysis. Assistance with data analysis was sought from collaborators who have experience in this field and have also previously worked with the CFAS II cohort.

## 2.16 Declarations:

### *2.16.1 Funding*

This study is funded via a Clinical Training Fellowship from the Alzheimer's Society awarded to Sarah Richardson (239 (AS-CTF-14-001)). CFAS II has been supported by the Medical Research Council (G0601022) and received support from the Clinical Research Network for North East and Cumbria (dementia and neurodegenerative disease division).

# Chapter 3: Results – Demographics

## 3.1 Recruitment

Of the 2,582 participants originally interviewed in wave 1 of the CFAS II-Newcastle cohort, 1751 were re-interviewed at wave 2 (67.1%). Of these, 1328 participants were surviving and non-objecting at the start of the DECIDE study in January 2016 (Figure 9).

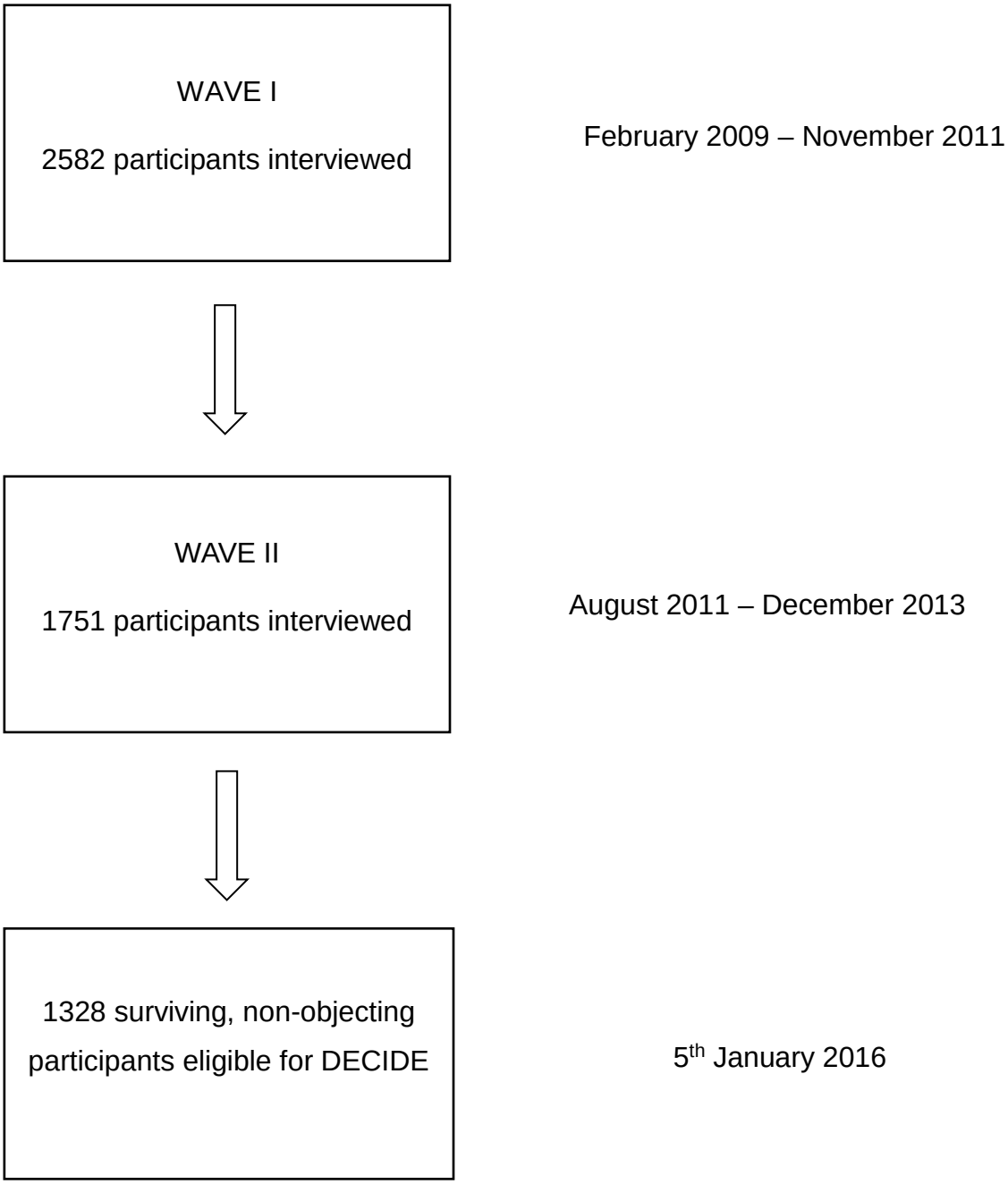



*Figure 9: Flowchart showing the number of CFAS II - Newcastle participants interviewed at Wave I and Wave II and eligible for DECIDE*

1328 RAPAs (recurring admission patient alerts), or electronic flags, were applied to the medical records of surviving, non-objecting CFAS II-Newcastle participants on 5th January 2016. Those participants who were inpatients on the day that the flags were applied were not approached at this time. Only newly admitted participants from 5th January 2016 were approached and invited to take part. For participants to activate a RAPA alert, they had to be admitted to a ward within the hospital. Therefore, attendances to Accident and Emergency did not trigger an alert unless they were admitted to the observation ward which forms part of Accident and Emergency. Patients are often held here whilst they await a bed or review by the multi-disciplinary team regarding safety for discharge.

During the year of hospital ascertainment, between 5th January 2016 and 5th January 2017, 363 (27.3%) CFAS-II Newcastle participants were admitted to the Newcastle upon Tyne Hospitals NHS Foundation Trust (Figure 10). 83 of these participants did not fulfil the inclusion criteria: 60 were admitted for less than 24 hours, 12 were not approached as it was felt to be inappropriate due to their diagnosis, 6 died prior to being approached and 5 were barrier nursed throughout their admission due to infections.

Of the remaining 280 eligible participants, 205 were recruited to the study (73.2%). 75 were not recruited: 49 declined, 12 had no capacity and no next of kin to act as a consultee and 14 were not approached by the study team and therefore missed.

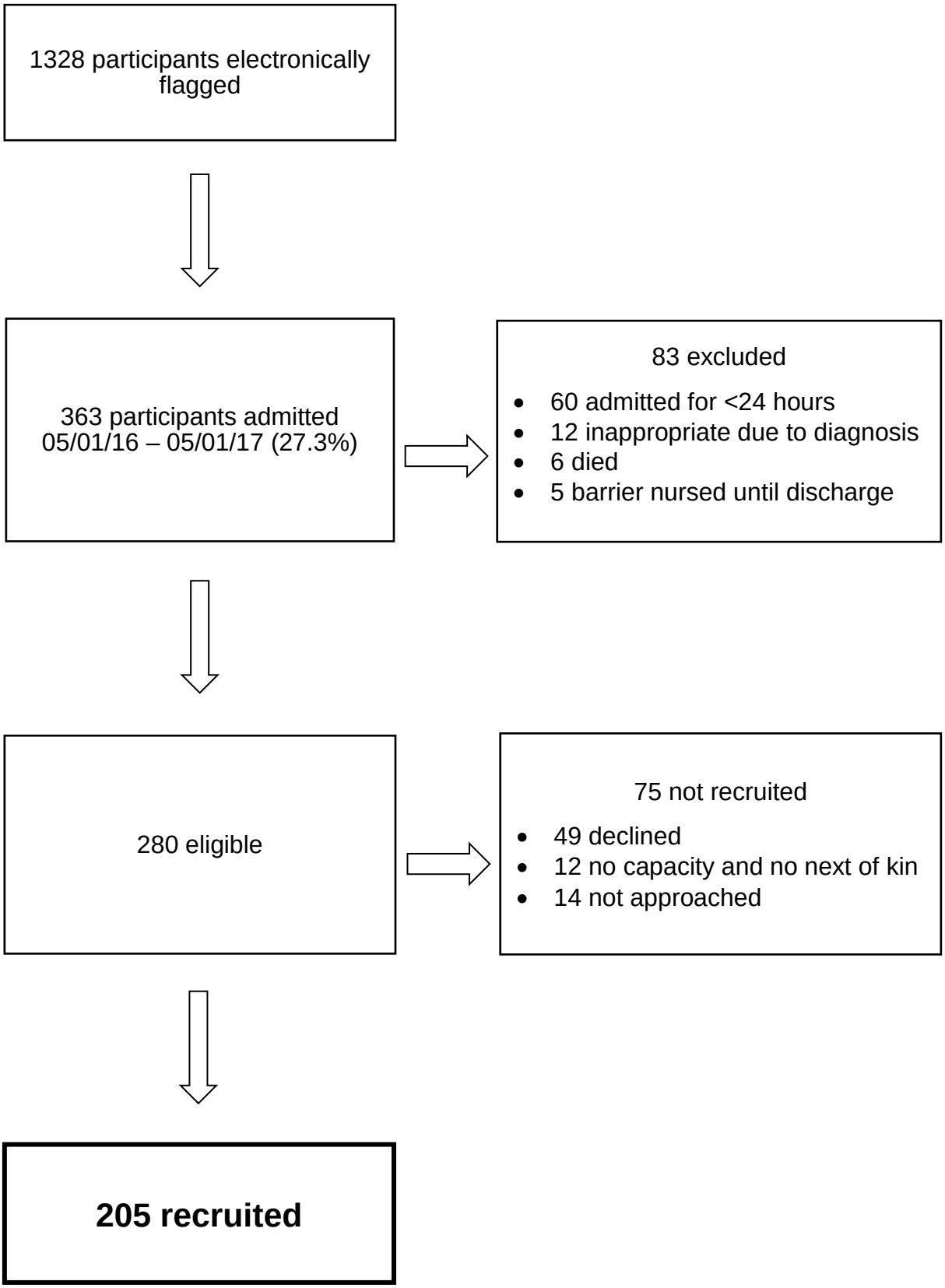



*Figure 10: DECIDE recruitment flowchart*

## 3.2 CFAS II-Newcastle participants admitted in 2016

### *3.2.1 Admission rates*

Between 5th January 2016 and the 5th January 2017, there were 607 admissions by 363 participants. Of these admissions, 476 were for a duration of over 24 hours (Figure 11).

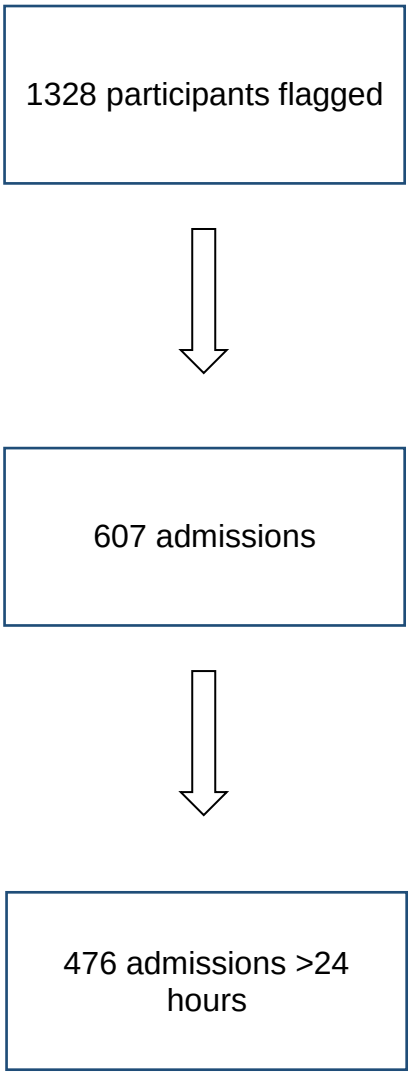



*Figure 11: Number of admissions during the study period*

The RAPA was active for the study during 2016 and 2017 so it is possible to compare the rates of admissions per month between the two years (Table 7). By dividing the number of admissions per month by the number of days in the particular month that were studied, it is possible to calculate the mean number of admissions per day each month (Figure 12).

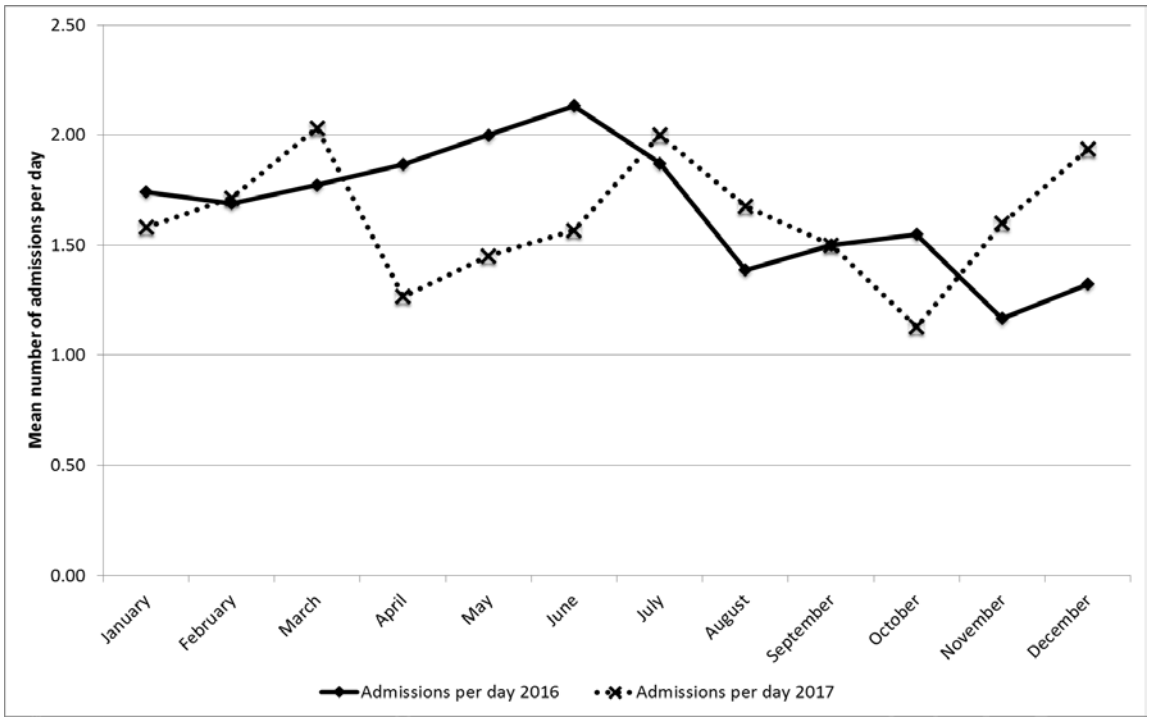



*Figure 12: Mean number of admissions per day by month*

| Month | Number of days assessed in month in 2016 | Number of admissions per month in 2016 | Admissions per day 2016 | Number of days assessed in month in 2017 | Number of admissions per month in 2017 | Admissions per day 2017 |
|---|---|---|---|---|---|---|
| January | 27 | 47 | 1.74 | 31 | 49 | 1.58 |
| February | 29 | 49 | 1.69 | 28 | 48 | 1.71 |
| March | 31 | 55 | 1.77 | 31 | 63 | 2.03 |
| April | 30 | 56 | 1.87 | 30 | 38 | 1.27 |
| May | 31 | 62 | 2.00 | 31 | 45 | 1.45 |
| June | 30 | 64 | 2.13 | 30 | 47 | 1.57 |
| July | 31 | 58 | 1.87 | 31 | 62 | 2.00 |
| August | 31 | 43 | 1.39 | 31 | 52 | 1.68 |
| September | 30 | 45 | 1.50 | 30 | 45 | 1.50 |
| October | 31 | 48 | 1.55 | 31 | 35 | 1.13 |
| November | 30 | 35 | 1.17 | 30 | 48 | 1.60 |
| December | 31 | 41 | 1.32 | 31 | 60 | 1.94 |

*Table 7: Flowchart of admissions 05/01/2016 – 31/12/17*

NB: Due to the fact that the flags were applied on 5th January 2016, January 2016 contained fewer days studied than January 2017. The total number of admissions in 2016 according to the table above is 603, 4 less than the total given previously in Figure 11. This is due to the fact that the total number of admissions during the year study period ended on the 5th January 2017, and so included a further 4 admissions, while the table above included these 4 admissions in the January 2017 data.

### *3.2.2 Demographics*

When comparing those who were admitted during the study period from 5th January 2016 to 5th January 2017 (n=363) to those who were not (n=965), those who were admitted were significantly older, more cognitively impaired, more likely to be living in 24 hour care, more likely to be from an unskilled, partly skilled or skilled manual social class household, more disabled and with 10 or fewer years of full time education (Table 8).

| Variable | Admitted during study (n=363 unless stated) | Not admitted during study (n=965 unless stated) | Statistically significant? (statistical test used) |
|---|---|---|---|
| Gender (% females) | 55.37% | 54.82% | No (p=0.857) (Chi-squared test) |
| **Age at wave 2 interview in years (mean, SD)** | **78.40 +/- 6.49** | **75.69 +/- 5.92** | **Yes (p<0.000)** (Independent t test) |
| **Accommodation at wave 2 (% living in 24-hour care)** | **2.20%** | **0.52%** | **Yes (p=0.005)** (Chi-squared test) |
| **Social class (% in social class IIIM (skilled manual occupations), IV (partly-skilled occupations) or V (unskilled occupations)** | **53.56%** N=351 | **42.89%** N=942 | **Yes (p=0.001)** (Chi-squared test) |
| **Modified Townsend disability score (% with more functional incapacity (score 11-18))** | **17.22%** N=360 | **5.96%** N=956 | **Yes (p<0.000)** (Chi-squared test) |
| **Cognition at wave 2 - CAMCOG total score (mean, SD)** | **86.50 +/- 9.89** N=339 | **91.19 +/- 7.84** N=905 | **Yes (p<0.000)** (Two-sample Wilcoxon rank-sum test) |
| **≤10 years in full time education (%)** | **72.38%** N=362 | **62.85%** N=961 | **Yes (p=0.001)** (Chi-squared test) |

*Table 8: Characteristics of CFAS II-Newcastle participants admitted to hospital compared to those not admitted during the study period using baseline data from CFAS II-Newcastle (variables with a significant difference demonstrated shown in bold)*

Multiple logistic regression analysis was used to determine which (if any) of the variables shown in Table 8 were independently associated with admission. In this analysis, age, baseline cognition measured using CAMCOG and functional incapacity, according to the modified Townsend disability score, remained statistically significant predictors of admission when adjusting for the other variables (Table 9). This equates to an increased risk of admission to hospital of 5% for each year older you are or a decreased risk of admission to hospital of 4% for every additional point scored on the CAMCOG at wave 2.

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Female | 0.936 | 0.704 – 1.245 | 0.650 |
| **Age at wave 2 interview (years)** | **1.047** | **1.023 – 1.071** | **0.000** |
| Institutionalised at wave 2 interview | 1.554 | 0.259 – 9.312 | 0.629 |
| Social class IIIM, IV or V | 1.180 | 0.872 – 1.598 | 0.283 |
| **Modified Townsend disability score 11-18 (more functional incapacity)** | **1.818** | **1.156 – 2.859** | **0.010** |
| **Cognition at wave 2 interview measured using total CAMCOG score (points)** | **0.960** | **0.943 – 0.978** | **0.000** |
| ≤10 years in full time education | 1.138 | 0.834 – 1.552 | 0.415 |

*Table 9: Results of regression analysis exploring variables which independently predicted admission during the study period*

## 3.3 DECIDE participants recruited in hospital

### *3.3.1 Admission rates*

As per Figure 10, 205 participants were recruited to the DECIDE study on admission to hospital. 96 of these participants were readmitted during the study period (46.8%). There were 186 readmissions in total (Table 10).

| **Number of admissions** | **Number of participants** |
|---|---|
| *1* | *109* |
| *2* | *55* |
| *3* | *19* |
| *4* | *8* |
| *5* | *8* |
| *6* | *2* |
| *7* | *3* |
| *8* | *0* |
| *9* | *0* |
| *10* | *1* |

*Table 10: Number of admissions for DECIDE participants during the study period from 5th January 2016 to 5th January 2017*

Mean length of stay overall was 10 days with a range from 0 to 100 days. The mean length of stay per admission is shown in Table 11.

| **Admission number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of participants** | 205 | 96 | 41 | 22 | 14 | 6 | 4 | 1 | 1 | 1 |
| **Total number of inpatient days** | 2097 | 835 | 326 | 162 | 148 | 124 | 114 | 8 | 16 | 22 |
| **Mean length of stay (days)** | 10 | 9 | 8 | 7 | 11 | 21 | 29 | 8 | 16 | 22 |

*Table 11: Mean length of stay by admission for the 205 participants recruited to DECIDE in hospital during the study period from 5th January 2016 to 5th January 2017*

### *3.3.2 Demographics*

205 participants were recruited to the DECIDE study during their inpatient stays in 2016. These participants had a mean age of 82 years ranging from 69 to 99 years (Figure 13). 109 of the 205 participants recruited were female (53.2%).

Mean total CIRS-G score, a measure of comorbidity, for the 205 participants was 8.57 ranging from 0 to 22 (Figure 14). Mean Rockwood Clinical Frailty Score for the first admission during the study period was 4.25 (Figure 15). Mean total Barthel Index of Activities of Daily Living Score for the first admission during the study period was 18.2 (Figure 16).

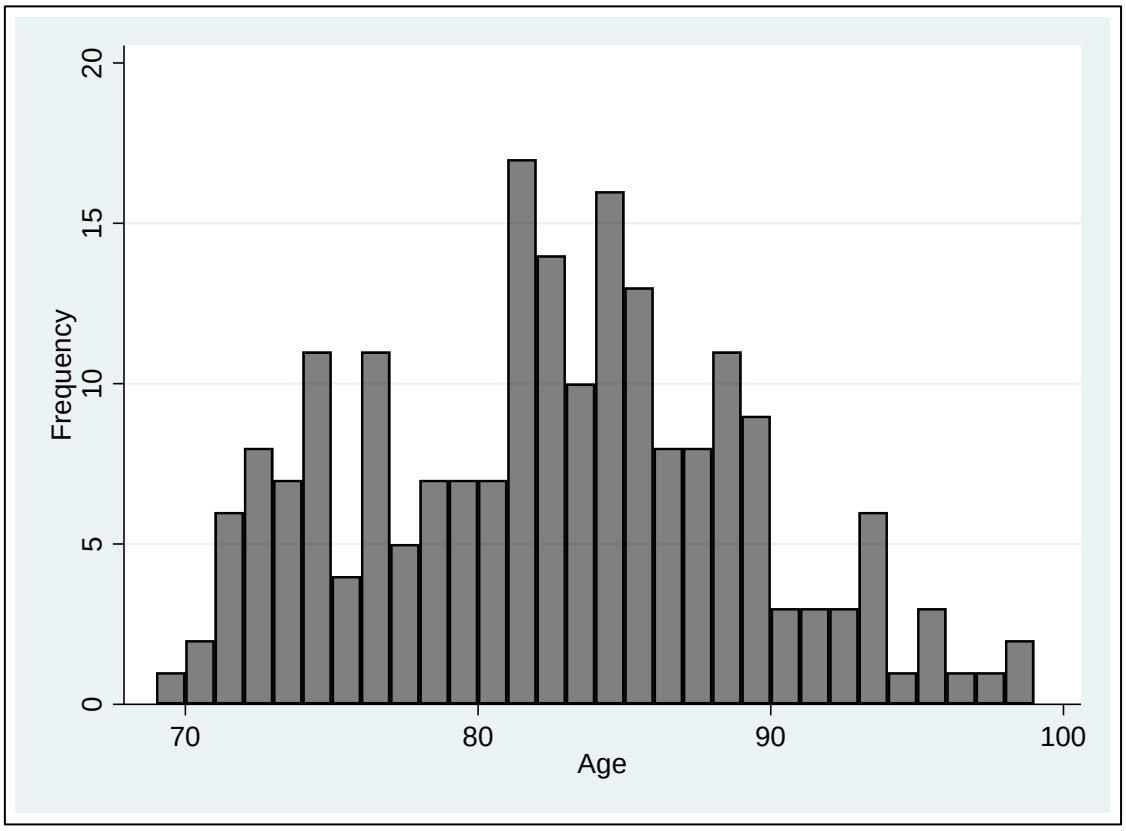



*Figure 13: Histogram representing age distribution of DECIDE participants recruited in hospital during 2016 (drawn using STATA Version 15)*

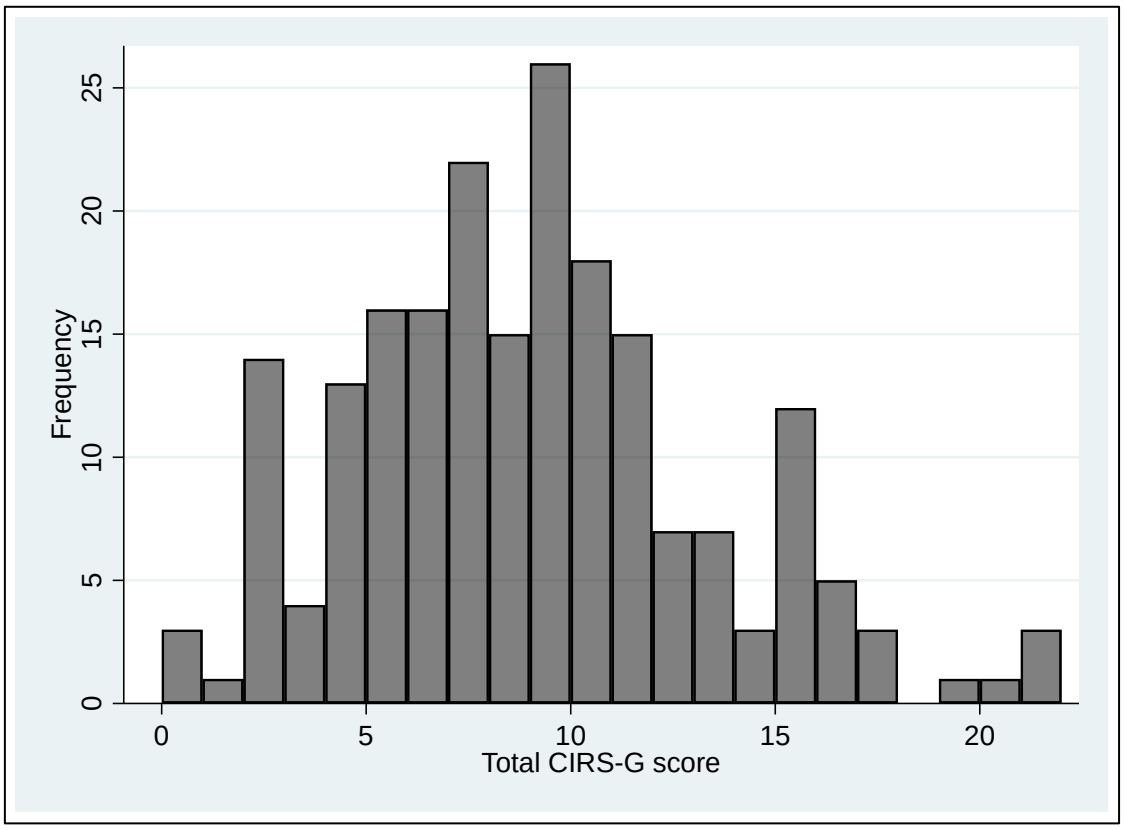



*Figure 14: Histogram representing total CIRS-G score for DECIDE participants recruited in hospital (drawn using STATA Version 15)*

On their first admission during the study period, 12 participants (5.85%) lived in 24 hour care. Of the remaining 193 participants, 104 lived in a house, 47 in a bungalow, 27 in a flat and 15 in sheltered accommodation. 15 of those who were not in 24-hour care had formal care packages (7.77%).

