

**The value of electronic patient records for determining
the prevalence and prognosis of cognitive and physical
frailty in a large hospital-based cohort**



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ABSTRACT

The value of electronic patient records for determining the prevalence and prognosis of cognitive and physical frailty in a large hospital-based cohort

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Older people with frailty account for an increasing proportion of hospital admissions but access to specialised geriatric care varies. Data on the burden of cognitive and physical frailty hospital-wide and by specialty are currently limited but such data are necessary for informing clinical guidance, service-planning and policy. Routine clinical data captured in hospital electronic patient records (EPRs) offers an alternative to existing prospective and administrative coding data study designs but the value of these data for measuring frailty has not yet been studied. Therefore, my thesis aimed to evaluate ‘the value of hospital EPRs for determining the prevalence and prognosis of cognitive and physical frailty’ primarily using data from a large hospital-based cohort, i.e., the Oxford Cognitive Comorbidity, Ageing and Frailty Research Database-Electronic Patient Records (ORCHARD-EPR) study.

First, in a systematic review/meta-analysis of 45 hospital-wide and general medicine cohorts, I showed that global frailty, measured using validated tools, was prevalent in older people with unplanned hospital admissions although heterogeneity was high and not explained by frailty tool, setting, or risk of bias. Despite variation in prevalence, frailty was consistently associated with mortality, length of stay (LoS) and discharge destination including after adjustment for confounders, although findings on readmissions were mixed. Notably, cognitive impairment and in particular delirium was poorly ascertained by all the frailty measures used in included studies and therefore the prevalence of cognitive frailty and degree of overlap with physical frailty was uncertain. All studies were either small prospective studies or large administrative datasets based on ICD-10 diagnostic coding except for three which used routine clinical EPR data but were not validated.

Second, I assembled, cleaned and validated data from the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Record (ORCHARD-EPR) 2017-2019 dataset which contains pseudo-anonymised Oxfordshire University Hospital NHS Foundation Trust EPR data for >100,000 unplanned hospital admissions. Importantly, ORCHARD-EPR includes the results of mandatory cognitive screening in those ≥ 70 years (existing dementia diagnosis, delirium diagnosis informed by the Confusion Assessment Methods-CAM and recorded as “certain” or “uncertain”, Abbreviated Mental Test-AMT). I validated

cognitive frailty data from the cognitive screen for general medicine admissions in ORCHARD-EPR against a reference cohort. The prevalence of cognitive frailty (certain delirium, dementia, AMT<8) in general medicine admissions was 35% in ORCHARD-EPR (increasing to 41% when uncertain delirium diagnosis was included) compared to 50% in the reference data with the difference in prevalence largely explained by lower rates of delirium diagnosis in ORCHARD-EPR .

Third, I determined that cognitive frailty (certain+uncertain delirium, dementia, AMT<8) was present in 35% of all ORCHARD-EPR admissions (n=51,202) across 29 specialties, with delirium the most common diagnosis. I also showed that any cognitive frailty predicted survival over up to four years of follow-up as well as LoS, delayed discharge, and discharge destination over and above age, sex, comorbidity and illness severity, with associations strongest for delirium. Additionally, only delirium in non-care home residents predicted readmission.

Fourth, using a modified version of the Hospital Frailty Risk Score to measure physical frailty from ICD-10 codes, I found that moderate/severe physical frailty was present in 73% of individuals with cognitive frailty, but only 46% with physical frailty were cognitively frail. Despite being independently associated with survival, physical frailty added little to mortality risk in those with cognitive frailty but added markedly to LoS and risks of delayed discharge and discharge to a destination other than home.

In conclusion, routinely acquired clinical frailty data is a valuable tool for research, capable of combining large, inclusive, hospital-wide sampling with accurate ascertainment as shown using ORCHARD-EPR. Similar approaches could be adopted at other centres but will likely only be useful if routine screening is embedded into the EPR and shown to reliably identify frail patients. Moreover, findings of high frailty prevalence across multiple specialties and impact on outcomes supports more widespread implementation of routine cognitive and physical frailty screening in older people with unplanned hospital admission in line with current guidance. Additionally, findings support increased emphasis on delirium in policy and research.

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DECLARATION

I completed this thesis while I was a full-time postgraduate student at the University of Oxford. I declare that this thesis is of my own composition and has not been submitted for any other degree or professional qualification. The research presented is entirely my own, done under the supervision of Professors Sarah Pendlebury, Sasha Shepperd and Peter Rothwell except where indicated otherwise by reference or acknowledgement.

CONTRIBUTIONS

I completed all work (e.g., analyses, figures, writing) unless otherwise specified with input from my supervisors Professors Sarah T Pendlebury (STP), Sasha Shepperd (SS) and Peter M Rothwell (PMR). Work which formed part of jointly authored publications has been included in this thesis and the contributions of colleagues are acknowledged below:

Systematic review: I developed the search strategy for the systematic review (Chapters 2 & 3) with input from Mr. Neil Thurley (NT), a medical science librarian at the University of Oxford. Selection of studies was done independently by myself, Dr. Jasmine Gan (JG) and STP. STP also approved the final list of studies, independently verified data extraction and performed risk of bias assessments in duplicate. SS provided valuable input on risk of bias assessment and approved the final list of studies. PMR suggested the meta-regressions of effect size versus prevalence and tests for trend for frailty severity and outcomes. I drafted the systematic review manuscript, with STP, SS and PMR providing advice and contributing to revisions (see peer-reviewed publications, next page).

ORCHARD-EPR: I analysed pre-existing data in the ORCHARD-EPR database and from audit cohorts, which was provided by STP. All data in ORCHARD-EPR, including cognitive screening, are obtained from assessments completed by medical, nursing, allied health and administrative staff as part of routine patient care in Oxfordshire University Hospitals Foundation Trust (OUHFT) hospitals. As the first person to complete a major project delivering on the key objectives of the database (see Boucher et al., 2024), my contributions include assembling, cleaning and analysing ORCHARD-EPR data which was originally provided to me a series of spreadsheets on a secure server. Preparatory work included formatting variables, sense-checking, evaluating missing data and identifying/excluding ineligible care episodes. Several variables had to be derived or calculated from ORCHARD-EPR and/or external data. STP provided advice on sense-checking data, Assoc. Professor Ramon Luengo-Fernandez (RL), University of Oxford provided deprivation data and advised on my analysis plan for Chapter 7. Professor Linda Sharples (LS), London School of Hygiene and Tropical Medicine reviewed preliminary analyses and suggested I use the Standard Mean Difference in Chapter 5 comparisons of certain and uncertain delirium. I drafted a protocol for ORCHARD-EPR with STP and SS providing advice and contributing to revisions (see peer-reviewed publications, next page).

PUBLICATIONS AND PRESENTATIONS

Peer-reviewed publications

1. **Boucher E**, Jell A, Singh S, Davies J, Smith T, Pill A, Varnai K, Woods K, Walliker D, McColl A, Shepperd S, Pendlebury ST. (2024). Protocol for the Development and Analysis of the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database - Electronic Patient Records (ORCHARD-EPR). *BMJ Open*, 14(5):e085126.
2. **Boucher EL**, Gan JM, Rothwell PM, Shepperd S, Pendlebury ST. Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts. (2023). *EClinicalMedicine*, 59:101947.

Manuscripts in preparation

1. **Boucher EL**, Gan JM, Lovett NG, Smith SC, Shepperd S, Pendlebury ST. Delirium screening at scale in older hospital patients as part of routine practice: frequency of diagnostic uncertainty, prevalence and outcomes of certain and uncertain delirium diagnosis. (2024). **[In preparation]**.
2. **Boucher EL**, Shepperd S, Pendlebury ST. Specialty-specific prevalence of delirium and other cognitive frailty. (2024). **[In preparation]**.