44 of the 205 participants were recruited via a consultee (21%) because they lacked the capacity at the time of admission to take part in the study. 21 participants had a documented diagnosis of dementia according to their medical records on admission to hospital.

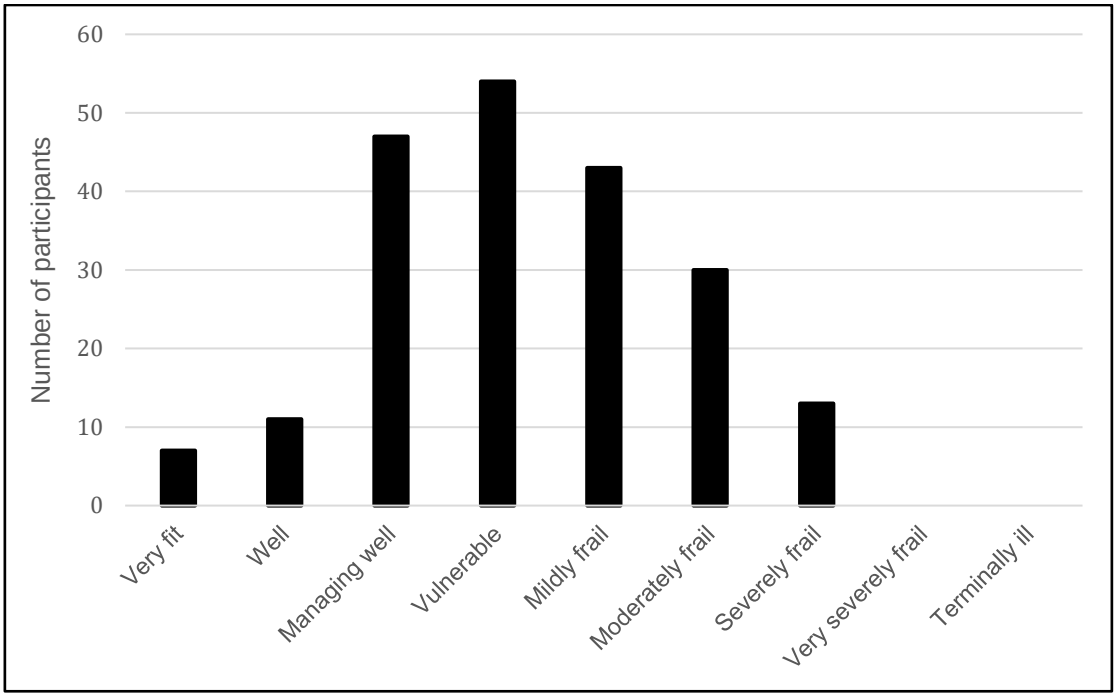



*Figure 15: Histogram representing total Rockwood Clinical Frailty Score on first admission during the study period*

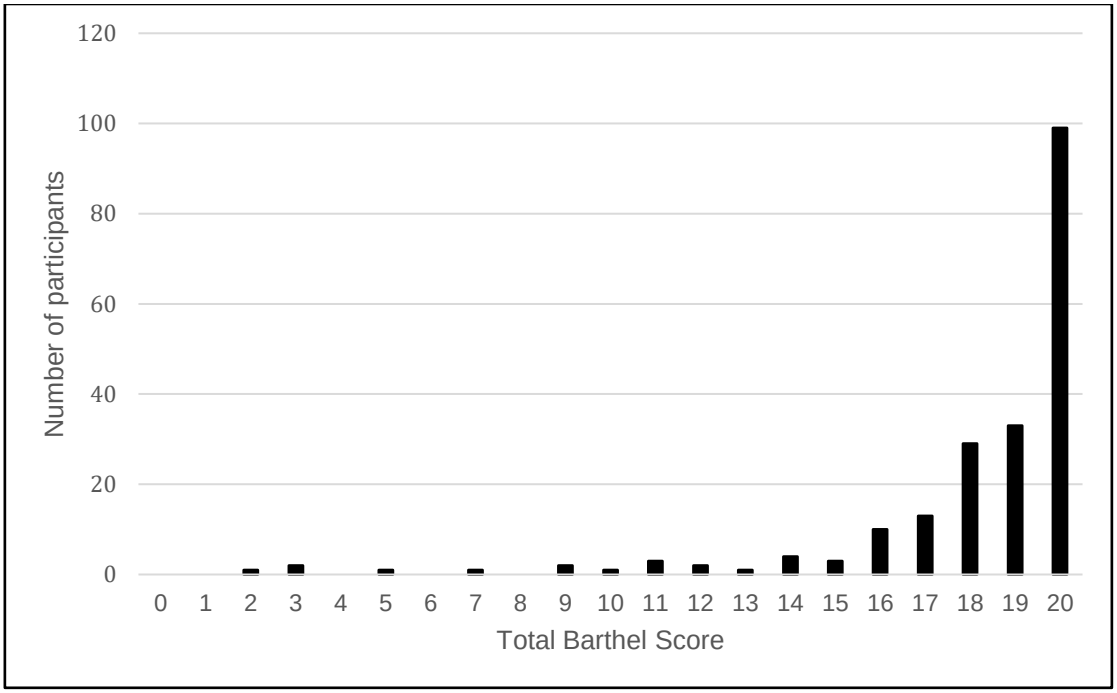



*Figure 16: Histogram representing total Barthel Index of Activities of Daily Living Score on first admission during the study period*

### 3.4 Non-recruits

Of the 363 participants admitted to hospital during the study period, 205 were recruited to DECIDE. 158 participants were not recruited, for reasons as detailed in Figure 10. Due to the fact that these people are all part of CFAS II-Newcastle, it was possible to compare the baseline characteristics of those recruited with those not recruited to ensure there was no sampling bias. Table 12 shows that there were no significant differences in baseline characteristics between the two groups.

| **Variable** | **Admitted but not recruited** (n=158 unless stated) | **Recruited to DECIDE** (n=205 unless stated) | **Statistically significant?** (statistical test used) |
|---|---|---|---|
| Gender (% females) | 58.23 | 53.17 | No (p=0.337) (Chi-squared) |
| Age at wave 2 interview in years (mean, SD) | 78.11 (+/- 6.50) | 78.62 (+/- 6.49) | No (p=0.457) Independent t-test |
| ≤10 years in full time education (%) | 73.89 (n=157) | 71.22 (n=205) | No (p=0.574) (Chi-squared) |
| Accommodation at wave 2 interview (% living in 24-hour care) | 3.16 | 1.46 | No (p=0.274) (Chi-squared) |
| Social class at wave 1 (% in social class IIIM, IV or V) | 56.95 (n=151) | 51.00 (n=200) | No (p=0.268) (Chi-squared) |
| Modified Townsend disability score (% with more functional incapacity (score 11-18)) | 18.59 (n=156) | 16.18 (n=204) | No (p=0.548) (Chi-squared) |
| Cognition at wave 2 interview - CAMCOG total score (mean, SD) | 86.20 (+/-10.2) (n=142) | 86.72 (+/- 9.69) (n=197) | No (p=0.553) (Two-sample Wilcoxon rank-sum test) |

*Table 12: Demographics of CFAS II-Newcastle participants admitted to hospital but not recruited compared to those who were recruited to DECIDE during the study period using baseline data from CFAS II-Newcastle*

## 3.5 Controls

### *3.5.1 Sampling and recruitment*

The 965 CFAS II-Newcastle participants who were flagged at the start of the study and had no admissions to hospital during the study period were eligible as controls. A further 33 were admitted to hospital between the end of the study period and the day of sampling and these participants were also excluded. A further 5 people were removed from the list of potential controls due to the fact that their GP had informed the study team that they had died. The remaining 927 CFAS II-Newcastle participants were eligible as controls (Figure 17).

The 4 to 1 oversampling used initially resulted in 406 controls being sampled from the 927 eligible participants. 202 of these participants were assigned an even number and therefore approached or excluded due to having been admitted since sampling or having died since sampling. Further controls were selected from the remaining participants from the sample of 406 by selecting those with the lowest random numbers in the groups still requiring matched controls.

In total, 187 control participants were approached and invited to be interviewed and 101 controls were recruited. During the interview with one of the control participants, it became apparent that they had been admitted to hospital just prior to the interview taking place. Therefore, they were excluded as a control, leaving 100 eligible controls.

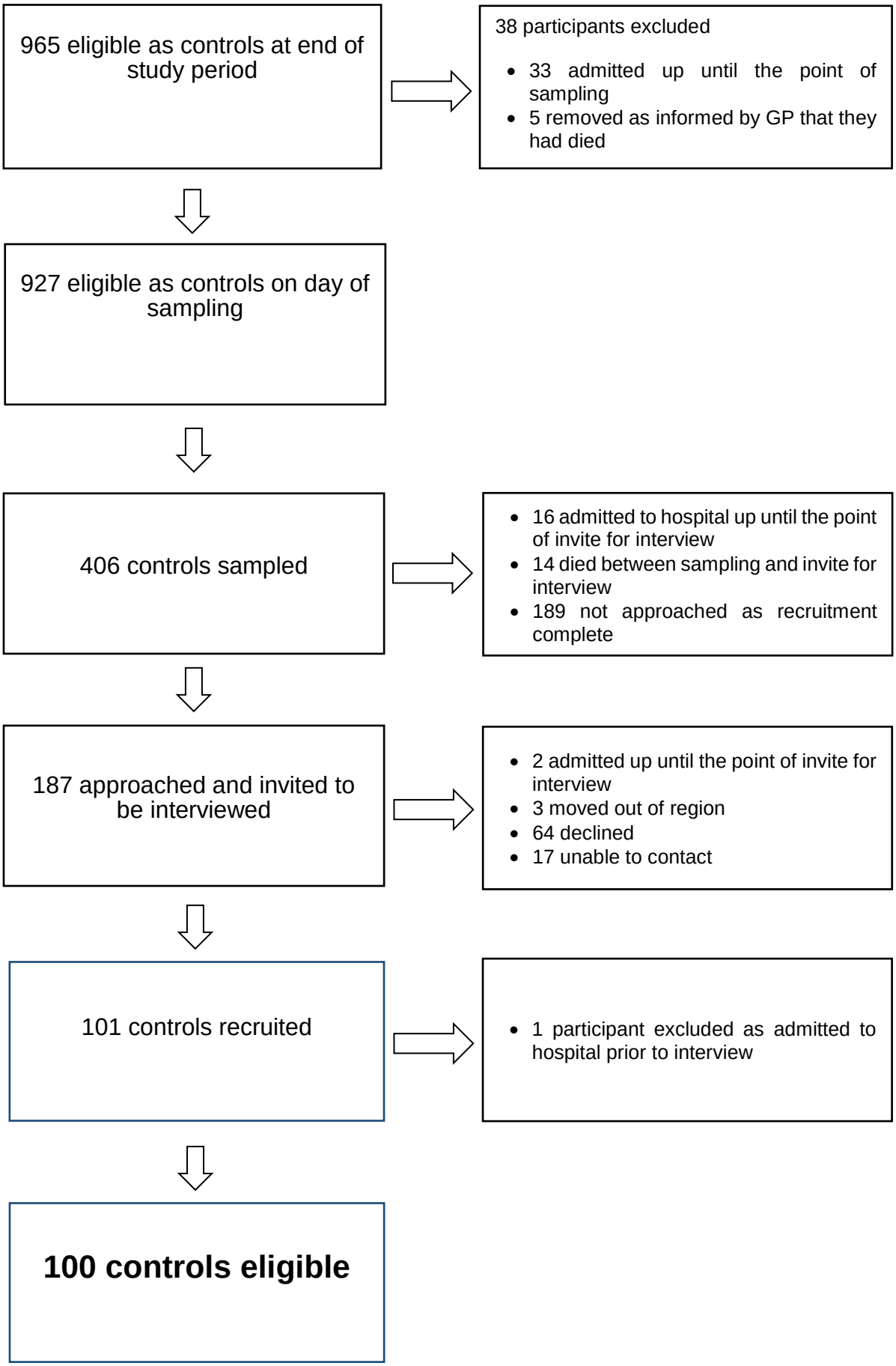



*Figure 17: Recruitment flowchart for controls*

### *3.5.2 Demographics of the control population*

Table 13 compares the control population to the DECIDE participants recruited in hospital. The control population is matched, as intended, for age, gender and years of education. The DECIDE participants recruited in hospital had significantly worse baseline cognition and were significantly more functionally incapacitated according to the modified Townsend disability score when compared to the controls recruited.

| **Variable** | **Controls** (n=100 unless stated) | **Recruited to DECIDE** (n=205 unless stated) | **Statistically significant?** (statistical test used) |
|---|---|---|---|
| Gender (% females) | 55.00% | 53.17% | No (p=0.764) (Chi-squared) |
| Age at wave 2 interview in years (mean, SD) | 77.69 (+/- 5.56) | 78.62 (+/- 6.49) | No (p=0.220) Independent t-test |
| ≤10 years in full time education (%) | 71.00% | 71.22% | No (p=0.968) (Chi-squared) |
| Accommodation at wave 2 interview (% living in 24-hour care) | 0.00% | 1.46% | No (p=0.224) (Chi-squared) |
| Social class (% in social class IIIM, IV or V) | 43.00% | 51.00% (n=200) | No (p=0.191) (Chi-squared) |
| **Modified Townsend disability score at wave 2 (% with more functional incapacity (score 11-18))** | **3.00%** | **16.18% (n=204)** | **Yes (p=0.001) (Chi-squared)** |
| **Cognition at wave 2 - CAMCOG total score (mean, SD)** | **92.54 (+/- 4.74) (n=93)** | **86.72 (+/- 9.69) (n=197)** | **No (p<0.000) (Two-sample Wilcoxon rank-sum test)** |

*Table 13: Comparison of demographics of controls recruited compared to DECIDE participants recruited in hospital*

# Chapter 4: Results – Delirium incidence

## 4.1 Incidence of delirium

82 of the 205 participants recruited to the DECIDE study had delirium at some point during their time as an inpatient during the study period between 5th January 2016 and 5th January 2017. This equates to a delirium incidence of 40%.

Compared to those who did not develop delirium, those who did develop delirium were older, were more likely to be from an unskilled or manual labour household, were more functionally impaired, had more co-morbidities, were frailer, were more likely to have “dementia” documented in their medical records and were more cognitively impaired when last interviewed as part of CFAS II (Table 14).

Multiple logistic regression analysis was used to determine which (if any) of the variables shown in Table 14 were independently associated with the development of delirium during the study period (Table 15). In this analysis, age and cognition at wave 2 interview measured using total MMSE score remained statistically significant predictors of delirium when adjusting for the other variables. The analysis showed that for each year older you are, the risk of delirium increased by 9% (OR 1.093 [CI: 1.029 – 1.161]). It also showed that for every point gained on the MMSE, your risk of delirium reduced by 5% (OR 0.952 (CI: 0.912 – 0.995)).

In Table 15, the number of participants living in 24 hour care was not included in logistic regression analysis because the proportion of people in both groups who were institutionalised was very small.

| **Variable** | **Delirium** (n=82 unless stated) | **No delirium** (n=123 unless stated) | **Statistically significant?** | **Statistical test used** |
|---|---|---|---|---|
| Gender (% females) | 48.78% | 56.10% | No (p=0.304) | Chi-squared |
| **Age when recruited to DECIDE (mean, SD)** | **84.71 +/- 6.52** | **80.27 +/- 5.88** | **Yes (p<0.000)** | **Independent t-test** |
| Accommodation when recruited to DECIDE (% living in 24-hour care) | 7.32% | 4.88% | No (p=0.466) | Chi-squared |
| **Social class at wave 1 (% in social class IIIM (skilled manual occupations), IV (partly-skilled occupations) or V (unskilled occupations)** | **60.76% (n=79)** | **44.63% (n=121)** | **Yes (p=0.026)** | **Chi-squared** |
| **Modified Townsend disability score at wave 2 interview (% with more functional incapacity (score 11-18))** | **27.16% (n=81)** | **8.94% (n=123)** | **Yes (p=0.001)** | **Chi-squared** |
| **CIRS-G total (mean, SD)** | **10.05 +/- 4.22** | **7.56 +/- 4.13** | **Yes (p<0.000)** | **Independent t-test** |
| **Cognition at wave 2 - CAMCOG total score (mean, SD)** | **82.10 +/- 11.34 (n = 78)** | **89.74 +/- 6.99 (n = 119)** | **Yes (p<0.000)** | **Two-sample Wilcoxon rank-sum test** |
| **MMSE wave 2 (mean, SD)** | **24.91 +/- 3.66** | **27.29 +/- 2.52** | **Yes (p<0.000)** | **Two-sample Wilcoxon rank-sum test** |
| ≤10 years in full time education (%) | 78.05% | 66.67% | No (p=0.078) | Chi-squared |
| **Dementia documented in medical records (%)** | **20.73%** | **3.25%** | **Yes (p<0.000)** | **Chi-squared** |
| **Rockwood Clinical Frailty Score (mean, SD)** | **4.94 +/- 1.20** | **3.80 +/- 1.40** | **Yes (p<0.000)** | **Independent t-test** |

*Table 14: Comparison of demographic data for DECIDE participants recruited in hospital who developed delirium during the study period with those who did not develop delirium during this time* (variables reaching statistical significance shown in bold).

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Gender (female) | 0.874 | 0.423 – 1.806 | 0.717 |
| **Age (per year)** | **1.093** | **1.029 – 1.161** | **0.004** |
| In social class IIIM (skilled manual occupations), IV (partly-skilled occupations) or V (unskilled occupations) at wave 1 | 1.795 | 0.851 – 3.784 | 0.124 |
| More functional incapacity (score 11-18) according to modified Townsend disability score | 1.945 | 0.703 – 5.378 | 0.200 |
| Total CIRS-G score (per point) | 1.093 | 0.996 – 1.201 | 0.062 |
| Clinical Frailty Score (per point) | 1.151 | 0.827 – 1.603 | 0.405 |
| ≤10 years in full time education | 1.467 | 0.638 – 3.374 | 0.367 |
| **Cognition at wave 2 interview measured using total MMSE (per point)** | **0.952** | **0.912 – 0.995** | **0.027** |

*Table 15: Results of logistic regression analysis exploring baseline characteristics which independently predict delirium.*

### *4.1.1 Diagnostic uncertainty*

In 18 of the 82 cases of delirium, the diagnosis was determined by a consensus panel due to the fact that the diagnosis was not clear during the prospective assessments. The panel consisted of 2 experts (LA and DD) who reviewed all of the available data, both prospective data collected at the time of the study by reviewing the data collection forms, and retrospective data recorded from the medical records using a validated tool (Kuhn et al., 2014). The two assessors were blinded to each other's decisions.

In 4 cases, there was disagreement in the decision and so a third expert panel member (SP) was required to create a majority decision. This panel member was also blinded to the previous assessors' decisions and had access to the same prospective and retrospective data. Sensitivity analyses were carried out by performing all subsequent analysis with and without these cases to explore whether these cases impacted on the results obtained.

The logistic regression analysis in Table 15 was performed without the 4 cases in which there was diagnostic uncertainty. Although there were minor variations in the odds ratios obtained, the same variables remained statistically significant, demonstrating that these cases did not significantly impact on the overall results Table 16).

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| Gender (female) | 0.878 | 0.421 – 1.833 | 0.729 |
| **Age (per year)** | **1.092** | **1.027 – 1.162** | **0.005** |
| In social class IIIM (skilled manual occupations), IV (partly-skilled occupations) or V (unskilled occupations) at wave 1 | 1.854 | 0.870 – 3.951 | 0.110 |
| More functional incapacity (score 11-18) according to modified Townsend disability score | 1.888 | 0.676 – 5.267 | 0.225 |
| Total CIRS-G score (per point) | 1.091 | 0.993 – 1.199 | 0.070 |
| Clinical Frailty Score (per point) | 1.194 | 0.853 – 1.672 | 0.301 |
| ≤10 years in full time education | 1.401 | 0.601 – 3.265 | 0.434 |
| **Cognition at wave 2 interview measured using total CAMCOG (per point)** | **0.955** | **0.914 – 0.997** | **0.035** |

*Table 16: Results of logistic regression analysis exploring baseline characteristics which independently predict delirium excluding the 4 cases in which the diagnosis was less certain and required a third expert assessor.*

## 4.2 Delirium specifics

### *4.2.1 History of delirium*

8 of the 205 participants recruited to the DECIDE study in hospital had a history of delirium prior to the study period documented in their medical records. 62 of the 205 had a history of delirium prior to the study period reported by them or their informant (30%). A history of delirium in the medical records or from the patient or their informant was significantly more likely in those who developed delirium (Table 17).

| **Variable** | **Delirium (n=82)** | **No delirium (n=123)** | **Statistically significant?** |
|---|---|---|---|
| Previous episode of delirium documented in medical records (%) | 7.32% | 1.63% | Yes (p=0.039) |
| Previous episode of delirium reported by participant or informant (%) | 47.56% | 18.70% | Yes (p<0.000) |

*Table 17: Comparison of the rates of delirium in those with and without a previous episode of delirium documented in their medical records or reported by the participant or their informant using Chi-squared test.*

### *4.2.2 Duration of delirium*

Mean total number of days with delirium during the study period was available for 76 of the 82 participants with delirium and was 5.88 days, with a standard deviation of 9.16 days. Minimum number of days with delirium was 1 day and maximum was 59 days.

### *4.2.3 Motor subtype of delirium*

The motor subtype of delirium was evaluated using item 9 of the MDAS. When more than one subtype occurred, this was recorded as mixed delirium. Of the 82 people with delirium, 34 did not have a motor subtype defined according to MDAS item 9. Of the participants with delirium who had a subtype defined, 14 had hyperactive delirium, 15 had hypoactive delirium and 19 had mixed delirium (Figure 18).

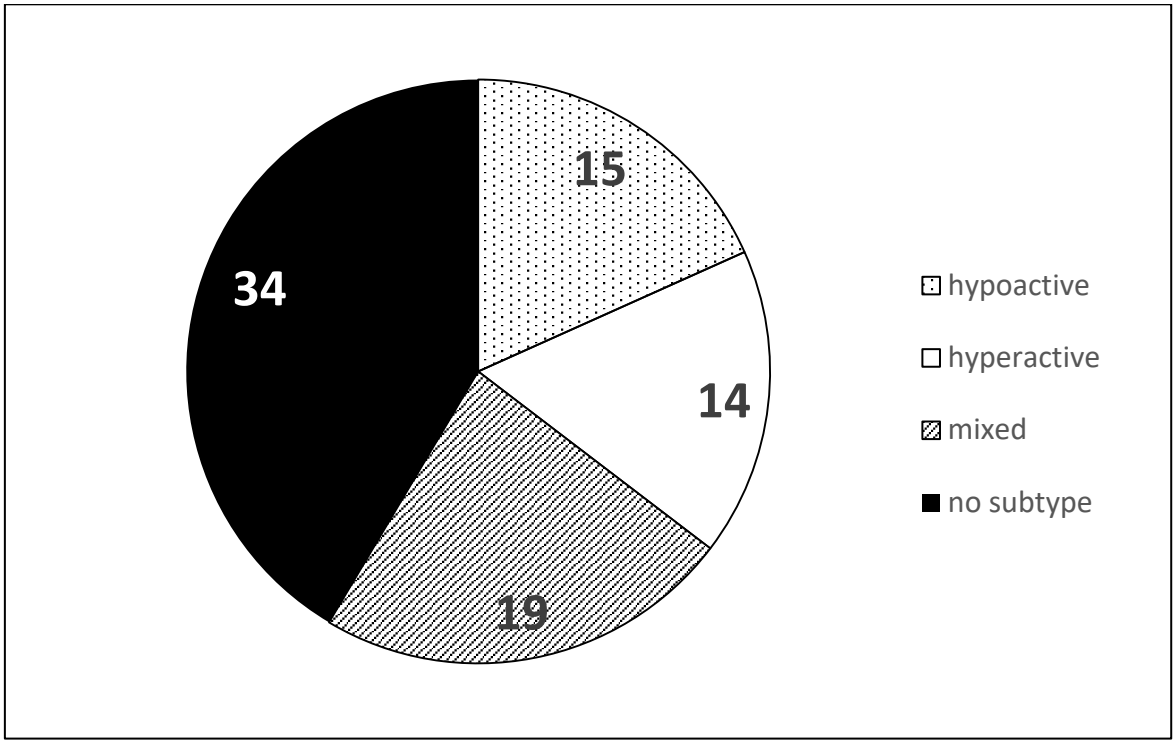



*Figure 18: Pie chart demonstrating the motor subtype of delirium, as per item 9 on the MDAS, experienced by participants with delirium*

### *4.2.4 Severity of delirium*

Delirium severity was measured using the Memorial Delirium Assessment Scale. It was possible to calculate a peak delirium severity for 200 of the 205 participants. 5 of the 205 participants remained untestable throughout their hospital admissions due to delirium and therefore did not have a recordable peak MDAS score. 3 of these people had delirium superimposed on advanced dementia.

Mean peak delirium severity was 5.37 (SD 4.42) with minimum total score of 0 and maximum total score of 23. When comparing those with and without delirium, using a Mann-Witney test due to the variable not being normally distributed, those who developed delirium during the study period had significantly higher peak MDAS scores (Table 18).

| | **Delirium** | **No delirium** | **Statistically significant?** |
|---|---|---|---|
| Peak total MDAS score during study period (mean, SD) | 9.29 +/- 4.39 | 2.92 +/- 2.04 | Yes ($p<0.000$) |

*Table 18: Comparison of peak total MDAS scores in participants with and without delirium during the study period*

### *4.2.5 Number of episodes of delirium*

123 of the 205 participants recruited to DECIDE over the study period experienced no episodes of delirium. 58 participants had one episode of delirium, 17 had 2 episodes and 7 participants had 3 or more episodes of delirium (Figure 19).

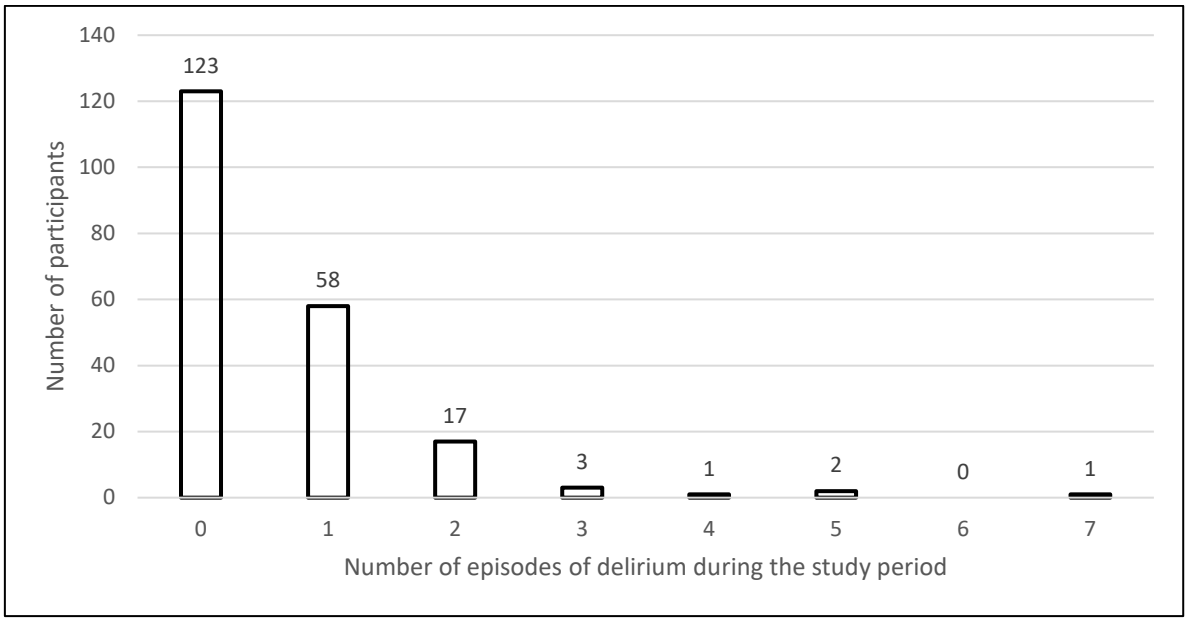



*Figure 19: Bar graph showing the number of episodes of delirium captured during the study period for the 82 people with delirium*

## 4.3 Perceptual disturbances

### *4.3.1 Prevalence of perceptual disturbances*

65 of the 205 participants (31.7%) recruited in hospital answered "yes" when asked the following question when they were assessed as an inpatient:

*"Sometimes people in hospital can see and hear things that perhaps are not really there. Have you had anything like that?"*

Most people reporting perceptual disturbances reported hallucinations (61%) (Figure 20), and the majority of these were visual hallucinations (95%). 17% reported delusions and the remaining 22% reported both hallucinations and delusions.

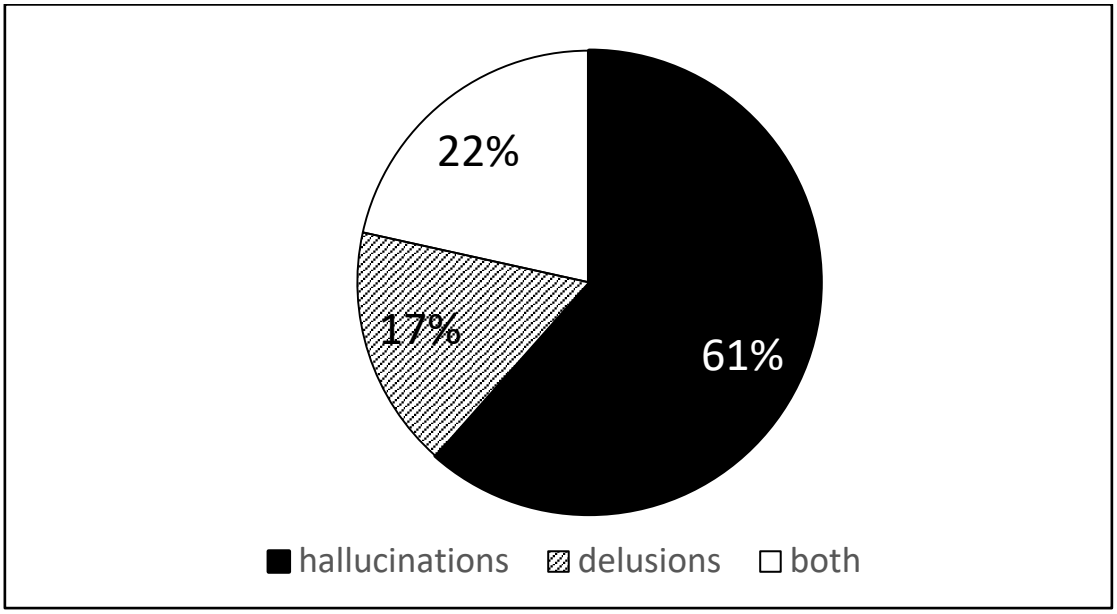



*Figure 20: Pie chart to show the type of perceptual disturbances reported by DECIDE participants in hospital*

### *4.3.2 Association with delirium*

45 of the 65 people who reported perceptual disturbances (69.2%) fulfilled DSM-5 criteria for delirium at the time and 30 reported feeling distressed at the time (46.2%).

20 people who reported perceptual disturbances did not fulfil criteria for DSM 5 delirium at the time that they reported the perceptual disturbances. When exploring this, 7 reported experiences that had happened at night, 2 reported experiences at home immediately prior to admission, 1 had Dementia with Lewy Bodies and 1 had

Parkinson's Disease Dementia and experienced hallucinations as part of these conditions. 1 participant was withdrawing from alcohol. 2 participants had dementia and had delirium before and after reporting perceptual disturbances. This may suggest that they needed to recover sufficiently from their delirium in order to communicate their experience. 3 people had "misperceptions or illusions related to sleep" according to the Memorial Delirium Assessment Scale which included 1 vivid dream which possibly continued on waking, 1 daydream and 1 misrepresentation when they saw their mother's face in a cloud. This left 3 people who reported true visual hallucinations but did not have delirium at the time.

### *4.3.3 What did participants report?*

Participants reported a variety of visual hallucinations including animals such as horses, dogs, mice, birds and people dressed up as animals. Participants reported seeing people, on the ward or at the window, including children, clowns and the Virgin Mary. Some participants reported seeing vehicles including tractors and a yellow bus whilst another participant could see prices on the ceiling tiles. Several participants reported seeing dirt everywhere on the ward.

In terms of the delusions, it was common for participants to report having been somewhere else including a space station, a football match, into town, to the doctor's surgery, on a boat and to prison. Several people mentioned that this was not a real hospital and that all the staff were "in on it". Several people thought that there had been fighting on the ward. One participant thought that the hospital had been sold to a brewery.

### *4.3.4 Demographics of participants with perceptual disturbances*

Participants who experienced perceptual disturbances were significantly older, more likely to have a diagnosis of dementia recorded in their hospital records and had more co-morbidities according to their mean total CIRS-G score (Table 19).

| | **Reported perceptual disturbances** (n = 65) | **Did not report perceptual disturbances** (n = 140) | **Significance level** (test used) |
|---|---|---|---|
| **Age (mean)** | **83.72** | **81.26** | **P=0.0114 (independent t test)** |
| Gender (% female) | 31 (47.69%) | 78 (55.71%) | P=0.284 (chi-squared test) |
| **Dementia reported** | **11 (16.92%)** | **10 (7.14%)** | **P=0.032 (chi-squared test)** |
| Visual impairment present | 62 (95.38%) | 136 (97.14%) | P=0.519 (chi-squared test) |
| Hearing impairment present | 23 (35.38%) | 39 (27.86%) | P=0.275 (chi-squared test) |
| **Co-morbidities (mean total CIRS-G score)** | **10.14** | **7.82** | **P=0.0003 (independent t test)** |
| **Total Rockwood Clinical Frailty Score on first admission** | **4.83** | **3.99** | **P=0.0001 (independent t test)** |

*Table 19: Comparison of baseline characteristics in those who reported and did not report perceptual disturbances*

# Chapter 5: Results – Outcomes at 1 year

## 5.1 Interviews at 1 year

### *5.1.1 Number of interviews completed*

135 of the 205 participants recruited to DECIDE in hospital completed follow up interviews one year after their hospital admission (65.9%) (Figure 21). 38 of the 205 participants died prior to the follow up interview (18.5%). Of the remaining 32 participants not seen at one year, 1 had moved out of the region and 31 refused (15.1%).

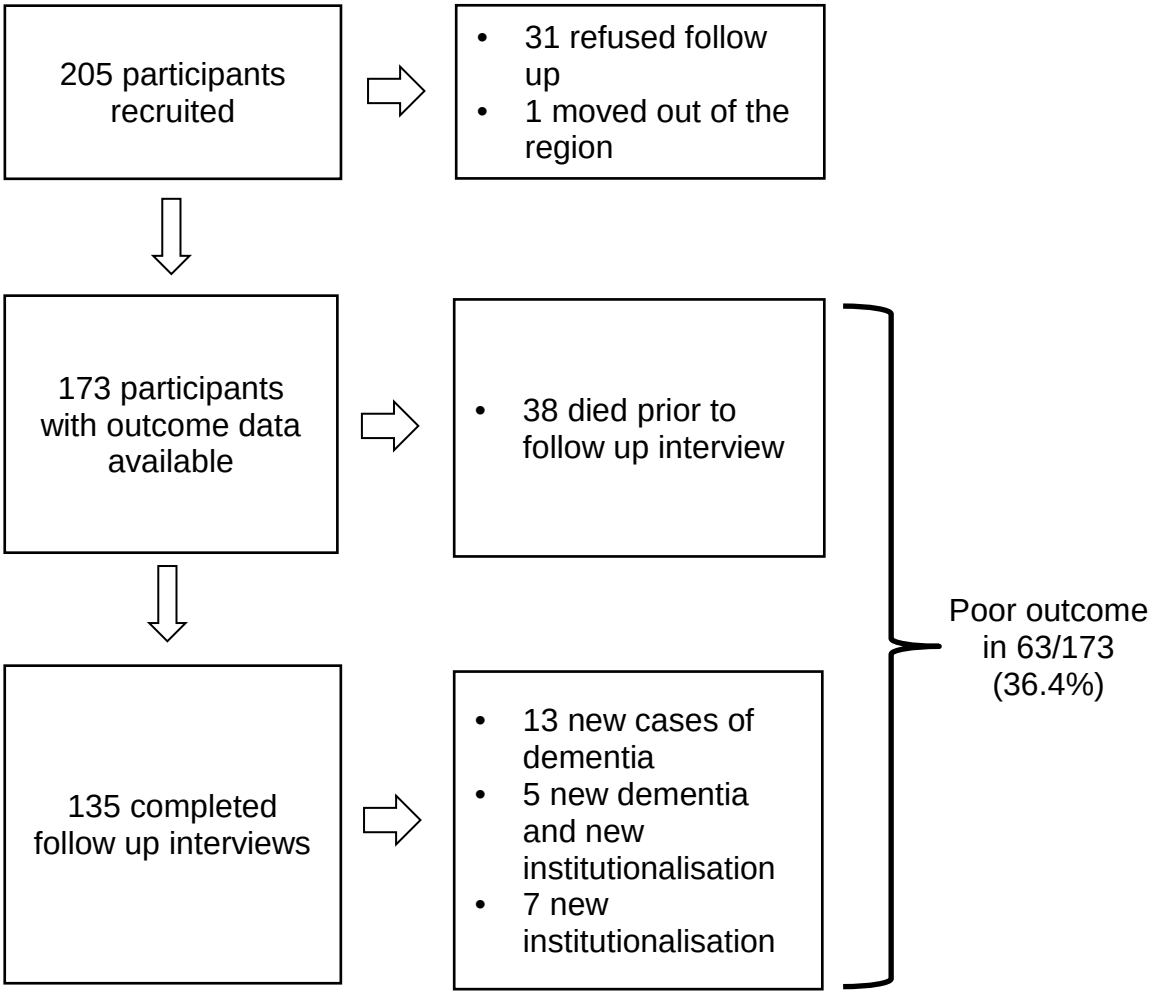



*Figure 21: Flowchart showing the proportion of DECIDE participants who completed follow up interviews at 1 year and the reasons for non-completion.*

### *5.1.2 Time between interviews*

For the 135 participants who completed a follow up interview, mean number of years between participants' wave 2 interview, as part of CFAS II-Newcastle, and their follow up interview for DECIDE, was 4.51 years (SD 0.83 years) with minimum 3 years and maximum 6 years. This was equal to a mean number of days between interviews of 1665 days (SD 264.21) with minimum 1221 days and maximum 2271 days.

## 5.2 Change in residence at 1 year

115 participants remained at the same level of accommodation between first admission to hospital and follow up interview. 20 of 135 participants had a change in their level of residence between first hospital admission during the study period and the follow up interview at one year (Figure 22 and Figure 23). At recruitment to DECIDE, 4 participants (2.96%) who were followed up at 1 year lived in residential or nursing care. However, at follow up, this figure had risen to 12 participants (8.89%).

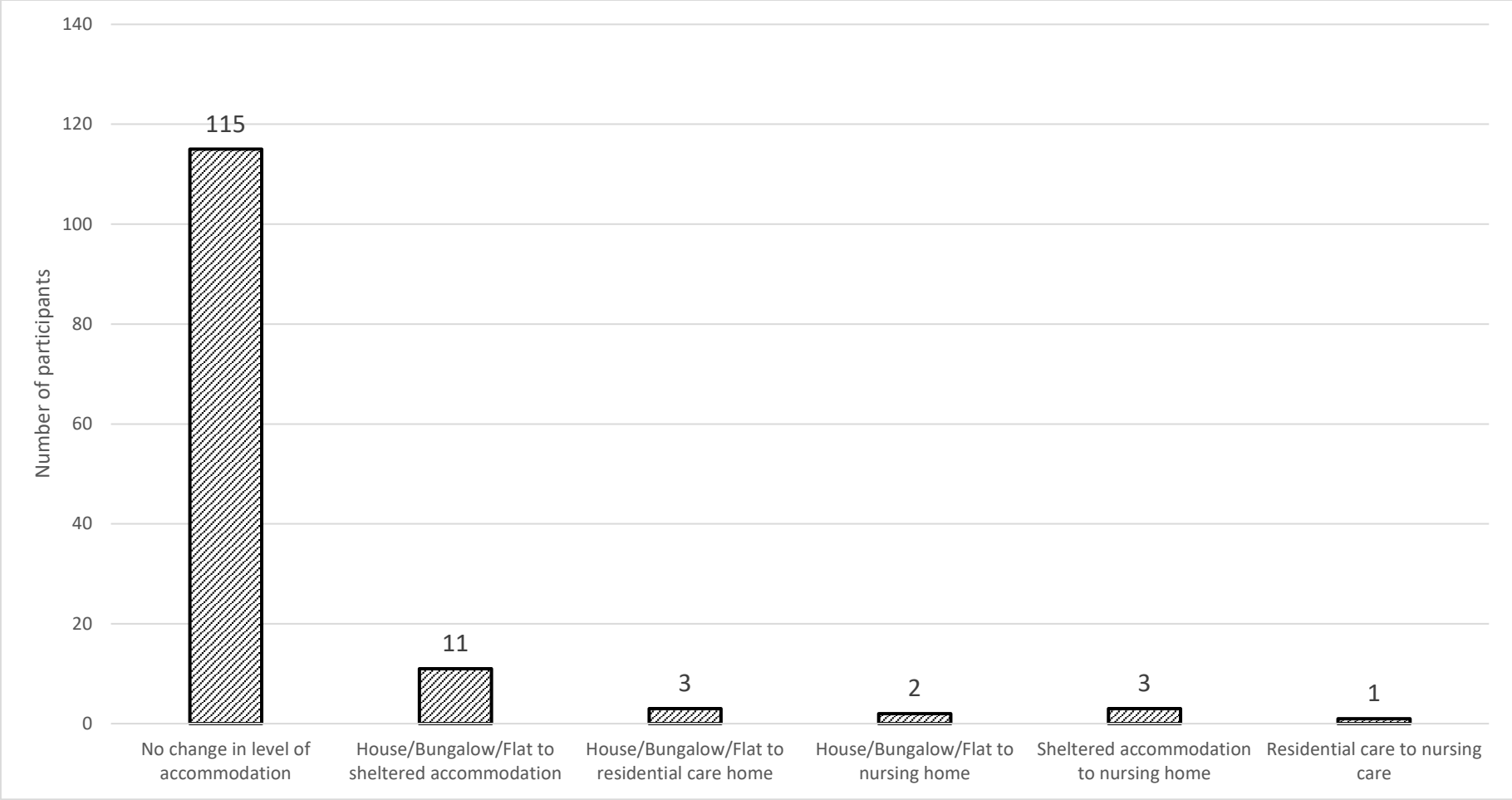



*Figure 22: Graph representing the transitions in place of residence of the 135 DECIDE participants followed up at 1 year*

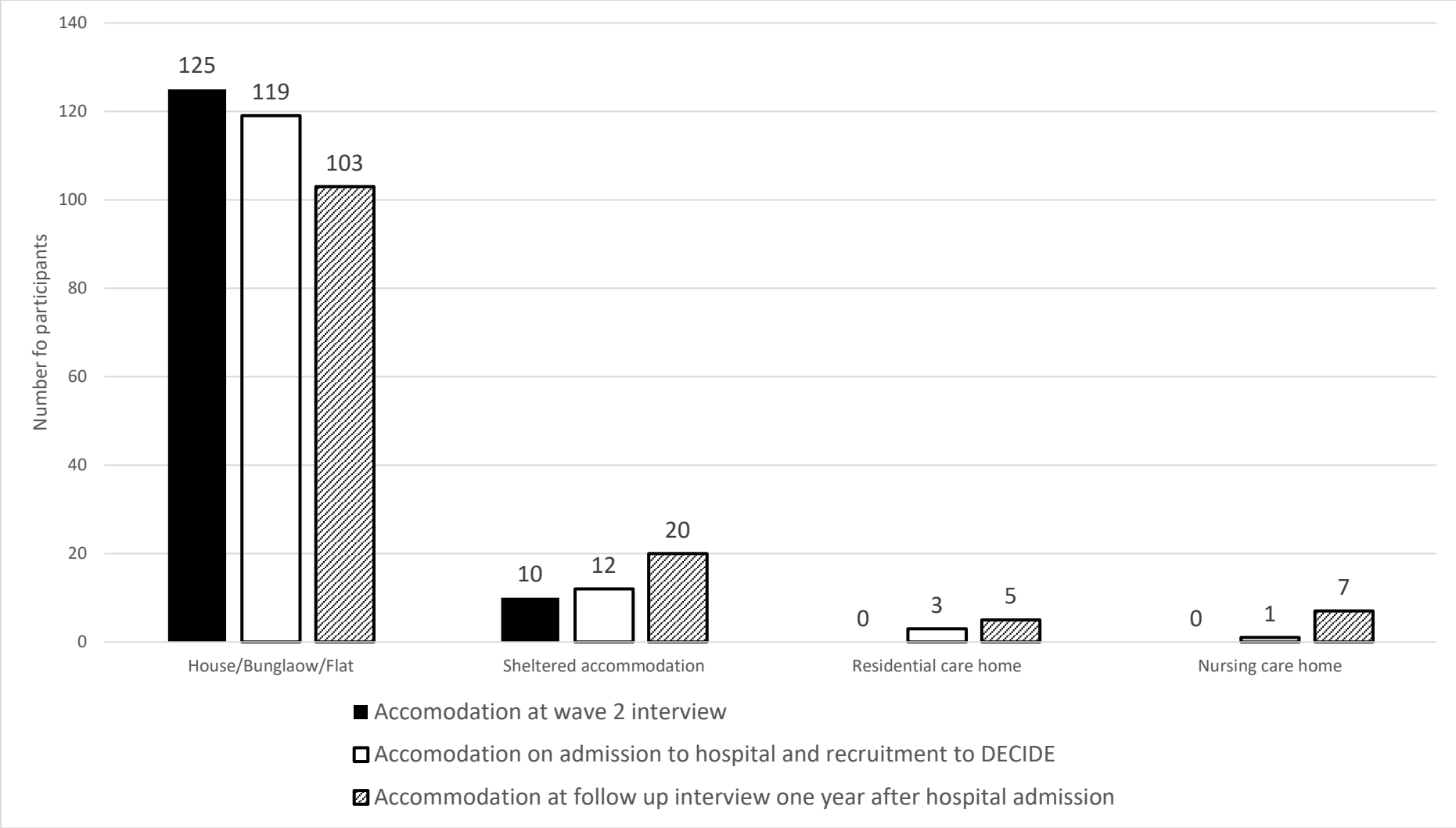



*Figure 23: Graph representing the proportion of DECIDE participants followed up at 1 year at each level of residence at wave 2 interview, recruitment to DECIDE and 1 year follow up interview*

## 5.3 Cognitive assessments at follow up

### *5.3.1 CAMCOG*

117 of the 135 DECIDE participants who were interviewed one year after their last hospital discharge of the study period completed a CAMCOG. Of the 18 participants who were not able to complete a full CAMCOG:

- 13 were not able to complete a full CAMCOG due to cognitive impairment and received an AGECAT diagnosis of dementia. 10 were able to complete a MMSE.
- 1 received an AGECAT diagnosis of depression and had a MMSE score of 24.
- 4 were unable to complete a full CAMCOG due to hearing or visual impairment in 3 cases and due to refusal in one case. All 4 were able to complete a MMSE and achieved scores of 19, 20, 20 and 22. None received an AGECAT diagnosis of dementia, depression or anxiety.