Oral presentations

1. Penfield R, **Boucher E**, Saxena S, Vardy E, MacLulich A. (2024). Creating population-scale datasets for delirium epidemiologic and implementation research: leveraging cohort and linked health records. [American Delirium Society Conference; June 2024; Sacramento, California, USA]. **[Symposium]**.
2. **Boucher E**, Gan J, Shepperd S, Pendlebury ST. (2024). Prevalence of delirium, dementia and cognitive test deficits, hospital-wide and by specialty in >50,000 unplanned admissions. [British Geriatric Society Spring Forum; May 2024; Birmingham, UK]. **[Oral presentation]**.
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Poster presentations

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6. Colbourne E, **Boucher E**, Hanayik T, Wartolowska K, Pendlebury ST. Using routinely acquired electronic patients records (EPRs) and brain imaging to study novel risk factors for vascular dementia in older hospital patients. [VasCog; Sept 2023; Göteborg, Sweden].
7. **Boucher E**, Gan J, Shepperd S, Pendlebury ST. Prevalence and outcomes of frailty in older people with unplanned hospital admissions: Systematic review and meta-analysis. [British Geriatric Society Forum; November 2022; London, UK].
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ABBREVIATIONS

4AT	4A's Test
ACE	Addenbrooke's Cognitive Examination
ADLs	Activities of daily living
AMT	Abbreviated Mental Test
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio,
AVPU	Alert, verbal, pain, unresponsive
BP	Blood pressure
CAM	Confusion Assessment Method
CCI	Charlson comorbidity index
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI or CIs	Confidence Intervals
CMU	Complex Medicine Unit
CMO	Chief Medical Officer
CQC	Care Quality Commission
CQUIN	Commissioning for Quality and Innovation
DSM	Statistical Manual of Mental Disorders
DTOC	delayed transfers of care, aka delayed discharge
EAU	Emergency Assessment Unit
ED or A&E	Emergency Department or Accident & Emergency
ED-MEWS	Emergency Department-Modified Early Warning Score
EPR	Electronic Patient Record
GIRFT	Getting It Right First Time
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HFRS	Hospital Frailty Risk Score
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IMD	English Index of Multiple Deprivation
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile range
LoS	Length of stay
mCCI	Modified Charlson Comorbidity Index
MCI	Mild Cognitive Impairment
mHFRS	Modified Hospital Frailty Risk Score
MMSE	Mini Mental State Exam

MoCA	Montreal Cognitive Assessment
MUST	Malnutrition universal screening tool
NEWS	National Early Warning Score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORCHARD-EPR	Oxford Cognitive Comorbidity, Frailty, and Ageing Research Database-Electronic Patient Records
OUHFT	Oxford University Hospitals NHS Foundation Trust
PACS	picture archiving and communications system
PPI	Patient And Public Involvement
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
REC	Research Ethics Committee
RERI	relative excess risk of interaction
ROM	Ratio of means
RR	Relative Risk, aka Risk Ratio
SD	Standard deviation
SDEC	Same Day Emergency Care
SEND	System for Notification and Documentation
SHMI	NHS Summary Hospital-level Mortality Indicator
SIGN	Scottish Intercollegiate Guidelines Network
SIRS	Systemic Inflammatory Response Syndrome Criteria
SpO2	Oxygen saturation
STROBE	Strengthening the reporting of observational studies in epidemiology guidelines
UK	United Kingdom
USA	United States of America

Chapter 1

Introduction

1.1 Introduction to the thesis

Older people account for a rising proportion of hospital users in countries with ageing populations.¹⁻³ In the UK, people 65 years and over account for about 70% of days spent in hospital with the greatest increase in admissions seen in those over 84 years.⁴ Many older inpatients are cognitively and/or physically frail with complex medical and social needs.^{5,6} Most will be cared for on general medicine and older people's medicine wards, but specialist medical and surgical services are increasingly caring for frail, older patients as well.⁷⁻⁹ Access to good quality health and care services for older people with frailty is valued by the public as underscored by research on the priorities of older people and caregivers as well as high-profile initiatives such as the Group of Eight Dementia Summit and Prime Minister's Challenge on Dementia which aimed to make the UK a top country for dementia care.¹⁰⁻¹² However, the adaptation of services has lagged behind demographic changes. Hospitals are for the most part not organised around the needs of frail, older people with unplanned admissions and this population remains at risk of receiving suboptimal care as documented by the Francis Inquiry and other reports.¹³⁻¹⁵

The challenges of delivering good hospital care to growing numbers of complex older patients under resource constraints are considerable. Despite high quality

evidence from randomised trials supporting the effectiveness of frailty interventions in the acute care setting such as Comprehensive Geriatric Assessment (CGA), which increases the likelihood that patients will be alive and living at home in the year following admission, hospitals have struggled to scale frailty services.¹⁶ A survey found that access to CGA was often not available outside of general medicine, geriatric and orthopaedics wards and delivery varied. In response, a toolkit aimed at training non-geriatricians to deliver CGA in hospitals was piloted but had limited success.⁹ Hospital participation in a national frailty quality improvement program (Acute Frailty Network) did not improve length of stay, mortality, institutionalisation or readmission rates.¹⁷ National Health Service (NHS) policy has also encouraged the adoption of “out of hospital” and ambulatory acute care services to reduce hospital admissions in older people.¹⁸ There are concerns, however, that services such as Same Day Emergency Care (SDEC) might not be beneficial for all frail, older patients, particularly those with delirium. Therefore, more evidence is needed.¹⁹⁻²¹

Good quality evidence on the burden of frailty in hospitals is needed to inform decision-making at multiple levels, for example clinical guidelines, service-planning and broader policy decisions on research, service funding and workforce.²² The Getting It Right First Time (GIRFT) Geriatric specialty report identified a lack of reliable data on the burden of frailty in hospitals as a barrier to achieving better care. Additionally, a Lancet Review described the quality of the evidence in general medicine settings as “emerging,” despite most frail patients being cared for by such services.²³ Older people admitted to hospital with acute illness are a difficult population to study for ethical and practical reasons in addition to limited funding

and research capacity.²⁴ As such, most available studies on frailty prevalence are from small, specialty-specific cohorts many of which include elective admissions.^{5,25-36} These studies may not generalise to the hospital population at-large owing to differences in case-mix and potential biases introduced by selection caused by requirements for consent and participation in assessments.³⁷ “Big data” administrative data studies mainly using ICD (International Statistical Classification of Diseases and Related Health Problems) diagnostic coding have also been done, but these likely undercount frailty and particularly dementia and delirium due to the poor sensitivity of coding for these conditions (see section 1.2).³⁸⁻⁴¹

An alternative approach to studying frailty, particularly cognitive frailty, is the use of routine (cognitive) screening data. Several guidelines, mostly from UK organisations, recommend older people with unplanned admissions to hospital be screened for cognitive and physical frailty using standardised tools which can help identify patients for CGA and other specialist care pathways (see section 1.3).^{22,42-45} The introduction of pay-for-performance frameworks such as the Dementia Commissioning for Quality and Innovation (CQUIN) and national audits such as the National Dementia Audit have encouraged adoption of routine cognitive screening (see section 1.4).^{46,47} Where embedded into the electronic patient record (EPR) and appropriate permissions are in place, screening data can be accessed for research. If shown to be accurate, datasets derived from these routine clinical data may allow for improved accuracy of cognitive and physical frailty ascertainment compared to big data studies and provide data on a larger, more inclusive scale compared to prospective studies, achieving the benefits of both.

The value of routine clinical data for studying frailty hospital-wide, including across specialties has not yet been studied: most existing routine datasets are limited to general medicine admissions and have not been validated. In the sections below, I will review the epidemiology of frailty with a particular emphasis on the cognitive domain which has important implications for care needs.

1.2 Definition and ascertainment of frailty

Frailty is characterised by a loss of physiologic reserve across multiple systems (cognitive and physical) which results in increased vulnerability to stressors. In an older person with acute illness, this increased vulnerability may manifest as temporary or permanent declines in health status and functional independence that are out of proportion to the severity of the illness (Figure 1.1).⁴⁸ Although the prevalence of frailty increases with old age it is important to distinguish frailty from normal ageing: a systematic review reported pooled prevalence estimates for frailty of 11% in people age 50-59 (50 studies) compared to 51% in people 90 years and over (12 studies) in the community setting.⁴⁹ Additionally, frailty differs from the related constructs of multimorbidity which refers to the presence of two or more chronic diseases, and disability which describes an impairment with substantial, long-term impact on function.⁵⁰ A systematic review found that 72% of people with frailty have multimorbidity, but only 16% of people with multimorbidity were frail (9 studies).⁵¹ Similarly, although frailty is associated with a greater risk of developing a disability in activities of daily living, many people with disability are not frail.⁵²

Figure 1.1 Impacts of a stressor such as minor illness on function in frail (red) line and not frail (green line) individuals.

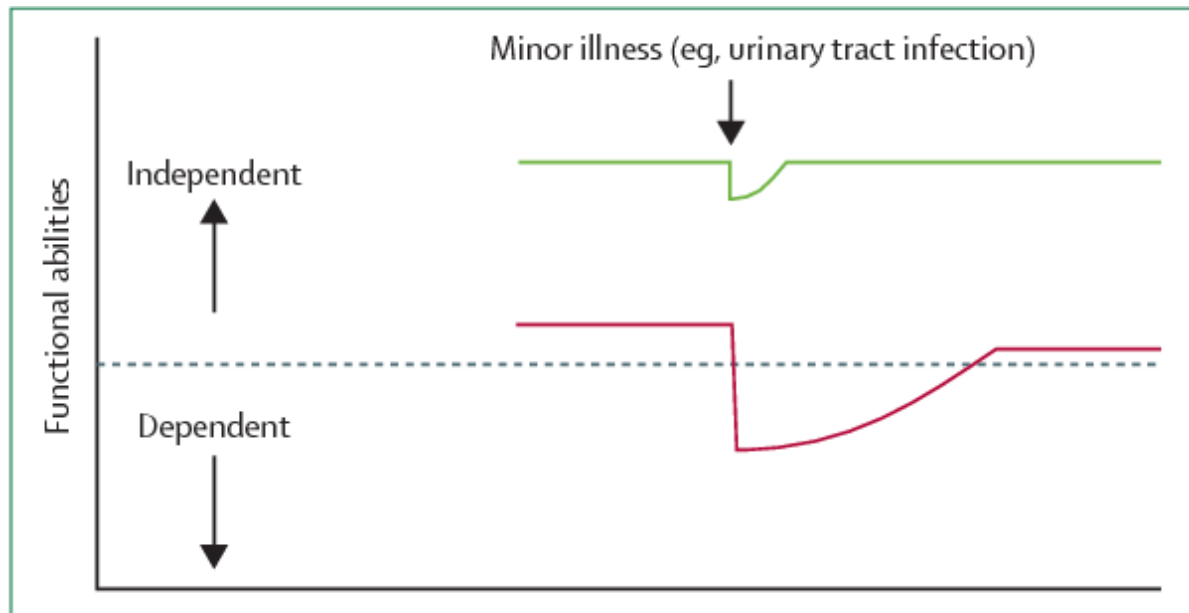


Figure from Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. (2013). Frailty in elderly people. *Lancet* 381:752–762. [https://doi.org/10.1016/s0140-6736\(12\)62167-9](https://doi.org/10.1016/s0140-6736(12)62167-9). Reused with permission from the rights-holder, Elsevier.

The frailty construct has been operationalised including with several widely used clinical measures with one review identifying 89 measures for evaluating frailty in the acute setting.⁵³ These measures include the:

- Clinical Frailty Scale (CFS), which is a global score of frailty;⁵⁴
- Fried Phenotype, which is based on a set of defined physical characteristics;⁵⁵
- Deficit accumulation models, which base frailty risk on the number of ‘deficits’ accumulated and can be calculated from administrative coding data;^{56,57}
- Other clinical tools and questionnaires, such as the Edmonton Frail Scale and Identification of Seniors at Risk.^{58,59}

A small number of measures include an assessment of cognitive decline, and an even smaller number assess for delirium. A systematic review published in 2016 reported that out of 94 frailty tools, 16 included an assessment of dementia and 8 of

delirium.⁶⁰ Frailty scores can be calculated from EPRs, such as the widely used Hospital Frailty Risk Score (HFRS).⁵⁷ The HFRS includes ICD codes for delirium and dementia, but in most routine data these are poorly coded with 1.5-49% of delirium cases recorded in hospital administrative datasets.^{38,39}

1.3 Definition and ascertainment of cognitive frailty

Despite the emphasis on assessing physical function and health in frailty tools, cognitive domains (hereafter “cognitive frailty”) are also important determinants of quality of life and health outcomes and may differentially impact current and future care needs. For example, in hip fracture patients, dementia appears to reduce engagement with physiotherapy and cognitive frailty has been associated with reduced recovery to previous level of function.^{61,62} Definitions and methods for ascertaining dementia and delirium in the literature as well as the related disorders of mild cognitive impairment and subsyndromal delirium are discussed below. I focused on dementia and delirium in my thesis because of their prevalence and impact on outcomes in inpatient populations.

Dementia and mild cognitive impairment

Dementia, known as major neurocognitive disorder in the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is defined by significant cognitive decline in at least one domain that limits independence in daily activities.⁶³ Mild cognitive impairment (MCI), known as mild neurocognitive disorder by contrast describes modest cognitive decline with no impact on independence even if additional effort is needed to compensate for deficits, with 5-10%

progressing to dementia per year in a meta-analysis of 41 studies.⁶⁴ Additional diagnostic criteria for both conditions include that deficits must not be exclusively present in delirium or better explained by another mental disorder.⁶³ Of note, most dementia in older people is caused by Alzheimer's disease, vascular or mixed pathologies.^{65,66}

Cognitive testing is recommended by the National Institute for Health and Care Excellence (NICE) as part of dementia assessment although diagnosis may be deferred in people who are acutely ill or have delirium.⁶⁷ The Mini Mental State Exam (MMSE) tests orientation, memory, language, attention and visuospatial domains and was widely used until it was copyrighted. In a meta-analysis of community-based studies, the MMSE had a sensitivity of 81% and specificity of 89% for dementia (n=108 studies).⁶⁸ Other common tests include the shorter, pragmatic Abbreviated Mental Test (AMT) which assesses orientation, memory, and attention and the Montreal Cognitive Assessment (MoCA) which additionally tests language, frontal/executive function and higher order thinking and can be used to identify mild cognitive impairment due to its high sensitivity.^{69,70} In the same review, the MoCA had a sensitivity of 91% and specificity of 81% for dementia (n=20 studies) and AMT had a sensitivity of 88% and specificity of 85% (n=14 studies).⁷¹ Compared to the MoCA, the AMT (scores<8) had a sensitivity of 73% for identifying moderate to severe impairment (MoCA<18) in a cohort of 205 consecutive medical admissions, but was less sensitive (45%) for mild impairment (MoCA<26).⁷² Notably, up to half of inpatients with dementia do not have a pre-existing diagnosis when they are admitted to hospital.⁷³

Delirium and subsyndromal delirium

Delirium in the DSM-5 is defined by an acute disturbance in attention and awareness (which tends to fluctuate in severity) accompanied by an additional disturbance in another cognitive domain neither of which are better explained by dementia, MCI or reduced arousal. The condition should be identified as the direct result of a medical condition, substance, toxin or multiple aetiologies, although risk depends on both the vulnerability of the patient and severity of the precipitant.⁶³ Examples of predisposing factors increasing vulnerability to delirium include age, dementia, MCI and other central nervous system pathology, physical frailty, vascular comorbidity, alcohol and polypharmacy.⁷⁴ Most delirium occurs in the acute care setting and is present at the time of admission rather than incident while in hospital; however, most literature is still focused on delirium prevention instead of treatment.⁷⁵⁻⁷⁷

NICE recommends the 4A's Test (4AT) be used to assess for delirium outside of the ICU setting, although the Confusion Assessment Method (CAM) is also widely used internationally.^{78,79} The 4AT does not require specific training and identified delirium against a reference standard (i.e., DSM criteria or CAM) with 88% sensitivity and 88% specificity in a meta-analysis of 17 studies in hospital patients 65 years and over.⁸⁰ The sensitivity of the CAM was 94% with 89% sensitivity compared to DSM criteria in a meta-analysis of 7 studies in hospitalised patients, but lower sensitivity has been reported in some studies.⁸¹ For example, a randomised prospective diagnostic test accuracy study in acute medical patients reported 76% sensitivity and 94% specificity for 4AT scores >3 and 40% sensitivity and 100% specificity for the CAM compared to the DSM-4. Low sensitivity of the