### *5.3.2 MMSE*

132 of the 135 DECIDE participants who were interviewed one year after last hospital discharge completed a MMSE. 3 participants were unable to complete a MMSE due to advanced dementia and all three received a study diagnosis of dementia, 1 of which was a new diagnosis since wave 2 interview.

### *5.3.3 AGECAT diagnosis of dementia*

23 of the 135 participants interviewed one year after their last hospital discharge received an AGECAT diagnosis of dementia. Only 5 of these participants had an AGECAT diagnosis of dementia at wave 2 meaning that there were 18 new cases of dementia between wave 2 and follow up as part of the DECIDE study.

At wave 2, 9 of the 205 DECIDE participants had a diagnosis of dementia. 4 of these died before their follow up interview but the remaining 5 were seen again.

## 5.4 Poor outcomes at follow up

A poor outcome was defined as death, new institutionalisation or a new AGECAT diagnosis of dementia since wave 2 interview. Excluding those participants who refused to be followed up at one year or had moved (32 participants of 205), a poor outcome occurred in 63 of the remaining 173 DECIDE participants (36.4%) (Figure 24).

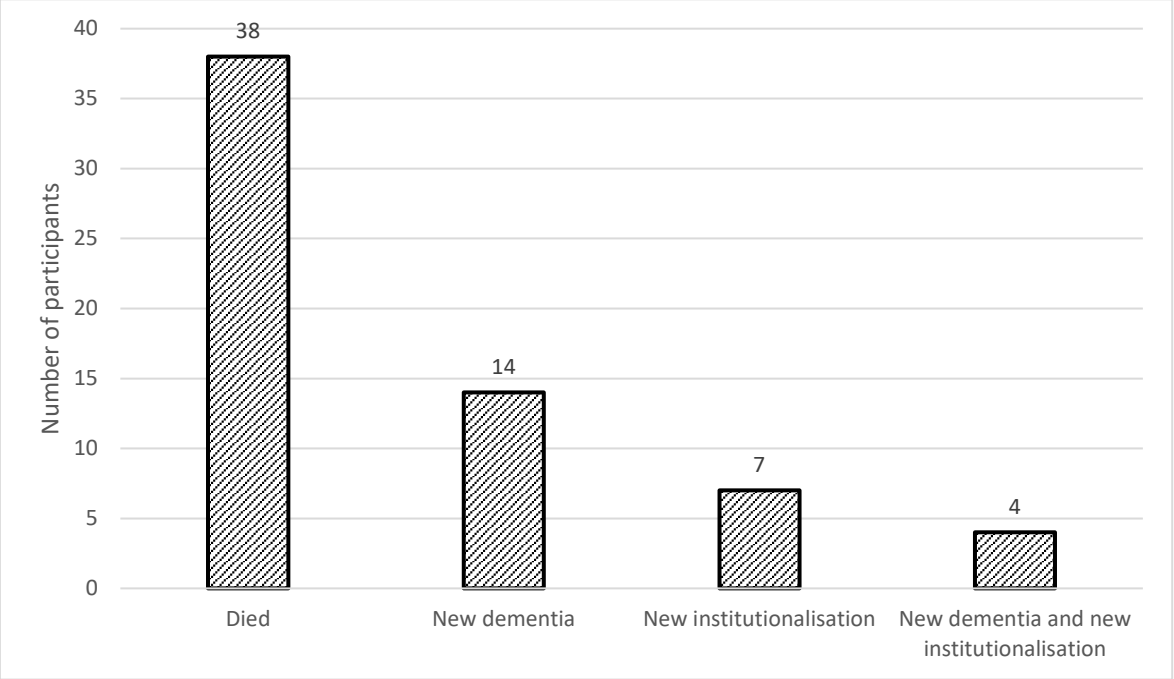



*Figure 24: Number of DECIDE participants followed up at 1 year experiencing a poor outcome defined as death, new institutionalisation or new dementia since wave 2 interview*

## 5.5 Impact of delirium on outcomes

Outcomes including cognition, new institutionalisation and mortality, in participants who did and did not have delirium during the study period, were compared (Table 20). All of the outcomes in the table showed a statistically significant difference between those with and without delirium when tested individually.

Multiple regression analysis was used to determine whether delirium remained a statistically significant predictor of the outcomes shown in Table 20 when controlling for the potentially confounding effects of age, gender, illness severity, comorbidity, frailty, baseline cognition, years of education and the time between the two interviews taking place.

| **Variable** | **Delirium** (n=48 unless stated) | **No delirium** (n=87 unless stated) | **P value** (statistical test used) |
|---|---|---|---|
| CAMCOG score at follow up interview (mean, SD) | 75.30 +/- 13.92 (n=33) | 86.75 +/- 9.34 (n=84) | P<0.000 (Two-sample Wilcoxon rank-sum test) |
| Difference in CAMCOG score between wave II interview and follow up interview for DECIDE (mean, SD) | -10.81 +/- 13.09 (n=32) | -4.60 +/- 6.51 (n=82) | P<0.011 (Two-sample Wilcoxon rank-sum test) |
| MMSE score at follow up interview (mean, SD) | 21.82 +/- 5.84 (n=45) | 26.68 +/- 3.21 (n=87) | P<0.000 (Two-sample Wilcoxon rank-sum test) |
| Difference in MMSE score between wave II interview and follow up interview for DECIDE (mean, SD) | -3.73 +/- 5.47 (n=45) | -0.82 +/- 2.34 (n=87) | P<0.001 (Two-sample Wilcoxon rank-sum test) |
| Number with AGECAT diagnosis of dementia at follow up interview | 20 (41.67%) | 3 (3.45%) | P<0.000 (Chi-squared test) |
| Number with *new* AGECAT diagnosis of dementia at follow up interview | 15 (31.25%) | 3 (3.45%) | P<0.000 (Chi-squared test) |
| Number of participants newly institutionalised | 10 (20.83%) | 2 (2.30%) | p=0.001 (Chi-squared test) |
| Number of participants who died prior to follow up interview | 24 (33.33%) (n= 48+24 =72) | 14 (13.86%) (n= 87+14 =101) | P=0.002 (Chi-squared test) |
| Number of participants with a poor outcome (defined as death before follow up interview, new institutionalisation or new dementia) | 45 (62.50%) (n= 48+24 =72) | 18 (17.82%) (n= 87+14 =101) | P<0.000 (Chi-squared test) |

*Table 20: Comparison of outcomes between those with and without delirium during the study period*

### *5.5.1 CAMCOG score*

The only variable that independently predicted cognition at one year, when using CAMCOG score at the follow up interview as the primary outcome measure, was CAMCOG score at wave 2 (p<0.000). The potentially confounding effects of years of education, illness severity, comorbidity, time between interviews, frailty, age and gender were considered by including these variables in the regression analysis (Table 21).

| **Variable** | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Delirium during 2016 (yes) | -4.078 | -8.514 - 0.358 | 0.071 |
| ≤10 years in full time education (yes) | -1.034 | -4.861 - 2.794 | 0.593 |
| Peak total adjusted APACHE score (points) | -0.195 | -1.006 - 0.616 | 0.634 |
| Total CIRS-G score (per point) | -0.045 | -0.564 - 0.473 | 0.862 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | -0.004 | -0.010 - 0.003 | 0.281 |
| Clinical Frailty Score (per point) | -0.693 | -2.376 – 0.990 | 0.416 |
| Age (years) | -0.302 | -0.622 - 0.018 | 0.064 |
| Gender (female) | -0.650 | -4.213 - 2.914 | 0.718 |
| **Cognition at wave 2 interview measured using total CAMCOG (per point)** | **0.881** | **0.591 - 1.171** | **0.000** |

*Table 21: Results of regression analysis exploring variables which independently predict cognition, measured using CAMCOG score, at one year after hospital admission*

Sensitivity analysis was carried out by excluding the 4 cases in which there was disagreement in the decision resulting in a third expert panel member creating a majority decision. This did not alter the results of the analysis and CAMCOG score at wave 2 interview remained as the only significant predictor of CAMCOG score at follow up interview when controlling for potentially confounding variables.

### *5.5.2 MMSE*

In the regression analysis using MMSE as the primary outcome measure, delirium, frailty score and MMSE score at wave 2 were the only variables remaining statistically significant predictors of MMSE score at follow up interview when controlling for the potentially confounding impact of years of education, illness severity, comorbidity, time between interviews and gender (Table 22). Having delirium during the study period was associated with a reduction in MMSE score of 1.828 points.

| Variable | Coefficient | 95% confidence interval | P value |
|---|---|---|---|
| **Delirium during 2016 (yes)** | **-1.828** | **-3.472 - -0.184** | **0.030** |
| ≤10 years in full time education (yes) | -0.183 | -1.640 - 1.275 | 0.804 |
| Peak total adjusted APACHE score (points) | -0.190 | -0.476 - 0.095 | 0.189 |
| Total CIRS-G score (per point) | -0.075 | -0.259 - 0.109 | 0.419 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | -0.001 | -0.004 - 0.001 | 0.362 |
| **Clinical Frailty Score (per point)** | **-0.638** | **-1.247 - -0.028** | **0.040** |
| Age (years) | -0.074 | -0.199 - 0.051 | 0.242 |
| Gender (female) | 0.290 | -1.053 - 1.634 | 0.669 |
| **Cognition at wave 2 interview measured using total MMSE (per point)** | **0.658** | **0.395 - 0.921** | **0.000** |

*Table 22: Results of regression analysis exploring variables which independently predict cognition, measured using MMSE score, at one year after hospital admission*

Sensitivity analysis, carried out without the 4 contentious cases, resulted in clinical frailty score no longer being a significant predictor of outcome. Delirium (coef. -2.027 [CI: -3.651 - -0.403], p=0.015) and baseline cognition (coef. 0.674 [CI: 0.413 – 0.935], p<0.000) remained the only independent predictors of outcome.

### *5.5.3 New dementia diagnosis*

In the logistic regression analysis using new AGECAT diagnosis of dementia as the primary outcome measure, delirium was the only variable remaining a statistically significant predictor (OR 8.759 [CI: 1.854 – 41.368], p=0.006) when controlling for the potentially confounding impact of years of education, illness severity, comorbidity, time between interviews, frailty, age, gender and baseline cognition (measured using MMSE score) (Table 23).

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| **Delirium during 2016 (yes)** | **8.759** | **1.854 – 41.368** | **0.006** |
| ≤10 years in full time education (yes) | 0.868 | 0.221 – 3.405 | 0.839 |
| Peak total adjusted APACHE score (points) | 0.844 | 0.654 – 1.090 | 0.195 |
| Total CIRS-G score (per point) | 1.066 | 0.907 – 1.254 | 0.437 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | 1.001 | 0.998 – 1.003 | 0.599 |
| Clinical Frailty Score (per point) | 1.393 | 0.783 – 2.479 | 0.259 |
| Age (years) | 1.022 | 0.920 – 1.135 | 0.685 |
| Gender (female) | 1.163 | 0.338 – 3.999 | 0.810 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 0.961 | 0.810 – 1.140 | 0.648 |

*Table 23: Results of regression analysis exploring variables which independently predict new dementia diagnosis, according to the AGECAT, at one year after hospital admission.*

The sensitivity analyses did not alter the results.

The analysis in Table 23 shows that an episode of delirium during the study period was associated with more than an 8 times increased risk of a new diagnosis of dementia at follow up, independent of illness severity and baseline cognition. The confidence interval is quite wide, demonstrating some uncertainty regarding the magnitude of the precise odds ratio, probably due to the relatively small sample size.

On further examination of this variable, Table 24 can be produced. This table shows that there were very few people who had a new diagnosis of dementia at follow up interview who had not had delirium during the study period (3 people). The small number of people in this category probably contributes to the large confidence interval surrounding the odds ratio.

| | Delirium during study period | No delirium during study period |
|---|---|---|
| New AGECAT diagnosis of dementia at follow up interview | 15 | 3 |
| No new AGECAT diagnosis of dementia at follow up interview | 33 | 84 |

*Table 24: Table demonstrating the number of participants with an AGECAT diagnosis of dementia who had delirium during the study period.*

The analysis in Table 23 included participants who had a diagnosis of dementia at wave 2 within the 'no new dementia' outcome group. However, if these 5 participants are excluded from the analysis, the odds ratio of new dementia associated with delirium is increased to 9.52 (Table 25).

9 of the 21 participants who had a documented diagnosis of dementia in their medical records on admission to hospital completed a follow-up interview. Only 3 of these participants had a diagnosis of dementia at wave 2. Therefore, 6 of the participants had potentially been diagnosed with dementia between their wave 2 interview and their admission to hospital and recruitment to the DECIDE study. The analysis in Table 25 was repeated, additionally excluding the 6 participants who had a documented diagnosis of dementia on admission to hospital (Table 26). Delirium remained the only independent predictor of new dementia.

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| **Delirium during 2016 (yes)** | **9.516** | **1.943 – 46.591** | **0.005** |
| ≤10 years in full time education (yes) | 0.897 | 0.218 – 3.697 | 0.881 |
| Peak total adjusted APACHE score (points) | 0.925 | 0.699 – 1.223 | 0.582 |
| Total CIRS-G score (per point) | 1.039 | 0.875 – 1.234 | 0.661 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | 1.001 | 0.998 – 1.003 | 0.662 |
| Clinical Frailty Score (per point) | 1.668 | 0.886 – 3.142 | 0.113 |
| Age (years) | 0.971 | 0.857 – 1.101 | 0.649 |
| Gender (female) | 1.180 | 0.317 – 4.396 | 0.805 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 0.850 | 0.694 – 1.040 | 0.114 |

*Table 25: Results of regression analysis exploring variables which independently predict new dementia diagnosis, according to the AGECAT, at one year after hospital admission, excluding the 5 participants who had a diagnosis of dementia at wave 2.*

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| **Delirium during 2016 (yes)** | **9.846** | **1.515 – 63.992** | **0.017** |
| ≤10 years in full time education (yes) | 0.591 | 0.128 – 2.735 | 0.501 |
| Peak total adjusted APACHE score (points) | 0.918 | 0.668 – 1.263 | 0.601 |
| Total CIRS-G score (per point) | 0.967 | 0.798 – 1.172 | 0.732 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | 1.000 | 0.998 – 1.003 | 0.707 |
| Clinical Frailty Score (per point) | 1.142 | 0.581 – 2.244 | 0.699 |
| Age (years) | 0.998 | 0.870 – 1.144 | 0.974 |
| Gender (female) | 0.987 | 0.235 – 4.154 | 0.986 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 0.812 | 0.649 – 1.016 | 0.069 |

*Table 26: Results of regression analysis exploring variables which independently predict new dementia diagnosis, according to the AGECAT, at one year after hospital admission, excluding the 5 participants who had a diagnosis of dementia at wave 2 and the 6 participants who had a diagnosis of dementia documented in their medical records on admission to hospital.*

### *5.5.4 New institutionalisation*

Delirium was not an independent predictor of new institutionalisation. However, illness severity, measured using peak total APACHE II score, and Clinical Frailty Score were independent predictors of new institutionalisation (Table 27).

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| Delirium during 2016 (yes) | 1.192 | 0.155 – 9.182 | 0.866 |
| ≤10 years in full time education (yes) | 0.255 | 0.038 – 1.710 | 0.159 |
| **Peak total adjusted APACHE score (points)** | **1.421** | **1.045 – 1.933** | **0.025** |
| Total CIRS-G score (per point) | 1.059 | 0.853 – 1.316 | 0.603 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | 1.001 | 0.998 – 1.005 | 0.507 |
| **Clinical Frailty Score (per point)** | **2.729** | **1.035 – 7.197** | **0.042** |
| Age (years) | 1.061 | 0.906 – 1.244 | 0.462 |
| Gender (female) | 0.846 | 0.137 – 5.210 | 0.857 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 0.886 | 0.709 – 1.106 | 0.285 |

*Table 27: Results of regression analysis exploring variables which independently predict new institutionalisation at one year after hospital admission*

The sensitivity analyses did not alter the results.

As with the analysis of cognitive outcomes at one year, the above analysis is subject to survival bias.

### *5.5.5 Death at 1 year*

Delirium was not an independent predictor of death by 1 year follow up but illness severity, measured using peak total APACHE II score, and Clinical Frailty Score did independently predict death by 1 year follow up (Table 28).

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Delirium during 2016 (yes) | 1.363 | 0.499 – 3.723 | 0.546 |
| ≤10 years in full time education (yes) | 0.573 | 0.224 – 1.469 | 0.246 |
| **Peak total adjusted APACHE score (points)** | **1.234** | **1.058 – 1.439** | **0.007** |
| Total CIRS-G score (per point) | 0.993 | 0.890 – 1.106 | 0.893 |
| **Clinical Frailty Score (per point)** | **1.790** | **1.192 – 2.690** | **0.005** |
| Age (years) | 0.957 | 0.886 – 1.033 | 0.256 |
| Gender (female) | 0.462 | 0.196 – 1.089 | 0.078 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 1.010 | 0.877 – 1.165 | 0.886 |

*Table 28: Results of regression analysis exploring variables which independently predict death before one year follow up*

The sensitivity analyses did not alter the results.

### *5.5.6 Poor outcome*

Delirium, illness severity, measured using peak total APACHE II score, and Clinical Frailty Score all independently predicted poor outcome (death, new dementia or new institutionalisation) according to logistic regression analysis (Table 29).

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| **Delirium during 2016 (yes)** | **3.536** | **1.412 – 8.856** | **0.007** |
| ≤10 years in full time education (yes) | 0.451 | 0.178 – 1.140 | 0.092 |
| **Peak total adjusted APACHE score (points)** | **1.181** | **1.006 – 1.387** | **0.042** |
| Total CIRS-G score (per point) | 1.042 | 0.932 – 1.166 | 0.466 |
| **Clinical Frailty Score (per point)** | **1.766** | **1.213 – 2.571** | **0.003** |
| Age (years) | 0.965 | 0.896 – 1.039 | 0.342 |
| Gender (female) | 0.629 | 0.275 – 1.439 | 0.273 |
| Cognition at wave 2 interview measured using total MMSE (per point) | 0.885 | 0.764 – 1.024 | 0.102 |

*Table 29: Results of regression analysis exploring variables which independently predict poor outcome*

On sensitivity analysis, and removal of the four contentious cases, only delirium (OR 3.482 (1.370 - 8.850), p=0.009) and Clinical Frailty Score (OR 1.739 (1.190 - 2.542), p=0.004) remained statistically significant predictors of poor outcome.

An episode of delirium during the study period was associated with a 3.5 times increased risk of poor outcome, independent of the other variables.

## 5.6 Impact of hospital admission on outcomes

It was possible to explore the impact of hospital admission itself on outcomes by comparing the cognitive scores at follow up interview in the 135 DECIDE participants recruited in hospital and followed up at one year to the 100 control participants who had no hospital admissions during the study period. As previously mentioned, the controls were matched to the DECIDE participants for age, gender and years of education.

### *5.6.1 MMSE*

Mean MMSE score at follow up interview in the control group was 27.17 (SD 2.910) compared to 25.023 (SD 4.854) if the hospitalised group. This difference was statistically significant (p = 0.0005) when using two-sample Wilcoxon rank-sum test as MMSE score was not normally distributed. When controlling for baseline cognition and time between wave 2 and follow up interview using regression analysis, hospitalisation remained a significant predictor of MMSE score at follow up interview (Table 30).

| **Variable** | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|
| **No hospital admission during 2016** | **1.182** | **0.252 – 2.113** | **0.013** |
| **Cognition at wave 2 interview (MMSE score)** | **0.915** | **0.739 – 1.091** | **<0.000** |
| Days between interviews | -0.001 | -0.003 – 0.001 | 0.426 |

*Table 30: Regression analysis exploring variables which independently predict MMSE score at follow up interview*

It is also possible to compare cognitive decline (measured using MMSE scores) in those admitted to hospital who had delirium, to those admitted to hospital who did not develop delirium, with those who had no admissions to hospital during the study period (Table 31).

The groups are significantly different from one another (p<0.000). However, when you remove the participants who had delirium during the study period and compare those who were hospitalised but did not have delirium (n=87) to those who were not hospitalised (n=100), there was no significant difference in their MMSE scores at follow up interview (p=0.2731). When controlling for the confounding effects of baseline

cognition and days between the baseline and follow up interviews, hospitalisation was not an independent predictor of MMSE score at follow up interview (Table 30).

| | **Mean MMSE score at follow up interview** | **Standard deviation** | **Frequency** |
|---|---|---|---|
| Hospital admission and delirium | 21.822 | 5.844 | 45 |
| Hospital admission, no delirium | 26.678 | 3.208 | 87 |
| No hospital admission | 27.17 | 2.910 | 100 |

*Table 31: Comparison of MMSE score at follow up interview in those admitted to hospital who had delirium compared to those admitted to hospital who did not develop delirium and those who had no admissions to hospital during the study period using one way ANOVA*

| **Variable** | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Hospital admission during 2016 but NO delirium (n=87) | -0.125 | -0.861 – 0.611 | 0.738 |
| **Cognition at wave 2 interview (MMSE score)** | **0.833** | **0.669 – 0.997** | **<0.000** |
| Days between interviews | -0.000 | -0.002 – 0.001 | 0.808 |

*Table 32: Regression analysis exploring whether hospitalisation without delirium compared to no hospitalisation independently predicted MMSE score at follow up interview*

This implies that the hospitalisation itself is not impacting on cognitive outcomes but the delirium in addition to hospitalisation results in adverse cognitive outcomes.

### *5.6.2 Number of hospital admissions*

Mean number of hospital admissions in those who did develop delirium during the study period was 2.037 compared to 1.813 for those who did not develop delirium. However, the number of hospital admissions did not differ significantly between participants who did and did not develop delirium (p=0.115). Additionally, when included as a potential confounder, number of admissions did not alter the results of regression analysis exploring variables which independently predict outcomes.

## 5.7 Informant history of delirium using I-AGeD

At all of the follow up interviews, with the verbal consent of the participant, a nominated next of kin was asked to complete the Informant Assessment of Geriatric Delirium Scale (I-AGeD). This was done in person, if the next of kin was with the participant, or over the telephone following the interview with the participant.

An I-AGeD questionnaire was completed for 113 of the 135 DECIDE participants interviewed 1 year after their hospital admission and 47 of the 100 controls interviewed. Figure 25 shows the scores obtained on completion of the questionnaire.