CAM may however, have been due to lack of familiarity with the tool which is subjective and scoring issues (for example, CAM requires at least three criteria to be met, but thorough assessment of all criteria may not be feasible if a patient has reduced consciousness whereas ‘Alertness’ and ‘Acute change or fluctuating’ course alone can make the 4AT positive).⁸² Where screening is not routinely performed, up to 70% of delirium is not diagnosed.^{25,83}

1.4 Guidance on cognitive and physical frailty identification in hospital

National-level guidance on routine screening for cognitive or physical frailty in hospitals exist in several countries although most is from the UK (Appendix Table 1.1, pg. 334). However, there are discrepancies between guidelines. The GIRFT Geriatrics National Specialty Report recommends routine screening in people 65 years and over in “emergency pathways” using the CFS for frailty and 4AT for delirium (i.e., “triple assessment” with the National Early Warning Score-NEWS for illness severity).²² However, NICE recommends using the 4AT in adults 18 years and over with indicators of delirium (i.e., changes in cognition, physical function, perception or social behaviour) but does not support routine screening.⁸⁴ The Scottish Intercollegiate Guidelines Network (SIGN) recommends routine screening in all patients at risk of delirium but does not identify a specific age threshold due to a lack of evidence.⁴⁴ Outside the UK, guidance varies. In the Netherlands, hospital patients 70 years and over have been required to be screened for cognitive and physical frailty dating back to 2012.^{85,86} The Australian Commission on Quality and Safety in Healthcare recommends routine delirium screening in patients 65 years and over or younger if at-risk in all settings although has been criticised for being

too broad in scope,^{42,87} and the Canadian Coalition for Seniors' Mental Health recommends delirium screening for older people in hospital but did not specify an age threshold.⁴⁵ Of note, while chronological and biological age can differ, current guidelines do not account for markers of increased biological age such as frailty.⁸⁸⁻⁹⁰

Uptake of guidance on cognitive and physical frailty identification in hospital has been mixed. Introduction of a pay-for-performance (CQUIN) dementia screening scheme from 2013-2016 by NHS England for patients 70 years and over with emergency admissions to hospital ≥ 72 hours resulted in over 80% of eligible patients being assessed with a dementia case-finding question although it is uncertain how reliable this figure is.⁹¹ A CQUIN scheme for identifying frailty using the CFS in patients 65 years and over in emergency departments and SDEC was recently introduced, in part to better target CGA and avoid unnecessary admissions.⁹² However, assessment of delirium is poor across acute NHS trusts with only 40% of cases identified on admission on average,²² although individual trusts have seen improvements in routine screening following quality improvement initiatives.⁹³ Barriers to uptake may include clinician beliefs, resource constraints and poor quality guidance. A 2016 survey of UK physicians identified uncertainty about the utility and feasibility of routinely identifying frailty in older people admitted to hospital as barriers to screening, despite most (79%) indicating that frailty affects their clinical decision making.⁹⁴ Qualitative studies, mainly of US nurses, identified additional barriers specific to delirium screening. These barriers included patient factors such as difficulty determining a patient's cognitive baseline and organisational culture, with lack of interest in delirium from physicians and hospital leadership a barrier but perceived benefits of screening for patients a facilitator.^{95,96}

For both cognitive and physical frailty, inconsistency across guidelines and a lack of clear, specific and actionable recommendations may also undermine uptake.⁹⁷

In the next section, I will review current evidence on the epidemiology of frailty and highlight key gaps in the evidence.

1.5 Epidemiology of frailty in hospitals: An overview of the literature

Current literature on the prevalence and outcomes of cognitive and physical frailty hospital-wide or in general medicine services, which comprise the majority of admissions, was reviewed to inform this introduction. Searches were run in MEDLINE and EMBASE using terms related to frailty, delirium, dementia, cognitive impairment and hospital from inception to February 28, 2024 (January 31, 2023 for frailty) and prospective and retrospective studies were both included. Prospective studies collect data using standard methods to answer predetermined research questions whereas retrospective studies use pre-existing data collected for other purposes, including routinely collected administrative (e.g., ICD-10 codes) and clinical data (e.g., cognitive screening data recorded in EPR forms; see Box 1.1). Their advantages and disadvantages will be discussed below (see section 1.5.3).

Box 1.1 Definitions of relevant study designs and related terms

Study designs

Prospective cohort study: These studies are designed to answer specific predetermined research questions. They involve ascertainment of the exposure using standard methods and following participants longitudinally until the outcome occurs. Informed consent is normally required.

Retrospective cohort study: An existing cohort for which data on the exposure has already been collected (usually for another purpose) and outcomes can be measured over a longitudinal follow-up period.

Retrospective cohort studies may use **routine data** (also known as real-world data). These data are routinely collected for administrative or clinical uses other than research. Examples include:

- **Routine clinical data:** In this thesis, this term describes routine data collected for clinical use for example, that captured in EPRs such as cognitive screening data collected via an EPR-embedded proforma.
- **Routine administrative data:** In this thesis, this term describes routine data collected for administrative use for example ICD-10 codes used to classify diseases and calculate reimbursement for services delivered in the NHS.

Nine relevant reviews were identified, but none included unplanned hospital-wide or general medicine admissions exclusively. Only one review of overall frailty was identified (n=19 studies mostly in geriatric or mixed settings) and it excluded retrospective studies using tools such as the HFRS.⁹⁸ Due to the lack of evidence synthesis on overall frailty in hospital outside of specific populations (e.g., surgery including elective procedures and acute coronary syndrome),⁹⁹⁻¹⁰³ I undertook a systematic review of frailty in the unselected acute hospital setting which is reported in Chapters 2 and 3. Dementia prevalence was reported in one review (n=14 general medicine, geriatric and mixed studies)¹⁰⁴ and outcomes in three (n=13, 20 and 60 studies from a variety of acute care settings), but findings were heterogenous, with prevalence ranging from 2.8-63%.¹⁰⁵⁻¹⁰⁷ Delirium prevalence and outcomes were reported in one review and recently updated (n=42 studies in general medicine and geriatric settings).^{108,109} Two other reviews on cognitive frailty in a variety of hospital and community populations were also identified (n=104 and n=141, respectively).^{110,111}

Relevant studies of dementia and delirium in representative hospital-wide and general medicine populations identified from the literature search and reviews above are discussed below.

1.5.1 Prevalence

Delirium prevalence was reported in 17 hospital-wide and general medicine studies and dementia in 10, with four studies reporting both (mean age 71 to 84 years; 48-61% female; see Appendix Table 1.2 and 1.3).^{5,25-36,40,57,112-120}

Studies included prospective (11/17 delirium and 3/10 dementia studies) and retrospective cohorts (5/17 delirium and 5/10 dementia studies; the remainder were unclear). Retrospective studies mostly used routine administrative (i.e., ICD codes; 2/17 delirium and 3/10 dementia studies)^{40,57,114,118,120} or clinical data (i.e., cognitive screening; 2/17 delirium and 2/10 dementia studies),^{113,117,119} although one chart review was done for delirium.¹¹² Of note, prospective studies identified pre-existing and undiagnosed dementia whereas retrospective cohorts were mostly limited to pre-existing dementia diagnoses.