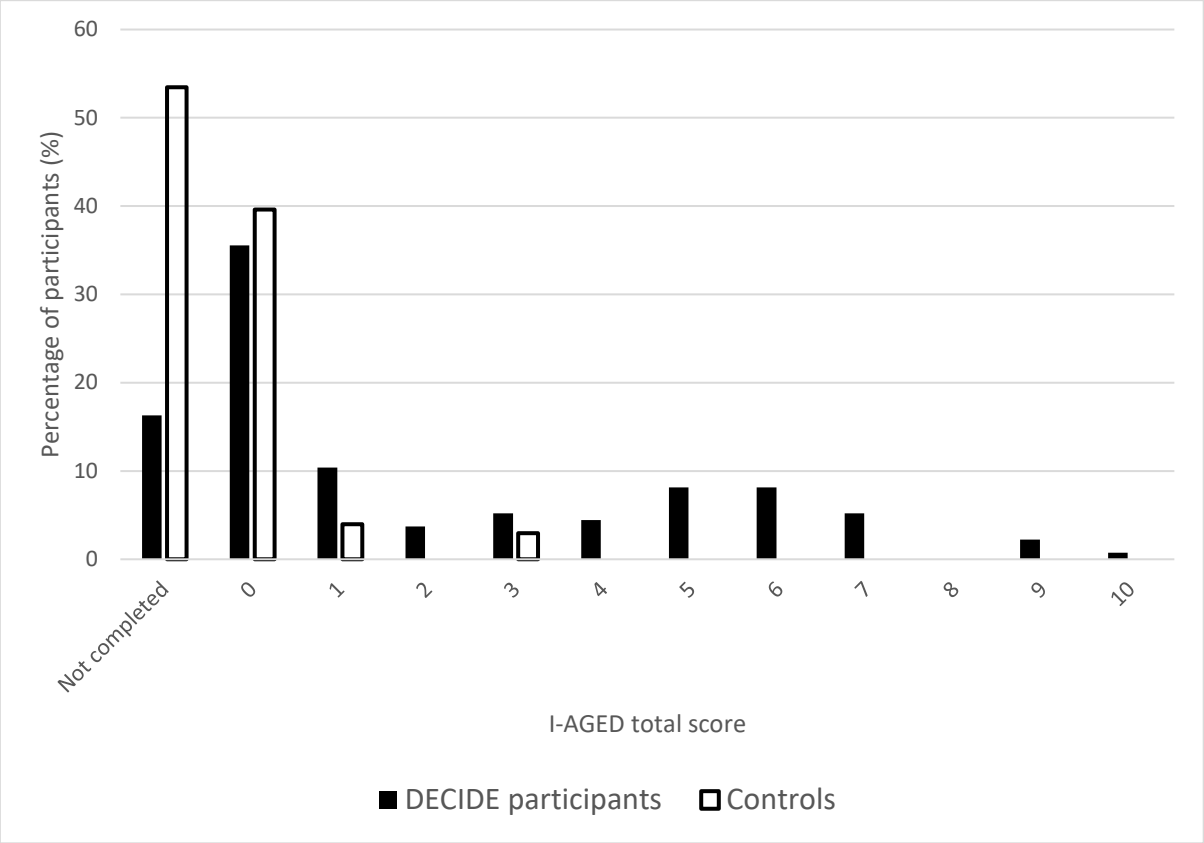



*Figure 25: Percentage of DECIDE participants and control participants interviewed at 1 year scoring 0 to 10 on Informant Assessment of Geriatric Delirium Scale (I-AGED) or not completed*

A cut-off of >4 was used for delirium in the original article (Rhodius-Meester et al., 2013). At this cut-off, none of the controls and 33 of the DECIDE participants had a history from their informant suggestive of delirium.

Using the diagnosis of delirium obtained prospectively for the DECIDE study as a gold standard, it is possible to assess the diagnostic accuracy of the I-AGeD for ascertaining a retrospective diagnosis of delirium over the preceding year. Using AUROC analysis, a cut off of >4 classifies the most cases correctly (78.76%) and gives a sensitivity of 60.47% and a specificity of 90.00% (Figure 26) and an area under the ROC curve of 0.8231.

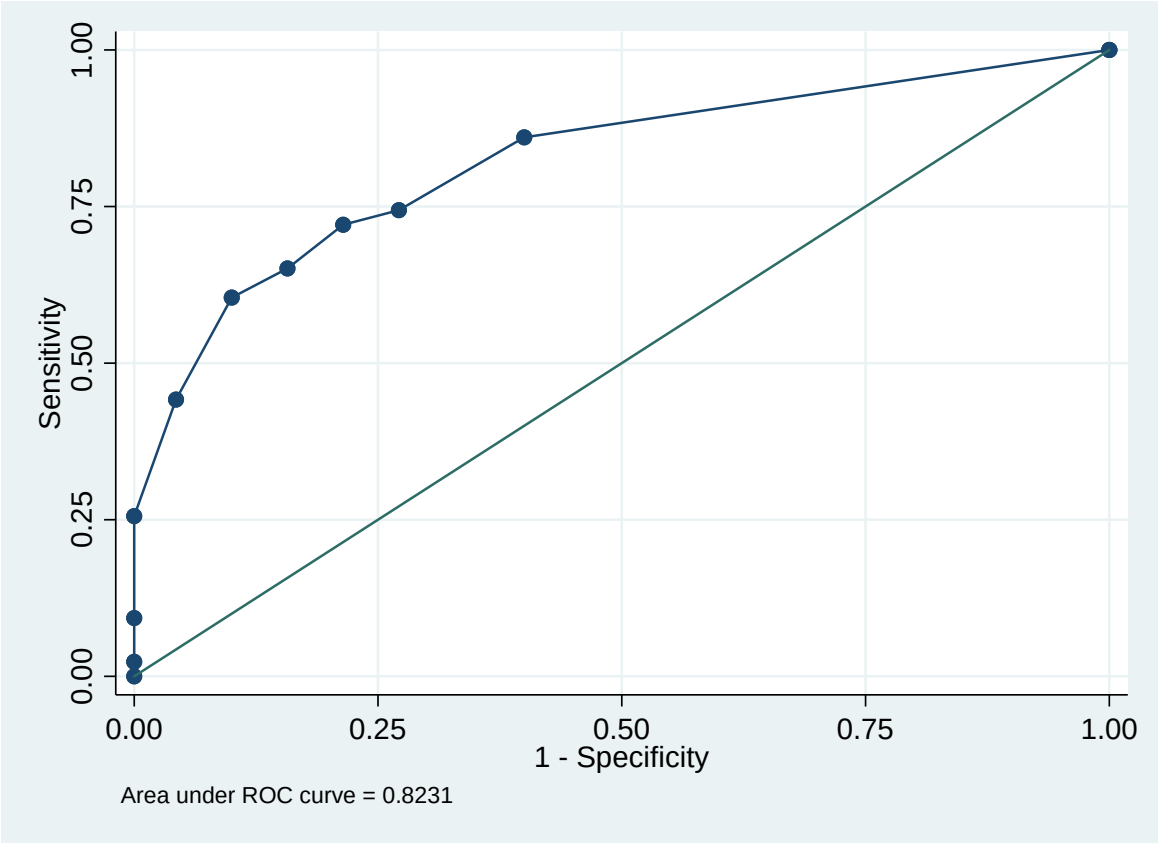



*Figure 26: ROC curve for delirium diagnosis using I-AGED compared to DECIDE study diagnosis of delirium according to DSM-5 criteria.*

# Chapter 6: Predictors of poor outcomes

Exploratory analysis was carried out to determine whether delirium duration, delirium severity, delirium motor subtype, presence of perceptual disturbances or number of episodes of delirium impacted on outcomes including CAMCOG score, MMSE score, new AGECAT diagnosis of dementia, new institutionalisation, death prior to follow up interview at 12 months and a combination of these. The potentially confounding effects of age, gender, years of education, baseline cognition, illness severity, comorbidity, frailty and the time between the interviews were controlled for in the analysis. All output from statistical analysis is summarised in this section where relevant.

## 6.1 Delirium duration as a predictor of outcome

Data on the total number of days of delirium during the study was available for 76 of the 82 participants with delirium. 48 of the participants with delirium were followed up at 1 year and 44 of these had complete data regarding total number of days of delirium.

Delirium duration was divided into 3 categories for the purpose of the analysis due to the fact that the variable was skewed, with large numbers of participants having no days of delirium (Table 33). The numbers of participants within each subgroup is small, particularly when examining cognitive outcomes, and so the analysis is exploratory and the conclusions that can be drawn are limited.

| **Total days with delirium during the study period (days)** | **Number of participants (n = 199)** | **Number of participants followed up at 1 year (% of total number of participants in subgroup)** | **Number of participants completing a CAMCOG at 1 year (% of total number of participants in subgroup)** |
|---|---|---|---|
| 0 | 123 | 87 (70.7%) | 84 (68.3%) |
| 1-5 | 52 | 35 (67.3%) | 25 (48.1%) |
| >5 | 24 | 9 (37.5%) | 5 (20.8%) |

*Table 33: Total number of days with delirium during the study period for the 76 participants who had delirium and had data regarding duration available. 123 participants did not experience delirium during the study period and therefore have a delirium duration of 0 days.*

### *6.1.1 CAMCOG score*

Total number of days of delirium was not an independent predictor of CAMCOG score. CAMCOG score at wave 2 interview was the only independent predictor of CAMCOG score at follow up (coef. 0.825 [CI: 0.552 – 1.099], p<0.000) (Table 34).

| **Variable** | | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | -0.243 | -0.545 – 0.058 | 0.112 |
| Gender (female) | | 0.537 | -2.866 – 3.939 | 0.755 |
| ≤10 years in full time education (yes) | | -2.653 | -6.315 – 1.009 | 0.154 |
| **Cognition at wave 2 interview measured using total CAMCOG score (per point)** | | **0.825** | **0.552 – 1.099** | **0.000** |
| Peak total adjusted APACHE score (points) | | -0.040 | -0.804 – 0.724 | 0.917 |
| Total CIRS-G score (per point) | | -0.028 | -0.516 – 0.459 | 0.908 |
| Clinical Frailty Score (per point) | | -0.376 | -1.972 – 1.220 | 0.641 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | -0.003 | -0.009 – 0.004 | 0.412 |
| Total number of days with delirium during study period | 1-5 days | -4.300 | -8.704 – 0.105 | 0.056 |
| | >5 days | -7.982 | -17.363 – 1.398 | 0.094 |

*Table 34: Results of regression analysis exploring variables which independently predict cognition, measured using CAMCOG score, at one year after hospital admission.*

### *6.1.2 MMSE score*

Having delirium for more than 5 days was independently associated with a 5 point reduction in MMSE score at follow up interview (coef. -5.132 [CI: -8.139 - -2.125], p=0.001). Having delirium for 1-5 days was also independently associated with a significant, although not as large, reduction in MMSE score at follow up interview (Table 35).

| **Variable** | | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | -0.044 | -0.166 – 0.078 | 0.475 |
| Gender (female) | | 0.466 | -0.856 – 1.788 | 0.486 |
| ≤10 years in full time education (yes) | | -0.326 | -1.762 – 1.109 | 0.653 |
| **Cognition at wave 2 interview measured using total MMSE score (per point)** | | **0.667** | **0.406 – 0.928** | **0.000** |
| Peak total adjusted APACHE score (points) | | -0.179 | -0.456 – 0.098 | 0.202 |
| Total CIRS-G score (per point) | | -0.027 | -0.207 – 0.154 | 0.770 |
| Clinical Frailty Score (per point) | | -0.459 | -1.065 – 0.146 | 0.136 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | -0.001 | -0.003 – 0.002 | 0.452 |
| **Total number of days with delirium during study period** | **1-5 days** | **-1.726** | **-3.405 - -0.048** | **0.044** |
| | **>5 days** | **-5.132** | **-8.139 - -2.125** | **0.001** |

*Table 35: Results of regression analysis exploring variables which independently predict cognition, measured using MMSE score, at one year after hospital admission.*

### *6.1.3 New dementia diagnosis*

Delirium duration of 1-5 days independently predicted a new AGECAT diagnosis of dementia at follow up interview (Table 36). The confidence interval is quite wide suggesting some uncertainty regarding the magnitude of the increased risk associated with this duration of delirium. Having delirium for more than 5 days did not reach statistical significance, perhaps due to the small numbers involved.

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 1.030 | 0.924 – 1.147 | 0.597 |
| Gender (female) | | 1.045 | 0.296 – 3.694 | 0.946 |
| ≤10 years in full time education (yes) | | 0.816 | 0.196 – 3.399 | 0.780 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.937 | 0.787 – 1.115 | 0.461 |
| Peak total adjusted APACHE score (points) | | 0.855 | 0.665 – 1.099 | 0.222 |
| Total CIRS-G score (per point) | | 1.070 | 0.901 – 1.270 | 0.440 |
| Clinical Frailty Score (per point) | | 1.359 | 0.752 – 2.453 | 0.309 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | 1.001 | 0.998 – 1.003 | 0.624 |
| **Total number of days with delirium during study period** | **1-5 days** | **9.321** | **1.964 – 44.231** | **0.005** |
| | >5 days | 8.368 | 0.824 – 84.946 | 0.072 |

*Table 36: Results of logistic regression analysis exploring variables which independently predict new AGECAT diagnosis of dementia at one year after hospital admission.*

### *6.1.4 New institutionalisation*

Delirium duration was not an independent predictor of new institutionalisation at follow up interview (Table 37).

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 1.039 | 0.876 - 1.232 | 0.660 |
| Gender (female) | | 0.817 | 0.132 – 5.063 | 0.828 |
| ≤10 years in full time education (yes) | | 0.318 | 0.039 – 2.566 | 0.282 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.917 | 0.733 - 1.146 | 0.446 |
| **Peak total adjusted APACHE score (points)** | | **1.393** | **1.028 - 1.887** | **0.033** |
| Total CIRS-G score (per point) | | 1.091 | 0.848 - 1.403 | 0.498 |
| Clinical Frailty Score (per point) | | 2.641 | 0.986 – 7.077 | 0.053 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | 1.001 | 0.997 - 1.005 | 0.762 |
| Total number of days with delirium during study period | 1-5 days | 1.392 | 0.168 – 11.499 | 0.759 |
| | >5 days | 0.701 | 0.034 – 14.416 | 0.818 |

Table 37: *Results of logistic regression analysis exploring variables which independently predict new institutionalisation at one year after hospital admission.*

### *6.1.5 Death prior to follow up interview*

Delirium duration was not an independent predictor of death prior to follow up interview (Table 38).

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 0.967 | 0.895 - 1.044 | 0.390 |
| Gender (female) | | 0.431 | 0.177 - 1.049 | 0.064 |
| ≤10 years in full time education (yes) | | 0.515 | 0.195 - 1.359 | 0.180 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.973 | 0.838 - 1.128 | 0.714 |
| **Peak total adjusted APACHE score (points)** | | **1.178** | **1.008 - 1.376** | **0.039** |
| Total CIRS-G score (per point) | | 0.971 | 0.864 - 1.092 | 0.627 |
| **Clinical Frailty Score (per point)** | | **1.737** | **1.146 - 2.631** | **0.009** |
| Total number of days with delirium during study period | 1-5 days | 1.079 | 0.356 - 3.270 | 0.893 |
| | >5 days | 2.716 | 0.660 - 11.182 | 0.166 |

Table 38: *Results of logistic regression analysis exploring variables which independently predict death prior to follow up interview at one year after hospital admission.*

### *6.1.6 Poor outcome*

Delirium duration of 1-5 days and >5 days independently predicted a poor outcome by follow up interview (death, new dementia or new institutionalisation) along with frailty (Table 39).

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 0.965 | 0.895 – 1.040 | 0.351 |
| Gender (female) | | 0.564 | 0.242 – 1.311 | 0.183 |
| ≤10 years in full time education (yes) | | 0.466 | 0.182 – 1.192 | 0.111 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.867 | 0.746 – 1.009 | 0.065 |
| Peak total adjusted APACHE score (points) | | 1.149 | 0.974 – 1.354 | 0.099 |
| Total CIRS-G score (per point) | | 1.029 | 0.918 – 1.153 | 0.623 |
| **Clinical Frailty Score (per point)** | | **1.673** | **1.141 – 2.452** | **0.008** |
| **Total number of days with delirium during study period** | **1-5 days** | **3.430** | **1.297 – 9.073** | **0.013** |
| | **>5 days** | **4.936** | **1.116 – 21.836** | **0.035** |

*Table 39: Results of logistic regression analysis exploring variables which independently predict poor outcome, defined as death, new dementia or new institutionalisation, at one year after hospital admission.*

## 6.2 Delirium severity as a predictor of outcome

Delirium severity was recorded as the peak MDAS score recorded during the study period. This data was available for 200 of the 205 participants recruited in hospital as it was recorded for people with and without delirium. Of these, 133 were followed up at 1 year.

### *6.2.1 CAMCOG score*

When including peak MDAS score during the study period in regression analysis, CAMCOG score at wave 2 interview was the only variable to reach statistical significance (coef. 0.857 [CI: 0.562 – 1.152], p<0.000) as an independent predictor of CAMCOG score at follow up interview.

### *6.2.2 MMSE score*

The analysis was run again with MMSE score at follow up interview as the outcome measure and MMSE score at wave 2 interview as the measure of baseline cognition. MMSE score at wave 2 interview, frailty and peak total MDAS score during the study period were all statistically significant independent predictors of MMSE score at follow up interview (Table 40). This suggests that having more severe delirium independently predicts worse cognitive outcomes. In fact, for each MDAS point gained, indicating more severe delirium, a decline in MMSE score of 0.387 points was expected, independent of other variables.

| **Variable** | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Age (years) | -0.063 | -0.184 – 0.058 | 0.307 |
| Gender (female) | -0.009 | -1.313 – 1.295 | 0.989 |
| ≤10 years of education (yes) | 0.305 | -1.108 - 1.718 | 0.670 |
| **Cognition at wave 2 interview measured using total MMSE score (per point)** | **0.605** | **0.346 – 0.863** | **0.000** |
| Peak total adjusted APACHE score (per point) | -0.118 | -0.400 – 0.163 | 0.408 |
| Comorbidity (total CIRS-G score) (per point) | -0.028 | -0.210 – 0.154 | 0.760 |
| **Clinical Frailty Score (per point)** | **-0.594** | **-1.185 - -0.002** | **0.049** |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | -0.002 | -0.004 – 0.001 | 0.144 |
| **Delirium severity according to peak MDAS score during the study period (per point)** | **-0.387** | **-0.606 - -0.168** | **0.001** |

*Table 40: Regression analysis exploring independent predictors of MMSE score at follow up interview including severity of delirium*

### *6.2.3 New dementia diagnosis*

In logistic regression analysis with new dementia diagnosis at follow up interview as the binary outcome measure, peak total MDAS score was the only variable that reached statistical significance as an independent predictor of outcome (OR 1.260 [CI: 1.052 – 1.510], p=0.012), again suggesting that more severe delirium is independently associated with worse outcomes (Table 41). Each MDAS point gained was associated with a 26% increased risk of dementia at follow up.

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Age (years) | 0.986 | 0.879 – 1.105 | 0.805 |
| Gender (female) | 2.168 | 0.559 – 8.407 | 0.263 |
| ≤10 years of education (yes) | 0.707 | 0.184 – 2.727 | 0.615 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | 0.886 | 0.732 – 1.073 | 0.215 |
| Peak total adjusted APACHE score (per point) | 0.875 | 0.685 – 1.117 | 0.282 |
| Comorbidity (total CIRS-G score) (per point) | 1.033 | 0.873 – 1.221 | 0.706 |
| Clinical Frailty Score (per point) | 1.677 | 0.914 – 3.079 | 0.095 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | 1.002 | 0.999 – 1.004 | 0.185 |
| **Delirium severity according to peak MDAS score during the study period (per point)** | **1.260** | **1.052 – 1.510** | **0.012** |

*Table 41: Logistic regression analysis exploring independent predictors of new AGECAT dementia diagnosis at follow up interview*

### *6.2.4 New institutionalisation*

In logistic regression analysis with new institutionalisation at follow up interview as the binary outcome measure, none of the variables reached statistical significance as independent predictors.

### *6.2.5 Death prior to follow up*

When exploring predictors of death prior to follow up interview, illness severity, measured using peak total APACHE score during the study period (OR 1.248 [CI: 1.059 – 1.471], p=0.008), clinical frailty score (OR 1.733 [CI: 1.129 – 2.659], p=0.012) and age (OR 0.919 [CI: 0.845 – 1.000], p=0.050) were the variables that reached statistical significance as independent predictors of death prior to follow up interview.

### *6.2.6 Poor outcome*

When exploring predictors of poor outcome as the binary outcome measure, defined as new dementia, new institutionalisation or death prior to follow up interview, illness severity, frailty score and delirium severity were all significant independent predictors of outcome (Table 42). This means that each point gained on the MDAS is associated with a 21% increased risk of a poor outcome.

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Age (years) | 0.967 | 0.897 – 1.042 | 0.377 |
| Gender (female) | 0.805 | 0.349 – 1.856 | 0.610 |
| ≤10 years of education (yes) | 0.479 | 0.186 – 1.232 | 0.127 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | 0.912 | 0.786 – 1.058 | 0.224 |
| **Peak total adjusted APACHE score (per point)** | **1.193** | **1.008 – 1.411** | **0.040** |
| Comorbidity (total CIRS-G score) (per point) | 1.042 | 0.931 – 1.165 | 0.477 |
| **Clinical Frailty Score (per point)** | **1.552** | **1.062 – 2.268** | **0.023** |
| **Delirium severity according to peak MDAS score during the study period (per point)** | **1.207** | **1.055 – 1.380** | **0.006** |

*Table 42: Regression analysis exploring independent predictors of poor outcome at follow up interview including severity of delirium*

## 6.3 Delirium motor subtype as a predictor of poor outcome

Delirium motor subtype was defined as none, hypoactive, hyperactive or mixed, as per item 9 of the MDAS, for all 82 of the participants who had delirium during the study period.

When including motor subtype during the study period in regression analysis, frailty score on first admission to hospital was the only variable to reach statistical significance (coef. -7.823 [CI: -14.776 - -0.869], p=0.029) as an independent predictor of CAMCOG score at follow up interview. Similarly, frailty score on first admission to hospital was the only variable to reach statistical significance (coef. -2.272 [CI: -4.347 - -0.197], p=0.033) as an independent predictor of MMSE score at follow up interview.

Delirium motor subtype did not predict new dementia, new institutionalisation or poor outcome at follow up, independent of the other variables.

Hyperactive delirium was a statistically significant predictor of death by follow up interview along with peak total APACHE score. However, the numbers are very small and the confidence intervals very large (Table 43).

| **Variable** | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|
| Age (years) | 1.021 | 0.918 – 1.135 | 0.707 |
| Gender (female) | 0.636 | 0.179 – 2.257 | 0.484 |
| ≤10 years of education (yes) | 1.403 | 0.282 – 6.972 | 0.679 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | 1.048 | 0.860 – 1.277 | 0.642 |
| **Peak total adjusted APACHE score (per point)** | **1.281** | **1.035 – 1.586** | **0.023** |
| Comorbidity (total CIRS-G score) (per point) | 1.010 | 0.861 – 1.186 | 0.898 |
| Clinical Frailty Score (per point) | 1.211 | 0.595 – 2.467 | 0.597 |
| Motor subtype - hypoactive | 1.634 | 0.230 – 11.596 | 0.624 |
| **Motor subtype - hyperactive** | **21.204** | **2.925 – 153.691** | **0.003** |
| Motor subtype - mixed | 4.782 | 0.721 – 31.701 | 0.105 |

*Table 43: Regression analysis exploring independent predictors of death prior to follow up interview including delirium motor subtype*

## 6.4 Presence of perceptual disturbances as a predictor of poor outcome

The presence or absence of perceptual disturbances did not independently predict CAMCOG score, MMSE score, new dementia, new institutionalisation, death prior to follow up or poor outcome at follow up.

## 6.5 Number of episodes of delirium during the study period as a predictor of poor outcome

The number of episodes of delirium during the study period was divided into 3 categories for the purpose of the analysis due to the fact that the variable was highly skewed. 123 participants had no episodes of delirium during the study period, 58 participants had 1 episode and 24 participants had more than 1 episode.

### *6.5.1 CAMCOG score*

Having 1 episode of delirium during the study period was independently associated with a decline in CAMCOG score at follow up (coef. -5.098 [CI: -9.743 - -0.453], p=0.032) whilst having more than one episode was not. However, the numbers are very small, with considerable subgroup differences in the proportion of participants surviving to one year follow up and also being able to complete a full CAMCOG, which may account for the slightly unexpected result. For example, 9 of the 24 people who had more than 1 episode of delirium completed a follow up interview (37.5%), with only 5 able to complete a full CAMCOG, whilst 39 of the 58 people with 1 episode of delirium were followed up (67.2%), with 28 completing a full CAMCOG.

### *6.5.2 MMSE score*

As with the CAMCOG as the primary outcome measure, having just 1 episode of delirium was an independent predictor of MMSE score at follow up interview, whilst more than 1 episode was not (Table 44). 1 episode of delirium is associated with a 1.9 point decline in MMSE score at follow up (coef. -1.873 [CI: -3.567 - -0.179], p=0.031). The reason for the non-significant relationship between more than 1 episode of delirium and MMSE score is probably due to the small number of participants in this subgroup.

| **Variable** | | **Coefficient** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | -0.073 | -0.199 – 0.053 | 0.254 |
| Gender (female) | | 0.289 | -1.060 – 1.638 | 0.672 |
| ≤10 years in full time education (yes) | | 0.198 | -1.271 – 1.666 | 0.790 |
| **Cognition at wave 2 interview measured using total MMSE score (per point)** | | **0.658** | **0.394 – 0.923** | **0.000** |
| Peak total adjusted APACHE score (points) | | -0.200 | -0.498 – 0.098 | 0.186 |
| Total CIRS-G score (per point) | | -0.076 | -0.260 – 0.109 | 0.420 |
| **Clinical Frailty Score (per point)** | | **-0.642** | **-1.256 - -0.029** | **0.040** |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | -0.001 | -0.004 – 0.001 | 0.385 |
| **Total number of episodes of delirium during study period** | **1 episode** | **-1.873** | **-3.567 - -0.179** | **0.031** |
| | >1 episode | -1.496 | -4.732 – 1.741 | 0.362 |

*Table 44: Regression analysis exploring independent predictors of MMSE score at follow up interview including number of episodes of delirium during the study period*

### *6.5.3 New dementia diagnosis*

1 or more episodes of delirium during the study period independently predicted new AGECAT diagnosis of dementia at follow up interview (Table 45). Once again, due to the exploratory nature of the analysis, the numbers are fairly small and the confidence intervals are large.

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 1.024 | 0.921 - 1.138 | 0.661 |
| Gender (female) | | 1.162 | 0.336 - 4.014 | 0.812 |
| ≤10 years in full time education (yes) | | 0.888 | 0.225 - 3.505 | 0.865 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.960 | 0.808 - 1.139 | 0.639 |
| Peak total adjusted APACHE score (points) | | 0.821 | 0.621 - 1.086 | 0.167 |
| Total CIRS-G score (per point) | | 1.063 | 0.903 - 1.252 | 0.465 |
| Clinical Frailty Score (per point) | | 1.390 | 0.778 - 2.482 | 0.266 |
| Days between wave 2 interview and follow up interview for DECIDE study (days) | | 1.001 | 0.998 - 1.003 | 0.546 |
| **Total number of episodes of delirium during study period** | **1 episode** | **8.585** | **1.792 - 41.132** | **0.007** |
| | **>1 episode** | **13.889** | **1.278 - 150.981** | **0.031** |

*Table 45: Regression analysis exploring independent predictors of new AGECAT diagnosis of dementia at follow up interview including number of episodes of delirium during the study period*

### *6.5.4 New institutionalisation*

Number of episodes of delirium did not independently predict new institutionalisation at follow up interview.

### *6.5.5 Death prior to follow up interview*

Number of episodes of delirium did not independently predict death prior to follow up interview. However, there was a significant difference between the proportion of people surviving to the one year follow up interview depending on the number of episodes of delirium experienced (p<0.000) (Table 46).

| **Number of episodes of delirium during the study period** | **Alive at follow up interview (n = 135)** | **Died prior to follow up interview (n = 38)** |
|---|---|---|
| 0 | 87 (86.14%) | 14 (13.86%) |
| 1 | 39 (76.47%) | 12 (23.53%) |
| >1 | 9 (42.86%) | 12 (57.14%) |

*Table 46: Number of participants surviving to one year follow up interview based on the number of episodes of delirium experienced during the study year*

### *6.5.6 Poor outcome*

Clinical frailty score and number of episodes of delirium independently predicted poor outcome at follow up interview (Table 47).

| **Variable** | | **Odds ratio** | **95% confidence interval** | **P value** |
|---|---|---|---|---|
| Age (years) | | 0.965 | 0.895 - 1.039 | 0.343 |
| Gender (female) | | 0.618 | 0.269 - 1.421 | 0.257 |
| ≤10 years in full time education (yes) | | 0.450 | 0.178 - 1.138 | 0.092 |
| Cognition at wave 2 interview measured using total MMSE score (per point) | | 0.886 | 0.765 - 1.025 | 0.103 |
| Peak total adjusted APACHE score (points) | | 1.164 | 0.985 - 1.374 | 0.075 |
| Total CIRS-G score (per point) | | 1.041 | 0.931 - 1.165 | 0.482 |
| **Clinical Frailty Score (per point)** | | **1.738** | **1.192 - 2.535** | **0.004** |
| **Total number of episodes of delirium during study period** | **1 episode** | **3.176** | **1.230 - 8.199** | **0.017** |
| | **>1 episode** | **5.956** | **1.331 - 26.646** | **0.020** |

*Table 47: Logistic regression analysis exploring independent predictors of poor outcome at follow up interview including number of episodes of delirium*

# Chapter 7: Discussion

## 7.1 Summary

The main finding from the DECIDE study is that delirium is independently associated with a significantly increased risk of future cognitive decline and dementia.

The DECIDE study has provided a unique opportunity to robustly evaluate the relationship between delirium and future cognitive decline and dementia, substantially adding to the current literature which has significant methodological limitations.

This chapter will summarise the main findings from the DECIDE study in the context of existing literature. It will discuss the strengths and weaknesses of the study and make suggestions based on the findings for future delirium research studies.

## 7.2 What the DECIDE study adds to current literature

### *7.2.1 Cognitive outcomes after delirium*

For the first time, delirium has been shown to be significantly associated with a new diagnosis of dementia, independent of baseline cognition and illness severity, in a population-based cohort of older people (odds ratio 8.76 [CI: 1.85 – 41.37]).

This supports findings from a study based upon data from the original Cognitive Function and Ageing Study cohort (CFAS I) which ascertained delirium retrospectively using an algorithmic approach (Davis et al., 2014). Despite the differing methodologies used to ascertain delirium, the increased risks of new dementia diagnosis at two years following study-defined delirium were remarkably similar (odds ratio 8.82 [CI: 2.76 – 28.2]). The sample size of 2197 was considerably larger than in DECIDE, which may account for the narrower confidence intervals.

The results from DECIDE were also very similar to a population based study of over 85 year olds which did not prospectively define delirium or control for illness severity (odds ratio 8.7 [CI: 2.1–35]) (Davis et al., 2012). The similarities seen in the results from the population based studies that exist regarding cognitive outcomes after delirium, despite the very different methods of delirium and dementia ascertainment, add weight to the argument that delirium is independently associated with cognitive decline and new dementia diagnosis. This association remains even when controlling for the potentially confounding effect of illness severity, which was recorded prospectively in DECIDE, addressing a key limitation of previous studies. This strengthens the argument for the hypothesis that delirium itself is neurotoxic, and not simply a reflection of severe illness or other confounding factors. This argument is further strengthened when examining the results in the context of the Bradford Hill criteria which are useful for establishing whether results from epidemiological studies provide sufficient evidence to suggest a causal relationship (Table 48) (Hill, 1965). The fact that such similar results have been obtained from such different cohorts, the strength of the relationship and the fact that it has been shown in DECIDE that longer duration and multiple episodes are associated with worse outcomes, all support the hypothesis that delirium in itself is toxic to the brain.

| Bradford Hill Criteria | Supporting evidence |
|---|---|
| 1. Strength | Delirium has been shown to be associated with an increased risk of dementia with a large odds ratio of 8.8. |
| 2. Consistency | Consistent findings have been observed from very different cohorts in different countries, using differing methodologies for delirium and dementia ascertainment (OR 8.8 from CFAS I (Davis et al., 2014); OR 8.7 from Vantaa (Davis et al., 2012)). |
| 3. Specificity | Not demonstrated in DECIDE |
| 4. Temporality | Demonstrated in DECIDE by controlling for participants' baseline cognition. |
| 5. Biological gradient | DECIDE has demonstrated that longer duration, greater severity and multiple episodes of delirium are associated with worse cognitive outcomes. |
| 6. Plausibility | A mechanism for the relationship between delirium and dementia is limited by current knowledge and further research is needed in this field. |
| 7. Coherence | As above, there is a lack of knowledge of the underlying pathophysiology. |
| 8. Experiment | Dementia prevention studies which focus on delirium intervention will provide the focus for future research. |
| 9. Analogy | It is possible that the relationship between delirium and dementia is analogous to the relationship seen in rheumatoid arthritis whereby an acute flare contributes to the accumulation of chronic joint damage. |

*Table 48: Interpreting the results from the DECIDE study in the context of the Bradford Hill Criteria demonstrates the strength of the argument that delirium is toxic to the brain and contributes to dementia.*

For the first time, the DECIDE study has also quantified the size of the cognitive decline that might be expected following an episode of delirium using a well-recognised and widely used cognitive testing tool. Having delirium during the study period was associated with a reduction in MMSE score of nearly 2 points between baseline and follow up interviews. For comparison, the mean difference in MMSE score at 6 months in patients with Alzheimer's disease treated with 10mg donepezil

(the optimal treatment for dementia currently) compared to those treated with placebo was 1.05 points (Birks and Harvey, 2018).

The prospective assessments facilitated exploratory analysis of delirium characteristics as predictors of poor outcome, which has not been possible previously in a population-based cohort due to the retrospective ascertainment of delirium. Previous work has demonstrated that increased duration and severity of delirium were associated with worse outcomes in terms of mortality and institutionalisation (Jackson et al., 2016b). The DECIDE study has additionally shown that these factors predict worse cognitive outcomes with more than 5 days of delirium shown to be associated with a 5 point reduction in MMSE score at follow up (coef. -5.132 [CI: -8.139 - -2.125]). This is in line with a previous study of intensive care unit survivors, which found that having delirium for more than 5 days was associated with considerably worse cognitive outcomes measured using a battery of cognitive tests (Girard et al., 2010).

The DECIDE study found that having more than 1 episode of delirium during the year long study period was associated with a nearly 14 times increased risk of new dementia (odds ratio 13.889 [CI: 1.278 - 150.981]) and a nearly 6 times increased risk of poor outcome at follow up (odds ratio 5.956 [CI: 1.331 - 26.646]). Although a degree of caution is necessary with respect to the precise size of the effect, due to the small numbers involved, these results are novel as no previous studies have been able to explore the effect of multiple episodes of delirium as they have either ascertained delirium retrospectively or have only followed participants during one hospital admission.

### *7.2.2 Delirium incidence*

The hospital associated incidence of delirium during the one year study period in the DECIDE participants was 40%. This is comparable to previous studies, which found occurrence rates per admission between 11 and 64% depending on precise setting (Siddiqi et al., 2006, Inouye et al., 2014, Eeles et al., 2010). The longitudinal monitoring for and detailed recording of delirium, including multiple hospital admissions, is entirely novel with no previous, comparable data.

The estimated community incidence of delirium was based upon the I-AGeD score in the 100 control participants who had no hospital admissions during the study period. None of the 47 participants with a completed I-AGeD scored above the previously

used cut-off of 4, suggesting that none of the control participants had delirium during the study year. This very low incidence is consistent with the community prevalence of delirium previously estimated to be around 1% (Inouye et al., 2014). However, the figures obtained from control participants in DECIDE are limited by the use of a retrospective tool and the low completion rates caused mainly by participants not giving permission to speak to a next of kin.

### *7.2.3 Risk factors for delirium*

Age and baseline cognition were found to be significant independent predictors of the development of delirium, which is in line with previous work on the predisposing factors for delirium (Inouye et al., 2014).

### *7.2.4 Dementia prevalence*

The overall prevalence of dementia at follow up in the DECIDE hospital participants was 17% (23/135). This is considerably higher than the expected prevalence of dementia in the general population over 65 years (6.5%), based upon data from CFAS (Matthews et al., 2013). The DECIDE participants had all been hospital inpatients in the year preceding follow up cognitive testing which may highlight the importance of hospital admission as a marker of risk of adverse outcome, including cognitive outcomes, in older people. However, the relationship is complex. Cognitive impairment has been shown to be a risk factor for hospital readmission (Craven and Conroy, 2015). In line with this, the DECIDE participants had lower cognitive test scores at baseline than the controls recruited who had no hospital admissions in the preceding year (Table 13). Additionally, when comparing those who were hospitalised but never experienced delirium to those who were not hospitalised during the study period, hospitalisation was not found to be an independent predictor of MMSE score at follow up interview. This implies that the hospitalisation itself is not impacting on cognitive outcomes but the delirium in addition to hospitalisation results in adverse outcomes. This is supported by the findings from DECIDE that 31% (15/48) of participants with delirium and 3% (3/87) of those without delirium had a new diagnosis of dementia at follow up. It has not previously been possible to explore this and tease apart the relationship between hospital admission, delirium and cognitive outcomes.

### *7.2.5 Relationship between frailty and delirium*

In line with previous work (Persico et al., 2018), Clinical Frailty Score (Rockwood et al., 2005) was shown to differ significantly between those who did and did not

develop delirium in hospital, with higher scores, indicating more frailty, in those who developed delirium. However, in multivariate analysis, only age and baseline cognition were independently associated with delirium. Many of the studies examining the link between delirium and frailty did not adequately control for relevant confounders (Persico et al., 2018), which may explain why our multivariate results differ from published studies.

It has previously been shown that delirium and frailty independently predict mortality (Dani et al., 2018). However, multivariate analysis in DECIDE showed that only frailty and peak illness severity independently predicted mortality. This may reflect the differing methodology used with DECIDE capturing incident delirium over a year as opposed to prevalent delirium within the first 72 hours of hospital admission (Dani et al., 2018). Frailty was also recorded differently with the Frailty Index being used by Dani et al, including acute physiological markers such as laboratory and examination findings, as opposed to the Clinical Frailty Score in DECIDE, which provides a brief, general overview of functioning prior to admission, determined by the rater following discussion with the participant or their next of kin.

Although delirium did not independently predict mortality in DECIDE, delirium, frailty and baseline cognition independently predicted MMSE score at follow up and delirium, frailty and illness severity all independently predicted poor outcome as a whole. Despite the fact that there is clearly overlap in what is captured when measuring cognition and frailty, with many frailty scores including a rating of cognition, they were both shown to independently predict cognitive decline.

It is well recognised that the degree of Alzheimer's neuropathology does not correlate well with clinical features of dementia (Wallace et al., 2019). For example, some people with high levels of classical Alzheimer's neuropathology found on post mortem, such as amyloid plaques and neurofibrillary tangles, do not have classical symptoms of dementia clinically, whilst other people may have very little in the way of classical neuropathology, but have very severe Alzheimer's disease clinically. It has been proposed that frailty may account for some of this heterogeneity and previous work has shown that frailty and classical Alzheimer's disease neuropathology were independently associated with Alzheimer's dementia (Wallace et al., 2019). They found that individuals with a higher frailty score, indicating more severe frailty, had a weaker association between classical Alzheimer's pathology and clinical dementia symptoms (Wallace et al., 2019). As such, more frail individuals were less able to

tolerate Alzheimer's neuropathology so even small levels resulted in clinical dementia.

A similar disassociation between classical neuropathology and dementia symptoms has also been shown with delirium (Davis et al., 2012). This study showed that there was no significant association between dementia and the classical neuropathological markers in patients who had a history of delirium. A further study, which included participants from the original Cognitive Function and Ageing Study, again showed that the cognitive decline expected with classical neuropathology of dementia was accelerated in the context of co-existing delirium (Davis et al., 2017). This suggests that delirium may be associated with an alternative neurodegenerative pathology that is, in these studies, unmeasured and currently unknown. This also supports the hypothesis that delirium itself is neurotoxic.

The independent contribution of frailty, delirium and baseline cognition to cognitive decline shown in DECIDE demonstrates the complex relationship between physical and cognitive function and support previous findings from studies including neuropathology. Clinically, the results demonstrate the prognostic role that frailty may have in older people with delirium. The results also emphasise the importance of measuring and recording both physical and cognitive function in research studies and not examining these factors in isolation.

A specific limitation in DECIDE was that baseline cognition and frailty were not measured simultaneously, with cognition measured when participants were last seen as part of CFAS II and frailty being recorded on recruitment to DECIDE, with 3 and 6 years between these time points. It is difficult to estimate the impact of this but time between interviews was included as a relevant confounder in multivariate analysis to try to account for this variability.

### *7.2.6 Perceptual disturbances in delirium*

There is very little published literature describing and recording the perceptual disturbances experienced by patients with delirium and the relationship between these symptoms and outcomes, as well as patient experience, is poorly understood.

The DECIDE study was in a unique position to document the reported perceptual disturbances in a population of older people in hospital with and without delirium. Perceptual disturbances were commonly reported by participants (31.7%) and frequently coincided with delirium (69.2%). Participants who experienced perceptual

disturbances were significantly older, more likely to have a diagnosis of dementia and had more co-morbidities.

Previous studies have not recorded the prevalence of perceptual disturbances in a general hospital population but have focused on specific patients, mainly people with delirium. In a study of 100 palliative care patients with delirium, 49 had evidence of psychosis which was defined as the presence of perceptual disturbances, delusions or thought disturbance as recorded using the Delirium Rating Scale-Revised-98 (Meagher et al., 2007). A study of 100 patients with delirium from a cancer hospital in New York found that the prevalence of perceptual disturbances and delusions was higher in patients with hyperactive (70.2% and 78.7% respectively) than hypoactive delirium (50.9% and 43.4% respectively), as recording using the Memorial Delirium Assessment Scale (MDAS) (Boettger and Breitbart, 2011). However, there is methodological uncertainty surrounding this study as none of the participants were unable to complete the full MDAS. In DECIDE, it was not always possible to complete the full MDAS, particularly those sections which required patients to demonstrate perceptual disturbances and delusions, due to delirium with severe inattention or deranged level of arousal or due to advanced cognitive impairment rendering patients mute. It is unclear whether these patients were simply excluded by Boettger et al, which would probably result in an underestimation of the true prevalence.

It was perhaps surprising to discover how many older people in hospital have these experiences, even when not associated with delirium. When focusing on the participants who did not have delirium at the time, nearly half of participants described these experiences happening at night. It is possible that these participants had a brief period of delirium, which was not captured by the daily assessments. This reflects the fluctuating nature of delirium and the challenges of prospectively capturing it. This may also be the case for the 2 participants who had these experiences at home immediately prior to admission. The 2 participants with dementia in whom the experiences were reported on a day with no delirium surrounded by days of delirium before and after may suggest that they needed to recover sufficiently from their delirium in order to communicate their experiences. 3 people had “misperceptions or illusions related to sleep” according to the Memorial Delirium Assessment Scale. The studies mentioned above would not have included these people in their analyses as they only included people with perceptual

disturbances or delusions rated 2 or above on the MDAS. This left 3 people who reported true visual hallucinations but did not have delirium at the time. There are many causes of visual hallucinations, other than delirium, and this was not explored. Further analysis of the data may explore the impact of factors such as visual impairment or medication use.

The presence or absence of perceptual disturbances was not independently associated with mortality, institutionalisation or cognitive decline at follow up. This differs from previous work, which has shown that patients with psychotic symptoms and delirium have higher risk of inpatient mortality than those with delirium without psychotic symptoms (Paik et al., 2018). This may be due to a diluting down of the impact in DECIDE due to the inclusion of people who did not have delirium and experienced only brief episodes of mild perceptual disturbances. It may suggest that perceptual disturbances in isolation are not a marker of poor prognosis in terms of mortality, institutionalisation or cognitive decline, although the analysis was not powered sufficiently to draw further conclusions.

These experiences were associated with feeling distressed in nearly half of participants and so staff should be encouraged to proactively question patients regarding these symptoms. They can then provide reassurance that they are relatively common in people in hospital and, due to the high association with delirium, these patients should be screened for delirium.

### *7.2.7 Impact on clinical practice*

The DECIDE study provides robust evidence that an episode of delirium significantly increases the risk of future dementia, with 31.25% of the participants with delirium having a new diagnosis of dementia at follow up as opposed to 3.45% of those without delirium during the study. This information, along with the novel exploratory findings from DECIDE regarding the adverse impact of delirium duration, severity and multiple episodes of delirium, will support more accurate discussions with patients and their relatives regarding prognosis following delirium.

This data will also provide further evidence that delirium is not a benign and transient condition or an inevitability of hospital admission for older people; it is a serious condition with significant consequences which needs to be recognised and acted upon by all members of the multidisciplinary team.

Of the 18 participants with a new diagnosis of dementia at follow up, 15 had delirium captured by the DECIDE study during the preceding year. This emphasises the importance of asking about a history of delirium when assessing patients for dementia in the memory clinic.

A large proportion of the participants who developed delirium during the study period had a history of delirium reported by them or their next of kin. Previous delirium is a recognised risk factor for delirium (Inouye et al., 2014) and this emphasises the importance of asking about previous episodes of delirium when risk stratifying patients for delirium on admission.

Given the relationship between delirium and dementia, with each acting as a risk factor for the other, it could be argued that delirium should be the red flag for dementia that, for example, unexplained weight loss is for cancer. A patient presenting with delirium should initiate an assessment of their baseline cognition, as it is possible that they have an undiagnosed dementia. Patients should also be followed up following the resolution of their delirium to complete cognitive testing due to their increased risk of developing dementia in the future. This will facilitate the prompt diagnosis and treatment of dementia. The time period of this follow up review is not certain and requires further research, particularly given the challenges of persistent delirium and differentiating this from dementia.

In summary, not recognising and documenting the diagnosis of delirium results in a missed opportunity, either to diagnose a pre-existing but undiagnosed dementia, or to highlight the patient as high risk for developing future dementia and therefore ensuring that they are followed up.

## 7.3 Strengths and weaknesses

A major strength of the DECIDE study was the fact that it was nested within an existing, well-characterised cohort with known baseline cognition. The CFAS II study is a world renowned cohort which has provided unique dementia prevalence estimates (Matthews et al., 2013). This meant that baseline cognition could be robustly accounted for when examining cognitive outcomes after delirium and meant that the follow up interviews were standardised and comprehensive.

A further strength of the DECIDE study were the robust prospective delirium assessments using a standardised approach which followed patients longitudinally. This has never been done before in the context of an existing cohort study.

The study recruited to target and consequently, had sufficient power when examining cognitive trajectories after delirium. The confidence intervals when examining dementia as a binary outcome are broad, reflecting some uncertainty in the size of the risk, probably due to a lack of participants. The sample size was relatively small which limited the exploratory sub group analysis looking into predictors of poor outcomes.

A further strength of the study was that only two people assessed patients in hospital and at follow up, one of whom was a trainee in geriatric medicine. This meant that it was easier to ensure inter-rater reliability but meant that participants were seen once a day at most, which might not have captured all days with delirium due to the fluctuating nature of the condition. However, the use of notes review and collateral history of preceding 24 hours as part of the assessment aimed to capture delirium that may not have been present at the time of the prospective assessment. The retrospective reviews (Kuhn et al., 2014) also helped to capture information when patients did not want to be seen or were too unwell to be assessed, both practical difficulties of real-world research. These two techniques have not been combined before.

There was very little missing data but if missing data was found, this was closely examined. For example, in the case of the CAMCOG, there was missing data and this was found to be not at random. Having personally carried out the majority of the follow up interviews, I was aware of the fact that the follow up interview designed by CFAS was long and challenging and would not be possible for those who had more severe cognitive impairment. Therefore, an inability to complete a full CAMCOG was

often a sign of very severe cognitive impairment. As such, CAMCOG had a significant floor effect which may account for the fact that when used as the primary outcome measure of cognition, delirium was not found to be an independent predictor whilst it was when MMSE or dementia status were used as primary outcome measures.

It was not possible to define the motor subtype in quite a number of participants. This may be because not all delirium affects motor function. It may also be due to the fact that delirium was not prospectively captured but was ascertained through notes review or collateral history within 24 hours of the event and participants had returned to their normal by the time a full MDAS was recorded. This has been noted previously in a study examining outcomes by motor subtype which found that 13% of participants had no motor subtype. They found that the no-subtype group had a better prognosis in terms of mortality, length of stay or institutionalisation (Evensen et al., 2019).