Delirium prevalence was heterogeneous, ranging from 10-49% across 11 prospective (n=200-1,507) and 1.7-25% across four retrospective studies (n=626-74,379; 1.7-10% in administrative [n=2] versus 14-25% in routine clinical data [n=2] studies). Dementia prevalence was also variable, ranging from 18-62% across three prospective (n=200-1,439) and 7-26% across 5 retrospective studies (n=8,202-3,695,278; 7-26% in administrative [n=3] vs 10-17% in routine clinical data [n=2] studies). Three hospital-wide studies stratified by specialty but were limited to medicine, surgery, orthopaedics/trauma, geriatrics and stroke (Appendix Table 1.4).^{5,35,112}

1.5.2 Outcomes

Most older people admitted to hospital are focused on the goals of recovering from illness and being able to go home.^{121,122} Data on mortality, length of stay, delayed discharge, discharge destination and readmissions can help clinicians communicate prognosis to patients and caregivers, inform treatment decisions and plan discharge.¹²³ In addition, these data are important for decision-makers aiming

to improve the quality of care and capacity within the acute care system, for example informing policy on hospital alternatives, discharge planning and the need for follow-up care in the community.¹²⁴ Evidence on the impact of dementia and delirium on these outcomes was mixed and findings are discussed below:

Mortality

Mortality was the most frequently reported outcome (see Appendix Table 1.5 and Appendix Table 1.6). Delirium was associated with inpatient and short-term mortality in all seven studies reporting data including after adjustment for age, sex, illness severity, dependency, frailty, dementia and specialty (n=225-43,946).^{25,29,33,34,111-113,115,117} Associations remained significant one year after admission (3 studies; n=278-43,946) including after adjustment for age, dementia, illness severity, comorbidity and dependency.^{111,113,115} Findings for dementia were mixed: dementia was associated with inpatient and short-term mortality in two studies including after age, sex, comorbidity, illness severity and delirium status were controlled for (n=617-10,014) but 'known dementia without a current cognitive concern' was inversely associated with inpatient mortality in one study (n=8,202).^{36,111,117,119}

Length of stay

Delirium was associated with increased length of stay (LoS), including after adjustment for age, sex, illness severity, dependency, frailty, dementia and specialty (2 studies; n=503-10,014),^{33,111,117} but the difference in LoS for patients with delirium versus no delirium was heterogenous, ranging from 0.2 fewer days to 13 more days (7 studies; n=225-74,379).^{25,34,40,112,115} Dementia increased LoS after

adjustment for age, sex, delirium, frailty, comorbidity, illness severity and specialty (n=8,202), but LoS was longer for patients with delirium on dementia versus dementia alone in one study (i.e., 22 versus 8 days; n=10,014), suggesting effect heterogeneity. No studies reported delayed discharge as an outcome.^{111,117}

Discharge destination

Evidence was mixed. Delirium was not associated with discharge to a new care home in one study adjusting for age, sex, dementia, frailty and specialty (n=626), but a second study reported that only 36% of patients with delirium were discharged home compared to 81% with no delirium (n=278) and a third reported increased odds of new care home placement and increased care needs (n=503) including after adjustment for age, illness severity, dementia and dependency.^{33,112,115} Dementia increased the risk of discharge to a care home in one study (n=10,014).^{111,117}

Readmission

Associations between cognitive frailty and readmission were mostly non-significant. Delirium did not increase the risk of readmission including after adjustment for age, illness severity, dementia and dependency (n=43,946), except for possibly severe cases (4AT ≥ 4) or in the absence of dementia (n=10,014).^{33,113} Dementia alone was not associated with readmission in hospital-wide studies after adjustment for age, sex, delirium, frailty, comorbidity, illness severity and specialty (n=10,014).^{111,117}

1.5.3 Impact of study design

Most studies on the prevalence and outcomes of cognitive frailty are prospective cohorts which are considered the “gold-standard” for observational study design. Prospective studies offer the best control over data quality (for example, trained research assistants might be hired to collect data according to a standard protocol), but their size is often limited by cost and selection can also be a problem (Table 1.1). Sample size in prospective studies of delirium and dementia ranged from n=200-1,507 (n=14), although the two largest studies (n>1,000) were convenience/single-day samples, which may introduce bias.^{5,25} For comparison, sample size ranged from n=8,202-43,946 in routine clinical data (n=3)^{113,117,119} and n=4,957-1,013,590 in administrative data studies (n=5).^{40,57,114,118,120} Larger studies allow for more precise estimation of prevalence and outcomes including when data are stratified into subgroups, for example, by age, specialty or frailty status.

Prospective studies also often have more restrictive eligibility criteria than routine data studies. Over half of prospective studies required patient/proxy consent (n=8) and the ability to complete assessments (n=7)^{5,26,28-30,32,115} which may preferentially exclude the frailest and most cognitively impaired introducing bias.^{24,37} Several also excluded patients at the end-of-life (n=6)^{5,25,30-32,35} which might lead to underestimation of prevalence because delirium is common in palliative care.¹²⁵ Other exclusion criteria including ‘too unwell’ in a delirium study and ‘unresolved delirium’ in a dementia study could introduce bias because severe illness and dementia increase delirium risk.^{34,36,126} In contrast, routine data studies had few restrictions on eligibility outside of age and LoS,^{40,57,113,114,117-120} whereas this was

only the case for one prospective study.³³ Overall, inclusion rates in prospective studies ranged from 33-100% (median 83%).

Retrospective datasets improve on some of the shortfalls of prospective designs: data are already collected for other uses so individual consent is normally not required and near-complete coverage of large samples can be achieved with minimal selection. However, routine administrative data are often not validated despite well-known concerns about coding accuracy—in a review of 16 studies, only 1.5-49% of delirium was coded.^{38,39} Additionally, administrative datasets may lack the granularity needed to answer some research questions. For example, illness severity data might be recorded in the EPR but is not coded. Routine clinical data may overcome both of these limitations and will be discussed in the next section.

1.5.4 Routine clinical data and the ORCHARD-EPR study

Studies using clinical data exploiting embedded routine cognitive screening may be able to combine accuracy of cognitive frailty ascertainment approaching that of prospective cohort studies with the inclusivity, large-scale and efficiency of administrative data studies, although few data have been published. Of the three routine clinical data studies identified above, two were limited to the general medicine setting and one was hospital wide. Completion rates for cognitive screens ranged from 77% (4AT only; n=43,946 ≥ 65 years) to 79% (known dementia, CAM or clinical delirium diagnosis and AMT-10; n=10,014 ≥ 65 years) in the two general medicine studies but were not reported for the hospital-wide study by Romero-Ortuno et al (2017) although the proportion of patients with known dementia was

comparatively low (i.e., 10%) and may be an underestimate.^{113,117,119} Romero-Ortuno et al. also screened for “known history of dementia” and “acute confusional state” based on the AMT-4, which is not a valid method for identifying delirium. Screening for acute confusion was only done in patients without known dementia.¹¹⁹ None of these studies has been validated.

The Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Record (ORCHARD-EPR) is a unique example of a clinical database using routinely acquired data. ORCHARD-EPR exploits almost 1.5 decades of work to embed cognitive screening with regular performance feedback for all patients aged ≥ 70 years with unplanned admission across four acute general hospitals serving a population of >800,000 in Oxfordshire, UK (screening rates reaching 70-80%). The routinely acquired cognitive screening data (i.e., known dementia, delirium diagnosis informed by the AMT-10 and CAM) in ORCHARD-EPR is accompanied by nursing assessments, laboratory test results and observations allowing illness severity scores to be calculated and diagnoses to be obtained from administrative data in contrast to existing routine data studies with the exception of Romero-Ortuno et al. as well as administrative datasets, such as NHS Hospital Episode Statistics (HES; see Table 4.1, pg. 161).^{113,119,123,127}

Cognitive screening data captured in ORCHARD-EPR was validated and analysed in this thesis. The database will be described in detail in Chapter 4.

Table 1.1 Advantages and disadvantages of prospective cohorts and retrospective cohorts using routine administrative and clinical data

Study design	Potential advantages	Potential disadvantages
Prospective cohorts	Control over data quality, <i>e.g.</i>, <i>trained research staff perform procedures/ tests according to a standard protocol</i>	- Burden of additional procedures/tests beyond routine care for patients - Expensive and labour-intensive, <i>e.g.</i>, <i>recruitment, consent, assessment, and follow-up</i> - Selection bias can be introduced via both the above factors, <i>e.g.</i> <i>'healthy volunteer bias'</i>
Retrospective cohorts using routine administrative data (<i>e.g.</i> , ICD-10 codes)	- No additional burden on patients, because data are collected as part of routine care - High inclusion rates, particularly with opt-out consent policies	- Data are collected for secondary use and may lack the granularity needed for research questions, <i>e.g.</i>, <i>prevalent versus incident delirium is not reported</i> - Problems with data quality and missingness, <i>e.g.</i>, <i>the absence of a given ICD-10 code can indicate either the absence of the condition or missing data</i>
Retrospective cohorts using routine clinical data (<i>e.g.</i> , routine frailty screening recorded in the EPR)	- Similar advantages to administrative datasets - Possibility of obtaining detailed and clinically relevant variables not available in administrative data (<i>note: free text not available in ORCHARD-EPR</i>) - Possibility of obtaining higher-quality data, <i>e.g.</i>, <i>introduce or exploit standard assessments, train staff and provide reporting/feedback</i>	- Similar disadvantages to administrative data - Sample size and scope may be smaller than for administrative data, <i>e.g.</i>, <i>one NHS trust due to challenges with EPR standardisation and data access</i>