The diagnosis of delirium is often challenging and quite subjective and the heterogeneity in previous delirium research is a significant limitation. The aim of this study was to use a standardised approach to delirium ascertainment, which combined a number of objective assessments with overall judgement. However, even so, there were cases which were not clear cut when it was not possible to definitely say whether delirium was present or absent. In these situations, a consensus panel was used to review all available study data, including from retrospective ascertainment, and a decision made as to whether delirium was present or absent. In 4 cases, the two assessors disagreed, and a third assessor was brought in to provide a majority decision. The sensitivity analyses that were carried out showed that these cases did not impact upon the outcomes of statistical analyses. This robust and transparent approach to delirium ascertainment is relatively unique but has been replicated in subsequent research (Davis et al., 2018).

A limitation of the follow up interviews used by CFAS is that they do not attempt to subtype the dementia. This meant that it was not possible to explore whether delirium rates and outcomes differed between different subtypes of dementia. There were also not sufficient numbers within the DECIDE study to perform subgroup analyses aiming to explore whether outcomes differed between those with delirium alone compared to delirium superimposed on dementia. These areas may provide the focus for future work.

A further limitation was the variable and considerable time that had elapsed between baseline and follow up cognitive assessments, between 3 and 6 years. The time between assessments was included in analysis as a potential confounder to attempt to address this. In order to address the possibility that a participant may have developed dementia between their wave II interview for CFAS II and their recruitment to DECIDE, sensitivity analysis was performed without the participants who had a diagnosis of dementia recorded in their medical records on recruitment to DECIDE but did not have a diagnosis at wave II of CFAS II. This demonstrated that delirium remained a strong, independent predictor of new dementia diagnosis. This was reassuring and suggests that this gap between assessments, and any potential decline in cognition that had occurred during this time, did not affect the overall results.

Due to the fact that there were only 2 people working on the study, interviewers were not blinded to delirium status during hospital admission. However, the follow up interview was objective and standardised and therefore, did not rely on subjective assessments of cognition, which may have been affected by knowledge of delirium status. The participants were also followed up a year after their hospital discharges and so interviewers had often forgotten the precise details of most hospital admissions by this point.

## 7.4 Implications for future research

### *7.4.1 Delirium: a modifiable risk factor for dementia*

Delirium has been shown to be robustly associated with trajectories of cognitive decline. Therefore, it is reasonable to hypothesise that delirium is a potentially modifiable risk factor for dementia. Given that delirium is preventable in around one third of cases (Inouye et al., 1999), this paves the way for future dementia prevention trials that focus on delirium intervention. Given the current lack of treatments for dementia, and the ageing population, prevention is becoming increasingly relevant and appealing and may have significant financial implications given the population cost of dementia is estimated to be £26 billion (Lewis et al., 2014).

The next step, having shown this association, is to demonstrate that preventing delirium does reduce rates of dementia. Previous studies exploring strategies for delirium prevention have not specifically examined cognitive outcomes. Delirium prevention is complex and although multicomponent interventions have been shown to be effective in research studies, their real world utility has not been demonstrated. A randomised controlled trial, which aimed to implement a multicomponent intervention in a busy acute medical admission system, did not demonstrate an impact on health status or service use, but the experience of patients and their carers was considerably improved (Goldberg et al., 2013). As with all multicomponent interventions, a further limitation is the fact that it is also not possible to determine the effectiveness of individual components.

Realistically, it may not always be possible to prevent delirium. An alternative focus for future research may be to enhance the recovery from delirium. Given the independent associations demonstrated in DECIDE between delirium, frailty and future cognitive decline, this would likely involve both cognitive and physical rehabilitation. This intervention would aim to resolve the delirium as quickly as possible and speed up the cognitive recovery with an aim to reduce the number of days with delirium and the number of episodes of delirium. This has not previously been examined but is an appealing area for future research and may have huge implications for rates of dementia, if shown to prevent cognitive decline, as well as lengths of hospital stay, if shown to resolve delirium more quickly.

There are currently no effective pharmacological interventions to prevent or treat delirium and, in fact, many of the medications prescribed can cause significant harm

(Barbateskovic et al., 2019, Scottish Intercollegiate Guidelines Network, 2019). Our understanding of the pathophysiology of delirium is very limited and good quality studies in this area are lacking. An improved understanding of the fundamental physiology underlying delirium may provide targets for potential interventions including pharmacological treatments.

### *7.4.2 Follow up after delirium*

There is a need for further research into the follow up of patients after delirium. Firstly, the DECIDE study has shown that these people are at high risk of dementia and so by following people up routinely following delirium, it may be possible to expedite a diagnosis of dementia and facilitate earlier treatment. However, the ideal time period before follow up is not known and is complicated by the fact that delirium can persist for several months. Therefore, it may be beneficial to leave a longer period between discharges and follow up. However, as demonstrated by DECIDE, these people are at high risk of further delirium and hospital admissions and may never experience a longer period free from admission to hospital.

The content of this follow up also requires further research. Simply limiting it to a cognitive assessment may miss the opportunity to address some of the longer-term psychological sequelae associated with delirium. This may also be an opportune time to address other risk factors for dementia such as hypertension, smoking status and hyperlipidaemia.

### *7.4.3 Outcome measure selection*

The DECIDE study emphasises the importance of selecting an appropriate outcome measure which thoroughly assesses multiple cognitive domains but remains achievable for people with a range of cognitive deficits. In the DECIDE study, despite the significant associations demonstrated between delirium and MMSE and delirium and dementia diagnosis, this was not replicated when CAMCOG was the primary outcome measure. This may be due to the missing data which exists when participants are unable to complete the CAMCOG, which occurred in 18 of the 135 participants followed up at 1 year. This is missing not at random and, in the DECIDE study, was due to participants being too cognitively impaired to complete the full assessment (13 participants) or due to poor hearing or vision (3 participants). The CAMCOG is a comprehensive assessment of cognition, which takes around 20-30 minutes to complete (Huppert et al., 1995). Although CAMCOG provides lots of detailed information about cognitive domains as well as being a sensitive measure of

cognition which avoids the ceiling effects of the MMSE (Huppert et al., 1995), it is susceptible to the floor effect associated with severe cognitive impairment. In the original study, 33 of 451 participants were unable to complete the CAMCOG due to cognitive impairment (Huppert et al., 1995). Therefore, CAMCOG score may not be an appropriate outcome measure in a cohort in which significant cognitive impairment may exist. In the DECIDE study, MMSE was found to be more inclusive as an outcome measure as only 3 people were too cognitively impaired to complete it. However, it lacks the sensitivity of the CAMCOG to subtle declines in cognition and is known to be confounded by levels of education and cultural norms (Devenney and Hodges, 2017).

Using a diagnosis of dementia as a binary outcome measure avoids the problems of missing data associated with using CAMCOG. However, such a binary outcome does not provide more nuanced information regarding cognitive domains specifically and also considerably reduces the power of the data, perhaps resulting in large confidence intervals. There were very few people who had a new diagnosis of dementia at follow up interview who had not had delirium during the study period (3 people). The small number of people in this category probably also contributes to the large confidence intervals seen in DECIDE.

Using a measure of cognition alone as an outcome measure results in significant survival bias as participants had to survive to a year after their hospital admissions in order to complete their follow up assessments. Delirium is associated with a significantly increased risk of death and mortality varied significantly between those who did and did not have delirium. Therefore, examining poor outcome as a whole, including death, dementia and institutionalisation, is more inclusive and avoids this survival bias. This survival bias may explain why delirium was not an independent predictor of new care home admission: it is possible that the people with delirium did not live long enough to move into a care home.

### *7.4.4 The involvement of older people in research*

The DECIDE study demonstrates that older people are keen to take part in research, even when admitted to hospital and acutely unwell. The recruitment rate was 73.2% and the follow up rate was 80.8% (135/167), when removing those who had died. This should support the argument against the exclusion of older people from many research studies, including those with dementia.

### *7.4.5 Further analysis of the DECIDE cohort*

The DECIDE cohort is a highly valuable resource and unique cohort. Although the primary aim of the study was to explore cognitive outcomes after delirium, it is appealing to use the data to investigate other hypotheses surrounding hospitalisation, delirium and dementia in older people:

- Physical function as a surrogate marker of delirium status

A novel measure of physical function, the Hierarchical Assessment of Balance And Mobility (MacKnight and Rockwood, 2000), was recorded each time participants were assessed. Within the scope of this project, there has not been time to investigate how this fluctuated with the presence or absence of delirium or whether this impacted on outcomes. It has been hypothesised that physical functioning may be a good surrogate marker of delirium status (Gual et al., 2018) but this has not been tracked longitudinally.

- Confounding effects of visual and hearing impairment

A further hypothesis which can be explored using the cohort is the possible confounding effect of visual and hearing impairment on the development of dementia following delirium, both of which were measured objectively as part of the CFAS interview at baseline and follow-up.

- Elective versus emergency hospital admission

It will be possible to compare the rates of delirium and risk of adverse outcomes in those with an elective as opposed to an emergency hospital admission.

- Prevalent versus incident delirium

No attempt was made in the analysis to differentiate between prevalent (present on admission to hospital) and incident (occurring during admission) delirium due to the small subgroups this would have created. No previous population-based studies have been able to explore the impact on outcomes of these differing diagnoses due to the retrospective nature of their delirium ascertainment (Davis et al., 2013). Due to the longitudinal nature of DECIDE, following participants throughout their hospitalisations over the study period of one year, it is possible to ascertain whether each case of delirium was prevalent or incident and explore whether these resulted in differing outcomes.

- Modelling delirium longitudinally

DECIDE also provides a unique opportunity to model delirium longitudinally in a population-based study using repeated measures analysis.

- Cognitive trajectories

Due to the fact that 3 measures of cognition are available for the cohort, two from CFAS II and one from DECIDE, it will also be possible to explore the impact of delirium on the rate of cognitive change measured using the MMSE.

## 7.6 Case study continued

…“Will she get dementia?”

The doctor takes a deep breath, and then replies:

“Research shows that older people who get delirium whilst in hospital have a higher risk of getting dementia in the future. However, most people will recover well from their delirium and not develop dementia. We know that the risks of developing dementia after having delirium are higher in people who have delirium more than once, people who have more than 5 days of delirium and people who have more severe delirium.”

## 7.7 Conclusions

An episode of delirium whilst an inpatient in hospital significantly increases your risk of future cognitive decline and new dementia, independent of illness severity and baseline cognition. This has been robustly shown for the first time in a population-based sample of older people in England.

# Chapter 8: Appendices

## Appendix A

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STUDY PROTOCOL Open Access

# Protocol for the Delirium and Cognitive Impact in Dementia (DECIDE) study: A nested prospective longitudinal cohort study

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**Abstract**

**Background:** Delirium is common, affecting at least 20% of older hospital inpatients. It is widely accepted that delirium is associated with dementia but the degree of causation within this relationship is unclear. Previous studies have been limited by incomplete ascertainment of baseline cognition or a lack of prospective delirium assessments. There is an urgent need for an improved understanding of the relationship between delirium and dementia given that delirium prevention may plausibly impact upon dementia prevention. A well-designed, observational study could also answer fundamental questions of major importance to patients and their families regarding outcomes after delirium.

The Delirium and Cognitive Impact in Dementia (DECIDE) study aims to explore the association between delirium and cognitive function over time in older participants. In an existing population based cohort aged 65 years and older, the effect on cognition of an episode of delirium will be measured, independent of baseline cognition and illness severity. The predictive value of clinical parameters including delirium severity, baseline cognition and delirium subtype on cognitive outcomes following an episode of delirium will also be explored.

**Methods:** Over a 12 month period, surviving participants from the Cognitive Function and Ageing Study II-Newcastle will be screened for delirium on admission to hospital. At the point of presentation, baseline characteristics along with a number of disease relevant clinical parameters will be recorded. The progression/resolution of delirium will be monitored. In those with and without delirium, cognitive decline and dementia will be assessed at one year follow-up. We will evaluate the effect of delirium on cognitive function over time along with the predictive value of clinical parameters.

**Discussion:** This study will be the first to prospectively elucidate the size of the effect of delirium upon cognitive decline and incident dementia. The results will be used to inform future dementia prevention trials that focus on delirium intervention.

**Keywords:** Delirium, Dementia, Cognitive outcomes, Cohort, CFAS II

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## Background

Delirium is a severe neuropsychiatric syndrome of brain dysfunction precipitated by acute illness. It is characterised by acute and fluctuating inattention and other cognitive and perceptual deficits.

Delirium is common, affecting at least 20% of older hospital inpatients [1]. Delirium is particularly common in older people and those with cognitive impairment. The occurrence rate of delirium in general medical and geriatric medicine wards was calculated at 29–64% [2]. However, delirium can occur in people of any age if the physiological insult is great enough and affects up to 80% of those in intensive care [3].

Delirium is highly unpleasant and frightening for patients and their families, causing considerable short and long-term distress [4]. People who have delirium during their hospitalisation have increased lengths of stay [5], more hospital-acquired complications, such as falls and pressure sores, are more likely to need to be admitted to long-term care following discharge from hospital and are more likely to die [6]. These complications lead to additional healthcare costs, estimated at an extra £13,000 per admission [7].

Emerging literature indicates that delirium is a strong predictor of new-onset dementia as well as acceleration of existing cognitive decline [8–11]. This is consistent across different settings: after hospitalisation [6]; in those with dementia [8, 12]; in post-operative patients [13, 14]; after critical care [11]; and in community populations [10, 15]. The only population-based study showed an 8 fold increased risk of cognitive decline following an episode of delirium [10]. Acute hospitalisation itself has been shown to adversely affect trajectories of cognitive decline, even when delirium has not been specifically ascertained [16–18]. This implies that delirium and/or its acute causes can contribute to the overall burden of dementia.

Delirium was previously thought to be a benign and transient condition and, consequently, is under-researched, well out of proportion to its prevalence and impact. The few studies that do exist have several key limitations.

In existing delirium research, good quality, large epidemiological studies in unselected populations are lacking which introduces selection bias and limits the generalisability of results [19]. Dementia is a major risk factor for delirium but many delirium studies list dementia as an exclusion criterion, potentially resulting in an underestimation of the true incidence of delirium.

It is likely that previous studies may have been confounded by incomplete ascertainment of cognitive status at baseline [10], particularly given that around half of dementia is undiagnosed [20]. Only one study of cognitive trajectories in delirium has included baseline cognitive assessments [10]. The major limitation of this work was that delirium could not be prospectively defined. There is a clear case for using prospective delirium assessments particularly in the context of a cohort study as this would allow for detailed assessment of the features of delirium including severity, duration, and aetiology. It is likely that such variations influence the risk of long-term cognitive impairment [21].

Given the above, there is a need for population-based studies to avoid the selection biases associated with much of the current literature based solely on hospitalised samples [19, 21]. A study that prospectively tracks cognitive change before, during and after delirium would address many of the clinically important questions, including:

- To what extent does delirium influence cognitive outcomes, over and above acute illness and progressing frailty?
- What are the clinical features of delirium that have the greatest impact on cognitive outcomes?
- Are there critical periods where delirium is more harmful?

In a population based cohort study of men and women aged 65 years and older, this study will measure the effect on cognition of an episode of delirium, independent of baseline cognitive status and illness severity. The study will also explore the predictive value of clinical parameters including delirium severity, baseline cognition, and delirium subtype on cognitive outcomes following an episode of delirium.

If this study shows that the relationship between delirium and dementia is highly likely to be independently contributory, it is reasonable to hypothesise that delirium is a potentially modifiable risk factor for dementia. This paves the way for future dementia prevention trials that focus on delirium intervention.

## Methods

### Design

The Delirium and Cognitive Impact in Dementia (DECIDE) study is a nested prospective longitudinal cohort study. The study design, protocol and paperwork have been reviewed and given favourable opinion by the Newcastle and North Tyneside 2 Regional Ethics Committee (REC reference: 15/NE/0353).

### Population

The study is embedded within the Cognitive Function and Ageing Study II-Newcastle centre (CFAS II-Newcastle). This is a large population based cohort of individuals aged ≥65 years at baseline.

At baseline (2008–2011), 2500 participants were recruited using primary care registration, which included care settings, to CFAS II-Newcastle. Participants were

re-seen two years later. Global as well as domain specific cognitive function was assessed at baseline and two years follow-up using the Geriatric Mental State (GMS), the Cambridge Cognitive Examination (CAMCOG) and the Mini Mental State Examination (MMSE). All participants sampled in CFAS II-Newcastle live within the catchment area of the Newcastle-upon-Tyne Hospitals NHS Foundation Trust. All surviving CFAS II-Newcastle participants will be eligible to participate.

### Recruitment

At the start of the DECIDE study, an introductory letter and participant information sheet will be sent to all surviving members of CFAS II-Newcastle by the CFAS team detailing the proposed study. They will be invited to contact the CFAS team if they do not want their NHS number to be shared with the DECIDE study team.

During a one-year period, members of CFAS II-Newcastle will be approached on emergency or elective admission to hospital. In order to identify participants admitted to hospital, an alert will be set up on the Newcastle upon Tyne hospitals electronic records system. This will flag up participants on admission to the two acute hospitals in Newcastle upon Tyne (Royal Victoria Infirmary and Freeman Hospital). They will be approached as soon as possible following admission.

### Inclusion criteria

Any participant in CFAS II-Newcastle admitted to hospital during the recruitment period will be invited to take part. If the participant themselves lacks capacity, according to a capacity assessment performed by the lead researcher (SR), an appropriate personal consultee must be available and provide written confirmation of willingness to participate.

### Exclusion criteria

Patients will be excluded from the study if they lack capacity to consent and the study team are unable to identify or contact an appropriate personal consultee. Participants will also be excluded if they are receiving end of life care. If the patient is being isolated for infection control reasons, invitation to participate will be delayed until they are no longer being isolated. Participants in hospital for less than 24 hours will not be included.

### Data collection

The primary exposure is delirium during hospital admission, ascertained prospectively using a standardised procedure based on DSM-5 criteria [22] (Table 1). This assessment combines objective testing of the participant, lasting approximately ten minutes, with information gained from informants (usually nurses, next of kin and clinical records) and assessor's judgement regarding subjective features. Along with determining whether delirium is present according to DSM-5, the assessment enables scores to be generated for delirium severity, based upon the Memorial Delirium Assessment Scale [23], and motor subtype, based upon the Delirium Motor Subtype Scale [24].

Participants will be assessed daily for the first five days by SR or a clinical research nurse, both trained in the assessment of delirium. From day 6, those with delirium will continue to be seen daily until delirium resolution. In the absence of delirium from day 6, or following resolution of delirium, participants will be screened regularly for delirium using a semi-structured interview including a modified version of the Delirium Observation and Screening Scale [25]. Should participants display any signs of delirium according to this, the full assessment described above will be performed to determine whether DSM-5 delirium is present.

These assessments will enable the recording of the duration and characteristics of delirium or the development of new delirium. It will be possible to follow the natural history of the delirium in terms of any fluctuations, potential resolution and therefore estimate duration. The subsequent development of delirium in previously non-delirious participants will also be captured. If it is not possible to review participants prospectively at any particular time point, due to illness, refusal or study capacity, a validated tool will be used to retrospectively review the medical records for a diagnosis of delirium [26].

Recruitment of hospital attendees will stop after 12 months. At this point, vignettes will be generated for each participant and these will be sent to an expert consensus panel (LA, SP, and DD). The panel will be tasked with determining whether delirium was present, its severity, duration and subtype. The use of a consensus panel enables an objective approach to determining these factors. Participants will be identified only by their unique study identifier and will therefore be anonymised.

Participants will be invited to the study on every admission during the one year study period.

Illness severity will also be recorded during admission using recognised illness severity measures (APACHE II [27]/SOFA [28]/SAPS II [29]). There are a lack of validated tools to measure illness severity in older people. Therefore, the utility of the HABAM [30] as a surrogate marker for illness severity and recovery along with delirium development/resolution will also be explored.

At random time-points throughout the study, joint assessments of a sample of participants will be completed to monitor inter-rater reliability and to optimise consistency between assessors.

The advantage of using CFAS participants is that the study population are well characterised at baseline.

**Table 1** Standardised diagnostic algorithm for DSM-5 delirium

| DSM-5 criteria | Test to be performed or information needed |
|---|---|
| A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). | Observations by the examiner during the interview (initiated by questioning such as "can you tell me what has been going on today?") |
| | Level of arousal measured using m-RASS and OSLA |
| | Months of the year backwards |
| | Digit span from MDAS |
| B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. | Acute onset and/or fluctuation obtained from informant history from nursing staff, next of kin and clinical notes |
| C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). | Impairment in any of the following domains:<br>SHORT-TERM MEMORY: three item recall at three minutes<br>LONG-TERM MEMORY: when did World War II end?<br>ORIENTATION: 10 orientation questions from MDAS<br>LANGUAGE: 3 stage command, naming an object and explain purpose of object along with fluency, comprehension and content of conversation<br>VISUOSPATIAL: Will a stone float on water?<br>PERCEPTUAL DISTURBANCE: evidence of illusions or hallucinations by collateral or direct observation/ questioning |
| D. The disturbances in criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma. | Information from history/chart/clinical examination |
| E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., because of a drug of abuse or to a medication), or exposure to a toxin or is because of multiple aetiologies. | Information from history/chart/clinical examination |

Abbreviations:
*m-RASS* modified Richmond Agitation and Sedation Scale [37]
*OSLA* Observational Scale of Level of Arousal [38]
*MDAS* Memorial Delirium Assessment Scale [23]

However, participants were last seen several years ago. Therefore, to obtain an up to date estimate of baseline functioning prior to admission, data will be collected on each admission regarding independence (based on Barthel Index of Activities of Daily Living), frailty (Rockwood Clinical Frailty Score [31]), co-morbidities (CIRS-G [32]), nutritional status (Malnutrition Universal Screening Tool and BMI), polypharmacy (number of medications) and anti-cholinergic burden (based on the ACB scale [33]). The predictive value of these parameters will be explored. During admission, possible causes of delirium will also be recorded along with relevant delirium risk factors such as ward moves, dehydration, constipation, pain and presence or absence of sensory aids.

## Outcomes

The primary outcome will be cognitive decline and/or dementia 12 months after hospital discharge, in comparison to pre-delirium cognitive function, measured by the CAMCOG. All participants, with and without delirium, recruited in hospital will be invited for follow up 12 months after their most recent hospital discharge. Follow up will consist of a home visit to complete the Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT) which provides a quantitative measure of cognition along with dementia status and was used in CFAS II. Other relevant data will also be recorded such as place of residence and an assessment of physical function.

A control group of non-hospital attendees without evidence of delirium will be sampled on a 2:1 basis, matched for age, sex and education. Absence of a history of delirium will be ascertained via clinical notes review and telephone interview based on the Informant Assessment of Geriatric Delirium Scale (I-AGeD) [34].

## Consent

Potential participants will be approached as soon as possible on admission to hospital. This will not interfere with clinical care. They will be approached by the chief

investigator (SR) or the research nurse. Participants will be given a maximum of 24 hours to decide. However, given the low risk and largely observational nature of the study, it is anticipated that participants or their personal consultees will be willing to consent before this. They will also previously have received a participant information sheet by post and so some participants may already be aware of the study.

The inclusion of some participants lacking capacity is inevitable as the study aims to look at the effect of delirium on cognition and both delirium and dementia can impair a person's capacity. A formal capacity assessment based on the Mental Capacity Act will be performed by a trained member of the research team, mainly the chief investigator (SR). Participants will be asked to give consent appropriate to their level of understanding, ranging from written informed consent to account being taken of verbal and non-verbal communication in determining willingness to participate. In those individuals found to be without capacity to give full written informed consent, a personal consultee will be identified and their advice sought regarding participation as per Section 32 of the Mental Capacity Act [35]. As per this guidance, the personal consultee cannot be a paid carer.

The advantage of re-evaluating CFAS II participants, as opposed to other study populations, is that they have already expressed an interest in research by virtue of their willingness to participate in CFAS II. This may make conversations with the personal consultee easier as they will be familiar with research and should be aware of the wishes and feelings of the participant about taking part in research studies.

Verbal reconfirmation of the study participant's willingness to continue with the study will be sought at each point of contact. Participants who are very distressed or refuse to engage (whether due to delirium or having the capacity to refuse assessment on that occasion) will not be assessed by the research team on that occasion but a record of the outcome of the interaction will be documented. Due to the fluctuating nature of delirium, further contact will be attempted later. Any patient appearing consistently distressed by participation or withdrawing consent whilst having capacity will be excluded from the study without prejudice to clinical care. As such, every effort will be made to respect the wishes of the person, both previously made and at the time the research is undertaken.

If they recover capacity, participants admitted to the study via a personal consultee will be given the opportunity to consider whether they would like to continue to be part of the study and if so, written consent will be obtained.

### Data handling and confidentiality

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. Participants will be allocated a unique study identifier which will be used on all data stored in order to ensure anonymity. Caldicott approval has been granted. Personal data will be regarded as strictly confidential. All study records, including the consent forms, and investigator site files will be kept in a locked filing cabinet with restricted access.

### Power calculations

We aim to detect a clinically and statistically significant difference in the annual decrease in the total CAMCOG (total score 107), between 6 points in delirium participants and 3 points in participants without delirium. Assuming that 10% of the cohort (the most conservative end of the range) is a delirium case and that the standard deviation of the decrease in CAMCOG is 2.7 points [36], then in order to detect the desired difference (2-fold) in the CAMCOG with 90% power, using a two-sided test at the 5% level, 10 participants with delirium at the time of admission to hospital and 90 participants without delirium would be needed, i.e. a total of 100 participants. The analysis would additionally allow for other factors using a regression approach, rather than simply comparing how the change in CAMCOG from admission to follow-up differs between the two groups. Also, whilst the calculation assumes complete data have been collected for all participants, the analysis will explore the possibility of incorporating participants with missing data. The above calculations are based on a very conservative prevalence of delirium of 10%. If, for example, the prevalence were 20%, then a total of 55 participants (11 with delirium, 44 without) would be required, based on the assumptions outlined above.

By applying the expected number of admissions per age group, based on best available data, to the number of people within these age groups remaining in the CFAS II-Newcastle cohort, it is possible to estimate that 450 people will be admitted during the year.

### Statistical analysis

The CAMCOG will be used as the primary measure of global cognitive status when examining the effect on cognition of an episode of delirium. The distribution of the values will be considered during the analysis process. The effect of an episode of delirium on cognition will be evaluated by comparing CAMCOG score at baseline and at one year after admission to hospital. Regression analyses will be used to evaluate the change in cognition in delirious and non-delirious participants whilst accounting for relevant confounders such as age, education and illness severity.

Drop-out due to mortality is anticipated in both groups due to the age of participants and the high mortality rates

associated with both severe illness and delirium. This will be explored as part of the analysis. The sensitivity of our results to patterns of missing data and methods for accounting for this will be explored. There is likely to be some survivor effect and this will be considered. Longitudinally, the labelling of "delirium" and "control" becomes blurred due to the fluctuating nature of delirium. The possibility of analysing delirium as a time-varying exposure will be explored as part of the data analysis. The overall approach is novel because no previous delirium ascertainment studies have been nested within an existing, well-characterised cohort allowing baseline characteristics to be controlled for in the final analysis. Assistance with data analysis will be sought from collaborators who have experience in this field and have also previously worked with the CFAS-II cohort.

The predictive value, in terms of cognitive outcomes, of the various markers recorded during the acute episode will be evaluated using multiple regression analysis. This might include the contributory and/or independent effects of delirium severity, duration, aetiology or baseline cognitive function on cognitive outcome.

## Discussion

Delirium is common and associated with poor outcomes, but existing studies are limited by a lack of generalisability and the use of retrospective delirium ascertainment. The novel design of this population-based study includes both baseline cognitive assessments and prospective delirium evaluation in order to assess robustly the likelihood of the relationship between delirium and cognitive decline being independent of any potentially confounding factors. This study will elucidate the size of the effect of delirium upon cognitive decline/dementia and may lead on to dementia prevention trials that focus on delirium intervention. Given the current lack of both modifiable risk factors and treatments for dementia, this would be a considerable advance. Validated methods of delirium prevention do exist but have not been widely implemented. This study will add to our understanding of the long-term importance of delirium prevention.

The prospective nature of the delirium assessments, and the data to be collected, will increase our understanding of the natural history of delirium. As such, this study could address many unanswered questions of clinical significance in delirium and dementia including the natural history of delirium, expected outcomes, and the prognostic value of parameters such as aetiology, duration, severity or underlying frailty. This would facilitate accurate and realistic conversations with families and will have important implications for healthcare planning and public health initiatives.

Patients and the public have been involved throughout the development of this study. Patient groups via the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) were consulted regarding study design, particularly in terms of acceptability. They also reviewed the lay summary. The proposal was also reviewed by lay members of the Cognitive Function and Ageing Study (CFAS) Management Committee. They supported the application and agreed that the combination of the two studies will be reciprocally beneficial with DECIDE enriching CFAS data and vice versa. As the study progresses, regular meetings with the Alzheimer's Society monitors will be used to provide updates on progress and to disseminate findings. There will also be an open Patient and Public Involvement dissemination event at the end of the study.

DECIDE will be the first study to prospectively elucidate the effect of delirium upon cognitive decline and dementia independent of baseline cognition and illness severity and may inform future dementia prevention trials that focus on delirium intervention.

### Abbreviations

CFAS II-Newcastle: Cognitive Function and Ageing Study II Newcastle cohort; DECIDE: Delirium and Cognitive Impact in Dementia; GMS-AGECAT: Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; CAMCOG: Cambridge Cognitive Examination; MMSE: Mini Mental State Examination; DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition [22]; APACHE II: Acute Physiology and Chronic Health Evaluation II [27]; SOFA: Sepsis-related Organ Failure Assessment [28]; SAPS II: Simplified Acute Physiology Score [29]; HABAM: Hierarchical Assessment of Balance and Mobility [30]; CIRS-G: Illness Rating Scale – Geriatrics [32]; BMI: Body Mass Index; ACB: anti-cholinergic burden; I-AGeD: Informant Assessment of Geriatric Delirium Scale [34]; DeNDRoN: Dementias and Neurodegenerative Diseases Research Network; m-RASS: modified Richmond Agitation and Sedation Scale [37]; OSLA: Observational Scale of Level of Arousal [38]; MDAS: Memorial Delirium Assessment Scale [23]

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### Availability of data and material

Not applicable.

### Authors' contributions

All authors were involved in study design, writing of the protocol and manuscript. SR will lead the study and will perform the majority of the data collection, assisted by a half time research nurse. DD and BS will particularly assist SR with data analysis. All authors read and approved the final manuscript.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publication

Not applicable.

**Ethics approval and consent to participate**
The study design, protocol and paperwork have been reviewed and given favourable opinion by the Newcastle and North Tyneside 2 Regional Ethics Committee (REC reference: 15/NE/0353). Written informed consent will be obtained from participants. In those individuals found to be without capacity to give full written informed consent, a personal consultee will be identified and their advice sought regarding participation.

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## Appendix B

Data collection forms

1. Demographics and Admission Information
2. Daily Review
3. One year follow up additional questions including I-AGeD

Entered onto database? ☐ (please initial)

Date: _____

Form completed by? ☐ (please initial)

Date: _____

# Demographics

| | |
|---|---|
| Unique Study Identifier | |
| Age | |
| Gender | |

| **Previous Medical History:** | | **Score:** |
|---|---|---|
| Heart | | |
| Vascular | | |
| Haematopoietic | | |
| Respiratory | | |
| Eyes, ears, nose and throat and larynx | | |
| Upper GI | | |
| Lower GI | | |
| Liver | | |
| Renal | | |
| Genitourinary | | |
| Musculoskeletal | | |
| Neurological | | |
| Endocrine/Metabolic/Breast | | |
| Psychiatric illness | | |

| | | | |
|---|---|---|---|
| History of depression? | Yes / No | History of metastatic disease? | Yes / No |
| History of delirium from clinical records? | Yes / No | History of haematological malignancy? | Yes / No |
| History of delirium from patient or their informant? | Yes / No | Acquired Immunodeficiency Syndrome? | Yes / No |

# Admission Information

| | | | |
|---|---|---|---|
| Unique Study Identifier | | | |
| Admission date | | Visual Impairment? | Yes / No |
| Previous wards | | Hearing Impairment? | Yes / No |
| Weight (kg) | | Place of residence | |
| Height (cm) | | Care package | |
| MUST score | | Frailty score | |
| Emergency surgery? | Yes / No | Elective surgery? | Yes / No |
| 4AT completed in clerking booklet? | Yes / No | Catheter in situ prior to admission? | Yes / No |
| Immunocompromised? | Yes / No | Anticholinergics? | Yes / No |
| Medications<br>(please number) | | | |
| Admission diagnosis | | | |

# The Barthel Index

| | |
|---|---|
| **Bowels** | |
| 0 = incontinent (or needs to be given enemata) | |
| 1 = occasional accident (once/week) | |
| 2 = continent | |
| | |
| **Bladder** | |
| 0 = incontinent, or catheterized and unable to manage | |
| 1 = occasional accident (max. once per 24 hours) | |
| 2 = continent (for over 7 days) | |
| | |
| **Grooming** | |
| 0 = needs help with personal care | |
| 1 = independent face/hair/teeth/shaving (implements provided) | |
| | |
| **Toilet use** | |
| 0 = dependent | |
| 1 = needs some help, but can do something alone | |
| 2 = independent (on and off, dressing, wiping) | |
| | |
| **Feeding** | |
| 0 = unable | |
| 1 = needs help cutting, spreading butter, etc. | |
| 2 = independent (food provided within reach) | |
| | |
| **Transfer** | |
| 0 = unable – no sitting balance | |
| 1 = major help (one or two people, physical), can sit | |
| 2 = minor help (verbal or physical) | |
| 3 = independent | |
| | |
| **Mobility** | |
| 0 = immobile | |
| 1 = wheelchair independent, including corners, etc. | |
| 2 = walks with help of one person (verbal or physical) | |
| 3 = independent (but may use any aid, e.g., stick) | |
| | |
| **Dressing** | |
| 0 = dependent | |
| 1 = needs help, but can do about half unaided | |
| 2 = independent (including buttons, zips, laces, etc.) | |
| | |
| **Stairs** | |
| 0 = unable | |
| 1 = needs help (verbal, physical, carrying aid) | |
| 2 = independent up and down | |
| | |
| **Bathing** | |
| 0 = dependent | |
| 1 = independent (or in shower) | |

## Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

**Scoring frailty in people with dementia**

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.



DALHOUSIE UNIVERSITY *Inspiring Minds*

## Guidelines for the Barthel Index of Activities of Daily Living

**General**
- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
- The need for supervision renders the patient not independent.
- A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses will be the usual source, but direct observation and common sense are also important. However, direct testing is not needed.
- Usually the performance over the preceding 24 – 48 hours is important, but occasionally longer periods will be relevant.
- Unconscious patients should score '0' throughout, even if not yet incontinent.
- Middle categories imply that the patient supplies over 50% of the effort.
- Use of aids to be independent is allowed.

**Bowels (preceding week)**
- If needs enema from nurse, then 'incontinent.'
- 'Occasional' = once a week.

**Bladder (preceding week)**
- 'Occasional' = less than once a day.
- A catheterized patient who can completely manage the catheter alone is registered as 'continent.'

**Grooming (preceding 24 – 48 hours)**
- Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.

**Toilet use**
- Should be able to reach toilet/commode, undress sufficiently, clean self, dress, and leave.
- 'With help' = can wipe self and do some other of above.

**Feeding**
- Able to eat any normal food (not only soft food). Food cooked and served by others, but not cut up.
- 'Help' = food cut up, patient feeds self.

**Transfer**
- From bed to chair and back.
- 'Dependent' = NO sitting balance (unable to sit); two people to lift.
- 'Major help' = one strong/skilled, or two normal people. Can sit up.
- 'Minor help' = one person easily, OR needs any supervision for safety.

**Mobility**
- Refers to mobility about house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided.
- 'Help' = by one untrained person, including supervision/moral support.

**Dressing**
- Should be able to select and put on all clothes, which may be adapted.
- 'Half' = help with buttons, zips, etc. (*check!*), but can put on some garments alone.

**Stairs**
- Must carry any walking aid used to be independent.

**Bathing**
- Usually the most difficult activity.
- Must get in and out unsupervised, and wash self.
- Independent in shower = 'independent' if unsupervised/unaided

Entered onto database? ☐ (please initial) Form completed by? ☐ (please initial)

Date: _____ Date: _____

# Daily review

## Part 1: From the medical records

| | | | |
|---|---|---|---|
| Unique study identifier | | Participant willing to be assessed? | Yes / No |
| Admission Date | | Date of assessment | |
| Place of assessment | | Time of assessment | |
| From file at end of bed: | | | |
| NEWS score | | AVPU | |
| Temperature | | Pain score | |
| Blood pressure | | Last bowels open when? | |
| Heart rate | | Urinary catheter in situ? | Yes / No |
| Respiratory rate | | FOCUS chart completed? | Yes / No |
| Saturations | | Mechanically ventilated? | Yes / No |
| Inspired oxygen ("0" if not on oxygen) | | CPAP? | Yes / No |
| Any emergency surgery? | Yes/No | Fluid chart completed? (if yes, document input) | Yes/No |
| Forget Me Not completed? | Yes/No | Food chart completed? | Yes/No |
| From e-record: | | | |
| Haemoglobin | | Urea | |
| Haematocrit | | Creatinine | |
| White blood cells | | CRP | |
| Platelets | | Albumin | |
| Fibrinogen | | Lipids | |
| Sodium | | Glucose | |
| Potassium | | Vitamin D | |
| Bicarbonate | | Adjusted calcium | |
| Any medication changes? | | | |
| From clinical notes: | | | |
| Physiotherapy input? | Yes/No | Delirium documented in notes? | Yes/No |

**Part 2: Semi-structured interview**

Hello.

My name is …… and I am a doctor/nurse carrying out a research project about older people in hospital.

Do you remember me?

Would it be OK to have a chat with you now?

How are you today?

Tell me what's been happening since I last saw you?

Are you feeling muddled at all?

Have you been getting along with the nurses +/- family OK?

One orientation question (Where are we now? / Do you know what day of the week it is? / Do you know what month it is? / Do you know what year it is? )

Sometimes when people are in hospital, they can see or hear things that are not there or that seem strange. Do you think you have experienced this?

Vigilance test – tapping for letter A in string of letters

Roughly what time of day is it at the moment?

**Score using the modified Delirium Observation Screening Scale:**

- □ Dozes off during conversation or activities
- □ Is easy distracted by stimuli from the environment
- □ Does not maintain attention to conversation or action
- □ Does not finish question or answer
- □ Gives answers that do not fit the question
- □ Reacts slowly to instructions
- □ Thinks they are somewhere else
- □ Does not know which part of the day it is
- □ Does not remember recent events
- □ Is picking, disorderly, restless
- □ Pulls cannulas, feeding tubes, catheters etc.
- □ Is emotionally labile
- □ Sees/hears things which are not there

- □ **IN PEOPLE WITHOUT DEMENTIA, IF ANY OF THE ABOVE ARE ABNORMAL, CONTINUE TO FULL MDAS.**

- □ **IN PEOPLE WITH DEMENTIA, CONTINUE TO MDAS IF THERE HAS BEEN AN ACUTE CHANGE OR IF ANY OF THE ABOVE ARE ABNORMAL EXCEPT:**
    - o Thinks they are somewhere else
    - o Does not know which part of the day it is
    - o Does not remember recent events

- □ If all of the above are normal and there is no suspicion of delirium, move to Part 5

| **Part 3: Ask the participant:** | |
|---|---|
| 1. What day of the week is it? | |
| 2. What month are we in? | |
| 3. What year is it? | |
| 4. What is the date today? | |
| 5. Which hospital is this? | |
| 6. Which floor are we on? | |
| 7. What season is it? | |
| 8. Which city are we in? | |
| 9. Which country are we in? | |
| 10. What time is it? | |
| What year did World War II end? | |
| Will a stone float on water? | |
| Listen and repeat these three words:<br>*(choose one set)*<br><br>• Lemon – Key – Ball<br>• Table – Apple – Cigar<br>• Sky – Penny – Duck | Document number repeated and then instruct to<br><br>remember all three words |
| Listen to the following numbers. I'd like you to repeat them in the order I say them:<br><br>*(start with 3 numbers and if correct, then 4 numbers and if correct then 5 numbers – move on only if answers correctly)*<br><br>3-1-6 \| 7-2-9<br>8-6-0-4 \| 2-5-3-8<br>3-9-6-5-0 \| 5-1-3-6-4 | Document number repeated (0, 3, 4 or 5) |
| Listen to the following numbers. I'd like you to repeat them backwards, in reverse order to how I say them.<br>• 7-5-2<br>• 4-9-0-7 | Document number repeated backwards (0, 3 or 4) |
| Can you tell me the months of the year, from January to December, but in reverse order, starting from December and finishing with January? | Month reached: D N O S A J J M A M F J<br>≥7 correct<br>Starts but scores <7 OR refuses to start<br>Untestable |
| Name this object (hold up pen). What is it used for? | |
| Take this pen in your right hand and use it to touch your left ear | |

| | |
|---|---|
| What were the 3 objects that I asked you to remember? | |
| Have you been sleeping well? | Yes / No |
| Have you been bothered by any vivid dreams? | |
| Have any dreams seemed to continue while you've been awake? | |
| Have you seen anything unusual? What do you think it was? | |
| Have you seen or heard anything you think shouldn't be there? | |
| Sometimes people in hospital have quite odd thoughts. Have you noticed anything? | |
| How have you been getting on with staff, family and friends? | |
| Have you felt distressed at all? | |
| MDAS items: | |
| Perceptual Disturbance | |
| Delusions | |
| Ability to shift and maintain attention | |
| Disorganised thinking | |
| **Part 4: Ask the informant (relative/friend/nurse):** | |
| Collateral history from? | |
| How have they been? | |
| Do you think they have been more confused lately? | Yes / No |
| Are they the same every time you see them? (fluctuations) | Yes / No |
| Have they been wandering? | Yes / No |
| Do they seem to get lost on the ward? | Yes / No |
| How have they been sleeping? | |
| Open visiting? | Yes / No |
| Summary of informant history: | |
| Onset | No significant change from usual<br>Gradual onset - several weeks to a month<br>Acute change occurring over days to a week<br>Abrupt change over several hours to a day |
| Fluctuations | |
| Sleep-wake cycle disturbance | |
| **Part 5: General observations:** | |
| Hearing aids in place? | Yes / No / N/A |
| Glasses in place? | Yes / No / N/A |
| Anyone with the patient? Who? | |

**GCS:**

Eye opening: _____ / 4
Voice: _____ / 5
Movement: _____ / 6

| Eye Opening | |
|---|---|
| Score | Description |
| 0 | Open on arrival and remain so, under patient's control, outlasts stimulus |
| 1 | Open on arrival but close if stimulus removed |
| 1 | Open to voice but then outlast stimulus |
| 2 | Open to voice but close if stimulus removed |
| 3 | Open to gentle physical stimulation (squeezing hand, gently shaking shoulder) |
| 4 | Open to pain only |
| 5 | No eye opening |

| Eye Contact | |
|---|---|
| Score | Description |
| 0 | Spontaneously makes and holds eye contact appropriately |
| 1 | Drowsy and makes eye contact to command but can't hold it for very long |
| 1 | Alert but eyes wandering, some appropriate eye contact |
| 2 | Alert but eyes wandering, little or no appropriate eye contact |
| 2 | Drowsy but makes brief eye contact |
| 3 | Eyes will/are open but no eye contact |

| Posture (NB take into account weakness due to stroke or neurologic disease etc.) | |
|---|---|
| Score | Description |
| 0 | Sitting out in chair or up in bed, holding appropriate posture |
| 1 | Slumped in chair or bed but attempts to sit upright and sustain posture on request |
| 2 | Slumped in chair or bed and unable to sustain posture |
| 3 | Lying in bed and unable or no response to request to sustain posture |

| Movement | |
|---|---|
| Score | Description |
| 0 | Moves spontaneously and purposefully with no restless or agitated movements |
| 1 | Occasional or mild restless or fidgety movements, no aggressive or vigorous movements |
| 1 | Reduced frequency of movement, mildly slowed up |
| 2 | Frequent restless or fidgety movements, no aggressive or vigorous movements |
| 2 | Moderately reduced frequency and speed of movement, interfering with assessment or self care |
| 3 | Aggressive or vigorous, recent pulling out of lines |
| 4 | Overtly combative, violent |
| 4 | Severely reduced frequency and speed of movement, few spontaneous movements |

Score (0–15)

**m-RASS:**

1. **Observe patient**
   a. Patient is alert, restless, or agitated. **(score 0 to +4)**

2. **If not alert, state patient's name and *say* to open eyes and look at speaker. Ask 'Describe how you are feeling?'**
   a. Patient awakens with sustained eye opening and eye contact. **(score –1)**
   b. Patient awakens with eye opening and eye contact, but not sustained. **(score –2)**
   c. Patient has any movement in response to voice but no eye contact. **(score –3)**

3. **When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.**
   a. Patient has any movement to physical stimulation. **(score –4)**
   b. Patient has no response to any stimulation. **(score –5)**

| Score | Term | Description |
|---|---|---|
| +4 | Combative | No attention; overtly combative, violent, immediate danger to staff |
| +3 | Very agitated | Very distractible; repeated calling or touch required to get or keep eye contact or attention.; cannot focus; pulls or removes tube(s) or catheter(s); aggressive; fights environment not people |
| +2 | Slightly agitated | Easily distractible; rapidly loses attention; resists care or uncooperative; frequent non-purposeful movement |
| +1 | Restless | Slightly distractible; pays attention most of the time; anxious, but cooperative; movements not aggressive or vigorous |
| 0 | Alert and calm | Pays attention; makes eye contact; aware of surroundings; responds immediately and appropriately to calling name and touch |
| -1 | Wakes easily | Slightly drowsy; eye contact>10 sec; not fully alert, but has sustained awakening; eye-opening/eye contact to *voice* **>10 seconds** |
| -2 | Wakes slowly | Very drowsy; pays attention some of the time; briefly awakens with eye contact to *voice* **<10 seconds** |
| -3 | Difficult to wake | Repeated calling or touch required to get or keep eye contact or attention; needs repeated stimuli (touch or voice) for attention, movement, or eye opening to *voice* **(but no eye contact)** |
| -4 | Can't stay awake | Arousable but no attention; no response to voice, but movement or eye opening to *physical* stimulation |
| -5 | Unarousable | No response to *voice or physical* stimulation |

**Level of consciousness** (from MDAS): _____

**Psychomotor activity** (from MDAS): _____ (including letter)

**HABAM:** (please mark with a cross the most appropriate for each of the three modalities):

| **BALANCE** | | **TRANSFERS** | | **MOBILITY** | |
|---|---|---|---|---|---|
| Stable ambulation | | Independent | | Unlimited | |
| Stable dynamic standing | | 1 person standby | | Limited to >50 m | |
| Stable static standing | | 1 person minimal assist | | Unlimited with aid | |
| Stable dynamic sitting | | 1 person assist | | With aid >50m | |
| Stable static sitting | | 2 person assist | | With aid 8-50m | |
| Impaired static sitting | | Total lift | | 1 person standby/ +/- aid | |
| | | | | 1 person hands-on/ +/- aid | |
| | | | | Lying to sitting independently | |
| | | | | Positions self in bed | |
| | | | | Needs positioning in bed | |

**Delirium present?** Yes / No

Comments:

**1 year follow up additional questions**

**REM sleep disorder**
*Ask*:
"Does [xxx] ever wake up in the night thrashing about or acting out their dreams?"

**Identifying episodes of delirium**
*Read*:
"This section is designed to ask about symptoms or behaviours that may suggest that [xxx] had an episode of delirium. Your observations of these behaviours can be very helpful in identifying delirium. We are looking for any changes in behaviour that happened quite quickly (days to weeks) and lasted for just a short time (days to weeks). If you can remember when this episode happened (which month), this would also be very useful.

Sometimes, several behavioural observations are mentioned in a single question. The answer should be 'yes' if any one of these observations were present."

*Ask:*
"Over the past year, score yes if you have noticed any of the following which lasted for a few days to weeks and state roughly when this occurred:"

| **Description of behaviour** | **Present? (please circle)** | **When?** |
|---|---|---|
| I did not recognise him/her as their usual self | Yes/No | |
| I often had to repeat things to get his/her attention | Yes/No | |
| He/she was less alert and/or appeared to be drowsy during the daytime | Yes/No | |
| He/she had little spontaneous movement and hardly moved their arms | Yes/No | |
| He/she was often awake at night and sleepy during the day | Yes/No | |
| He/she had recently become more forgetful | Yes/No | |
| When the conversation stopped, his/her eyes closed | Yes/No | |
| He/she was difficult to awaken | Yes/No | |
| He/she was combative and struggled to get free | Yes/No | |
| He/she said strange things that didn't make any sense | Yes/No | |

*Ask and document free text*:
"At the time of the above symptoms, was [xxx] unwell at all? Did they have to see a doctor? What was wrong with them? Did they get admitted to hospital?"

_____

_____

_____

# Chapter 9: References

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