1.5.5 Role for large scale epidemiology in informing frailty care and policy

Epidemiologic data on cognitive and physical frailty are important for informing policy, service-planning and enabling the provision of more individualised patient care by clinicians, among other uses such as trials. Better data on the burden of cognitive and physical frailty in hospitals from may help inform national guidance on routine screening for cognitive and physical frailty by providing evidence to address

gaps and inconsistencies in recommendations as outlined above, for example which patients should be screened. Data may also help decision-makers allocate resources more effectively, including for frontline care, research and public engagement: although guidelines underscore the importance of delirium to clinicians, most specialised care pathways, research funding and national campaigns are strongly focused on dementia which is better understood by the public.^{11,12,22,44,84,91}

Better data on the burden of frailty in hospitals could be used to improve service design and delivery. Data could be used to develop more individualised care pathways, for example for patients who are frail with versus without a cognitive component and risk-stratify patients for intervention. Where implemented locally, routine clinical data could be used to provide feedback to clinicians as part of a “learning health systems approach” for better quality and outcomes. For example, clinicians could use data to evaluate outcomes of patients with cognitive frailty and determine if screening and interventions can be delivered in a more targeted way based on local demographic and risk profiles. Fourth, data can be used for a wide range of research including risk-stratification for trials.

1.6 Objectives of thesis

This thesis aims to determine the value of EPRs for determining the prevalence and prognosis of cognitive and physical frailty. As discussed above, good quality epidemiologic data are needed to inform clinical practice, service-planning and policy for frailty in hospitals but are challenging to obtain. Routine data in hospital

EPRs can be exploited for this purpose but their value for this application has not yet been studied. To provide value to decision-makers and frontline clinicians (i.e., compared to other study designs), these data need to provide valid, population-representative estimates of the burden of frailty hospital-wide, including in specialties not traditionally associated with caring for older, complex patients. In addition, data should be associated with prognosis over and above other important factors in the acute hospital setting including but not limited to age, sex, comorbidity and illness severity that are not adjusted for in other large-scale studies.

The specific objectives of this thesis were therefore designed to address specific knowledge gaps I identified through determining the:

1. Prevalence, methods of measurement and outcomes of global and physical frailty in unplanned hospital admissions in a systematic review and meta-analysis (Chapters 2 & 3);
2. Validity of the cognitive frailty data in ORCHARD-EPR obtained from routine cognitive screening against prospectively collected reference data (Chapter 5);
3. Prevalence and outcomes of cognitive frailty hospital-wide in ORCHARD-EPR, including for each cognitive frailty subtype (Chapters 6 & 7);
4. Relative contributions of cognitive and physical frailty to overall frailty prevalence and outcomes in ORCHARD-EPR (Chapter 8)

Outcomes examined were short and long-term survival, length of stay in hospital, delayed discharge, discharge destination and readmission where available.

1.7 Outline of thesis

First, as stated earlier, there was limited synthesis of frailty research in representative acute hospital populations and no systematic evaluation of retrospectively administered, electronic frailty scores such as the HFRS. To provide an overall synthesis and to identify gaps in the evidence and better understand the limitations of existing studies, 'Objective 1' was to complete a systematic review and meta-analysis on frailty measurement, prevalence and outcomes in the acute hospital setting of studies using validated clinically administered and retrospective coding tools, including the HFRS (Chapters 2 & 3).

- **Chapter 2:** Describes the measurement and prevalence of global and physical frailty in representative hospital-wide and general medicine cohorts, including the domains assessed by validated frailty measures used in this setting.
- **Chapter 3:** Describes the outcomes associated with global and physical frailty in in representative hospital-wide and general medicine cohorts, including by degree of frailty and after adjustment for confounding.

Second, reliable hospital-wide prevalence and outcomes data for dementia and delirium were limited: the systematic review (Chapters 2 and 3) showed that cognitive frailty was poorly captured by global frailty measures. Most available studies on delirium and dementia specifically were from small, selected, prospective cohorts or routine administrative data studies which have not been validated. Implementation and integration of routine cognitive screening into EPRs

brings the opportunity to use such data for research, but existing studies were few, in part due to a lack of robust screening programmes. For this reason, I did not include a systematic review of cognitive frailty prevalence and outcomes in this thesis and instead validated and analysed the routine cognitive screening data obtained from the ORCHARD-EPR database as part of 'Objectives 2-3' (Chapters 5-7).

- **Chapter 4:** Provides an overview of ORCHARD-EPR, including assembly, cleaning, derivation of variables and a description of analysis methods used in subsequent chapters.
- **Chapter 5:** Compares routine cognitive screening data for established dementia, delirium diagnosis and AMTS in ORCHARD-EPR to prospectively collected (general medicine) audit data and investigates the prevalence and outcomes of 'certain' versus 'uncertain' delirium diagnosis in ORCHARD-EPR.
- **Chapter 6:** Describes the prevalence of cognitive frailty by age, sex, subtype (delirium alone, delirium superimposed on dementia, dementia alone and low AMTS in the absence of diagnosed delirium or dementia) hospital-wide and in 29 medical and surgery inpatient specialty services in ORCHARD-EPR.
- **Chapter 7:** Determines short- and long-term outcomes of cognitive frailty subtypes hospital-wide in ORCHARD-EPR including after adjustment for age, sex, comorbidity and illness severity.

Lastly, as shown in the systematic review (Chapters 2 and 3), there were limited data on the concurrence of cognitive and physical frailty hospital-wide despite the likely impact on care needs, therefore I described the concurrence of cognitive and

physical frailty and their relative contributions to outcomes in Objective 4 (Chapter 8).

- **Chapter 8:** Determines the overlap between cognitive and physical frailty measured using a modified version of the HFRS and impact on outcomes in ORCHARD-EPR.

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Chapter 2

Frailty prevalence and measurement in adults with unplanned hospital admission: a systematic review

ABSTRACT

Background: Older people account for an increasing proportion of unplanned hospital admissions, with many likely to be frail. Data on the burden of frailty in this population are needed to inform policy, service-planning and guidelines—including routine frailty screening in acute hospitals to inform care decisions. Previous evidence synthesis on frailty prevalence and measurement in the acute hospital setting was limited. Therefore, I undertook a systematic review to determine the prevalence and methods of measurement of global and physical frailty in adults with unplanned admissions hospital-wide and to general medicine services.

Methods: I searched MEDLINE, EMBASE and CINAHL up to 31/01/2023 and included observational studies using validated frailty measures in adult hospital-wide or general medicine admissions. I extracted summary data on the prevalence of

frailty and associated outcomes, measurement tools, study setting (hospital-wide vs general medicine), and design (prospective vs retrospective clinical, administrative and other designs) and assessed risk of bias (modified Joanna Briggs Institute checklist). Frailty prevalence and methods of measurement were summarised across studies.

Results: Across 45 cohorts (median/SD age = 80/5 years; n = 39,041,266 admissions), I identified 22 frailty measurement tools. The most common domains assessed were mobility, balance or falls (n=16), function (n=14) and cognition (n=13 overall, n=7 delirium), but delirium was assessed using insensitive or unvalidated measures in all tools but one. Moderate/severe frailty ranged from 14.3% to 79.6% overall (and in the 26 cohorts with low-moderate risk of bias). Considerable heterogeneity between studies ($p_{het} < 0.001$) prevented pooling but was not related to the method of frailty measurement.

Conclusions: Frailty is prevalent in older patients with unplanned hospital admissions regardless of method of measurement. Most frailty tools appeared impractical for routine hospital use, but the Clinical Frailty Scale appeared pragmatic supporting current guidance. Also, cognitive domains of frailty were poorly assessed by existing frailty tools and should be evaluated separately. In the next chapter, I will review the outcomes of cognitive frailty measured using clinically administered tools and retrospective administrative coding data in this population.

2.1 INTRODUCTION

Frailty is associated with hospital admission and poor health outcomes and although most common in older people, can present in adults of all ages.^{1,2} The importance of frailty in the acute hospital setting is highlighted in guidelines and regulations which recommend or mandate that all older people in hospital be screened for ('global') frailty using standard tools to inform clinical decisions, personalise care and target interventions such as comprehensive geriatric assessment (CGA) as described in the Introduction chapter (also see Appendix Table 1.1, pg. 334).³⁻⁵ Frailty constructs are commonly operationalised using the phenotype model comprising defined traits (for example, slow gait speed and weakness),⁶ the accumulation of deficits and related models (for example, the Hospital Frailty Risk Score-HFRS)^{7,8} or pragmatic Clinical Frailty Scale (CFS), and can include cognitive domains.⁹

Despite current guidance on frailty screening in hospital, uptake has been mostly poor.¹⁰ Limited awareness of frailty tools, insufficient resources for hospital-wide screening and uncertainty about the clinical utility of identifying frailty in acutely unwell patients were identified as barriers to screening, with limited certainty in the evidence an additional contributing factor.¹¹ Most admissions of older people to hospital are unplanned, predominantly to non-specialist general medicine services, where multi-morbidity and complex care needs are common. However, current guidance is based mostly on prospective studies conducted in specialty-specific or elective settings where the prevalence of frailty may be lower. Reliable estimates of 'global' or physical frailty prevalence in the acute hospital setting are needed to inform policy and plan services, including frailty screening programmes and CGA

implementation.¹² Hospital-wide routine clinical or administrative data studies could help overcome these limitations of existing prospective studies and fill this gap.

Previous evidence synthesis on 'global' or physical frailty measurement and prevalence in the acute hospital setting is limited.¹² A scoping review (published 2018) included studies across a wide variety of acute settings in which the majority identified frail patients using non-validated clinical tools/methods.¹³ A systematic review (published 2019) on hospitalised older people included a large number of cohorts from geriatric medicine services or unspecified acute settings for which case-mix and prevalence may differ compared to the hospital population at-large. Additionally, the study was undertaken prior to the development and widespread uptake of measures such as the HFRS that use administrative data and did not include routine clinical data studies.¹⁴ Therefore, I conducted a systematic review of the prevalence and measurement methods of 'global' and physical frailty in adults with acute, unselected, unplanned admissions hospital-wide and to general medicine services in prospective and retrospective studies using clinically administered and administrative coding data tools. In the next chapter, evidence on 'global' and physical frailty outcomes in this population is reviewed.

Work in this chapter is published in:

Boucher EL, Gan JM, Rothwell PM, Shepperd S, Pendlebury ST. (2023).

Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts. *EClinicalMedicine*, 59:101947.

Contributions: I developed the protocol and contributed significantly to the methods, including developing the search strategy in consultation with a healthcare librarian (NT) and a modified risk of bias assessment tool based on Joanna Briggs Institute Critical Appraisal Checklists and with input from SS and STP. I completed data acquisition (including running searches, screening abstracts and full texts, extracting detailed data and performing risk of bias assessment) and analysed and interpreted all data, in addition to drafting the manuscript.

2.2 METHODS

2.2.1 Search strategy and selection criteria

I conducted this systematic review in accordance with PRISMA guidelines and registered it prospectively on PROSPERO (CRD42021235663).^{15,16} I developed a search strategy in consultation with a healthcare librarian (NT) and searched MEDLINE, EMBASE and CINAHL from inception to January 31, 2023 without restrictions using search terms related to frailty, geriatric assessment, hospitalization and observational study design (Appendix Table 2.1). I also reviewed reference lists of included studies for other potentially eligible studies.

2.2.2 Eligibility

I included cross-sectional and cohort studies of adults >18 years with predominantly unplanned admissions (>70% unplanned as stated by the study authors or inferred from the study description) to hospital or general medicine services, who received

usual care. I defined unplanned admissions as unexpected admissions, occurring on short notice due to “clinical need” in line with the NHS Data Dictionary definition for “Admission Method.” This is in contrast to elective care in which the decision to admit occurs in advance and is separated in time from the admission.¹⁷ Unplanned hospital-wide and general medicine admissions were both included because most unplanned admissions are to general medicine services. Studies conducted in outpatient, emergency departments (EDs), short-stay, geriatric or rehabilitation and mixed settings or specialty-specific settings (except general medicine) were excluded.

Participants were also required to be assessed for ‘global’ or physical frailty using validated tools during their admission, including the Fried phenotype model,⁶ deficit accumulation methods,⁷ clinical measures (including multidimensional tools assessing a wide variety of domains and brief tools with ≤ 5 -6 items),^{18,19} global assessments (such as the CFS),⁹ measures adapted from these models, or CGA.²⁰ Studies using ineligible frailty measures, studies for which a full text could not be obtained (e.g., conference abstracts) and those that either did not report or did not provide sufficient information to calculate frailty prevalence were also excluded.

2.2.3 Screening and data extraction

I completed initial title-abstract and full-text screening and a second reviewer (JG, STP) assessed studies independently where eligibility was unclear. Articles not in English were translated using Google Translate with help from colleagues fluent in the relevant language where needed (EF). The final list of included studies was

approved by myself, SS and STP. I extracted and verified data from included studies using a standardised pro-forma including study and participant characteristics, recruitment method, frailty measurement, including characteristics of the tool, method of administration, if measurement was done for research or as part of routine practice, if data related to feasibility/acceptability were reported and also prevalence data stratified by moderate and severe frailty. Data extraction was verified independently by a second researcher (STP). I assessed risk of bias independently and in duplicate with a second researcher (STP) using a modified version of the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence (Appendix Table 2.1).^{21,22} Any discrepancies were resolved through discussion. I also assessed for publication bias by meta-regression of prevalence against study sample size.

2.2.4 Data analysis

I defined frailty categories (none, mild, moderate, severe frailty) using accepted cut-offs for each tool where possible (Appendix Table 2.3) as described in Box 2.1. For prevalence, I dichotomised frailty as moderate/severe versus no/mild, but also stratified data by the degree of frailty where relevant, because care needs may differ. For frailty prevalence, I calculated 95% confidence intervals (CI) for prevalence using Wilson's method for binomial proportions. Owing to high levels of heterogeneity across prevalence estimates, I did not undertake pooled analyses and instead reported the median, first and third quartiles across studies. I did a meta-regression to explore if heterogeneity was explained by differences in mean cohort age and performed pre-specified subgroup analyses i) for each frailty tool, as different tools might capture different aspects of frailty and ii) setting (general medicine versus all

admissions). When multiple estimates were reported for the same cohort (e.g., using different frailty measures), I took the estimate judged to have the best validity (i.e., internal, external, construct and conclusion).

I performed all statistical analyses in R version 3.6.3 (R Project for Statistical Computing)²³ using the package *meta*.²⁴

Box 2.1 Examples of varying degrees of frailty

No or mild frailty: As defined by the Clinical Frailty Scale (CFS), a person with no frailty is independent with varying levels of activity (CFS of 1-3). A person with mild frailty may experience symptoms that limit activity or need help with high-order instrumental activities of daily living such as transportation and could have mild dementia (CFS 4-5). On the Hospital Frailty Risk Score (HFRS), a person is considered low risk if they have a total of 5 points or fewer from relevant ICD-10 coded conditions, for example chronic renal failure (1.40 points) and pneumonia (1.10 points).

Moderate frailty: As defined by the CFS, a person with moderate frailty needs help with outside activities, most instrumental and some basic activities of daily living (CFS of 6). They could also have moderate dementia. On the HFRS, a person is considered moderate risk if they have ICD-10 codes for conditions with a total of 5-10 points, for example chronic kidney disease (1.40 points), pneumonia (1.10 points) and a tendency to fall (3.60 points) or unspecified dementia (2.10 points).

Severe frailty: As defined by the CFS, a person with severe frailty is completely dependent for personal care (CFS of 7). They could also have severe dementia. A person with very severe frailty (CFS 8) is also completely dependent, but likely could not recover from a minor illness. On the HFRS, a person is considered high risk if they have ICD-10 codes for conditions with a total of 15 points or more, for example chronic kidney disease (1.40 points), pneumonia (1.10 points), a tendency to fall (3.60 points), urinary incontinence (3.20 points), and dementia in Alzheimer's disease (7.10 points).

2.3 RESULTS

2.3.1 Description of studies

Search results

I screened 13,898 abstracts and 2,287 full texts, with 45 cohorts (n=39,041,266 admissions, 49 publications)^{8,25-72} ultimately included (Figure 2.1). Most studies (30/45) aimed to investigate outcomes associated with frailty. All except one was published after 2010,⁵⁹ with over half published in 2017 or later (24/45). The mean/SD age was 80/5 years (range=64-87 years; 39 cohorts) and minimum age for inclusion was ≥ 65 years in 35/45 cohorts (Table 2.1 & Table 2.2).

Population and setting

Studies included forty cohorts in 17 high-income countries with universal healthcare (11 based in the UK), three in the USA, one each in India and Indonesia, and were

mostly from urban tertiary care or teaching hospitals. Seventeen cohorts included hospital-wide unplanned admissions (n=39,002,111) and 28 included general medicine admissions only (n=39,155). Prior to admission, 68-97% of participants lived at home (12 cohorts) and four studies limited eligibility to community-dwelling adults. The prevalence of any-cause cognitive impairment ranged from 1-68% (24 cohorts), and Charlson comorbidity index scores ranged from 2-8 (14 cohorts). In general medicine cohorts, the most frequent (rank-sum) admission diagnoses were infection, circulatory or respiratory problems (Appendix Table 3.1-3.3).

Quality and reporting

Risk of bias was low-moderate for 26/45 studies of prevalence (Figure 2.2), with common sources of bias related to sample frame and coverage, for example due to restrictive eligibility criteria (Appendix Table 3.4 & Appendix Table 3.5). Of note, patient or proxy consent was required in 22/45 studies, but where frailty was retrospectively ascertained from administrative codes or routine frailty screening data (i.e., using clinically administered tools; n=3 studies), all eligible participants were included. Only one study indicated use of a reporting guideline.²⁷ There was no evidence of publication bias (Appendix Figure 3.1).

Figure 2.1 PRISMA diagram

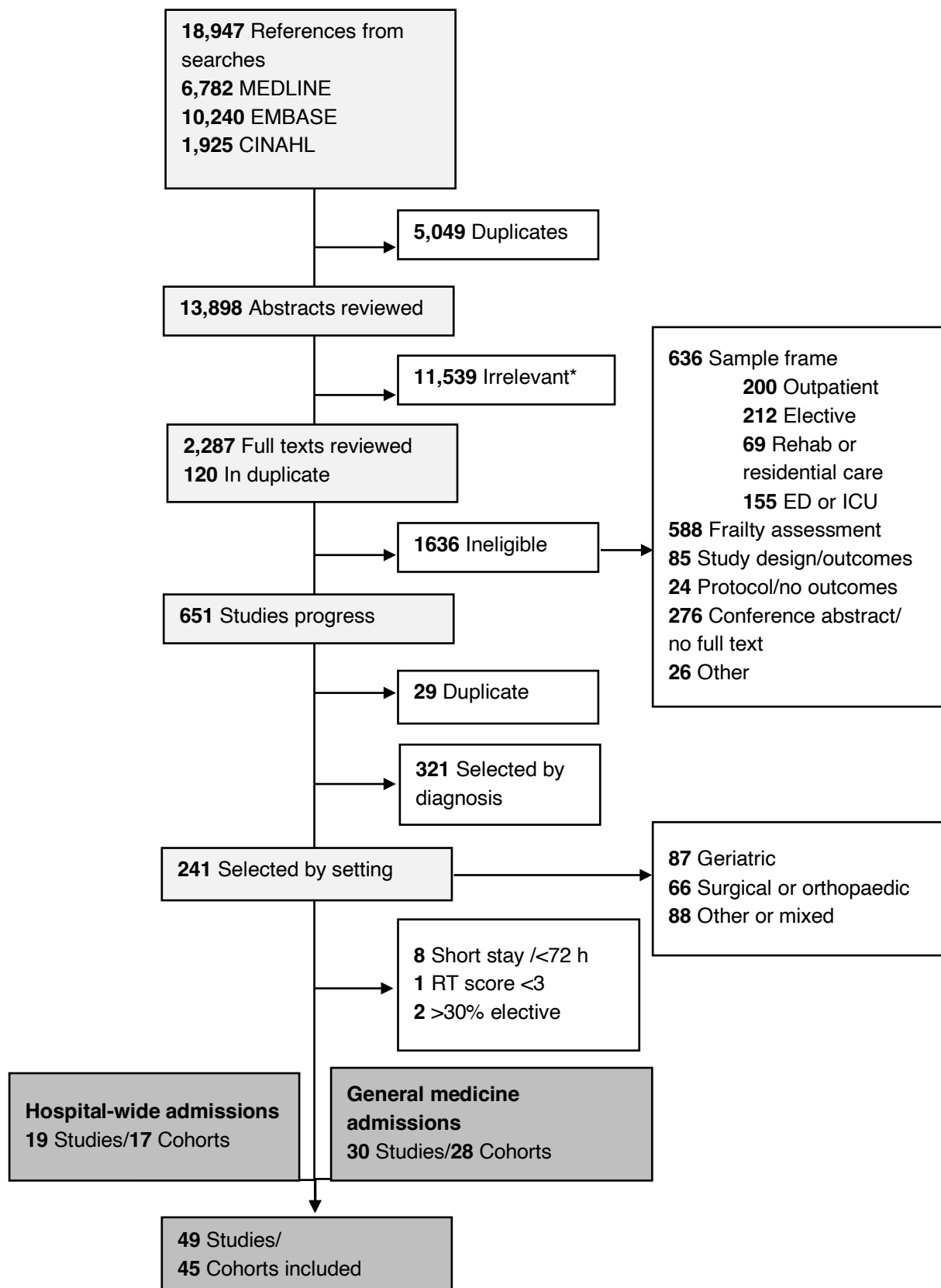


Table 2.1 Included studies of hospital-wide unplanned admissions (n=17 cohorts)

Study	Location	n	Age	% Female	Exclusion criteria (summary)	Frailty Tool	Type of tool
Asmus-Szepesi (2013) ³⁷	Netherlands	460	76	56%	Age <65 years, refused, terminally ill, unable to follow instructions, LOS <48 hours	ISAR-HP	CA
Fujita (2022) ³⁸	Australia	6771	84	52%	Age <75 years, <30 eFI-AH deficits assessed	eFI-AH, HFRS	CR/RC, RC
GMRC (2019) ³⁹	England	1507	80	53%	Age <65 years, CCU, end-of-life, logistics, missing 4AT or delirium status	9-point CFS	CA
Gilbert – local cohort (2018) ⁴⁰	England	569	80	56%	Age <75 years	HFRS	RC
Gilbert – national cohort (2018) ⁴⁰	England	1013590	84	57%	Age <75, non-emergency admission	HFRS	RC
Gilbert (2022) ⁴¹	France	1042234	85	60%	Age <75 years, non-emergency admission, missing socioeconomic data	HFRS	RC*
Hollinghurst (2021) ⁴²	Wales	126600	79	53%	Age <65 years, non-emergency admission, no GP registration	HFRS, eFI	RC*, OC
Lim (2023) ⁴³	Singapore	366	74	56%	Age <65 years, ICU, transferred from other hospital, terminally ill, cognitive impairment/dementia, admitted for stroke or LOS <48 h	Frail-PPS, FAM, ISAR-HP	CA, CA, CA
Lujic (2022) ⁴⁴	Australia	257535	83	57%	Age <75 years	HFRS	RC*

McAlister (2018) ⁴⁵	Canada	452785	83	60%	Age <75 years, psychiatric or non-urgent admission	HFRS	RC*
Romero-Ortuno (2016a, 2016b) ^{46,47,#}	England	5899	84	56%	Age <75 years, elective admission	9-point CFS	CA*
Soong (2015) ⁴⁸	England	50540141*	NR	50%	Age <65 years	Author	RC
Soong (2019) ^{49,50}	Multinational	1366187	NR	54%	Age <75 years, missing data, LOS <2 days	DF-GFS	RC
Street (2021) ⁵¹	England	282091**	NR	NR	Age <75 years, non-emergency admission	HFRS	RC*
Timmons (2015) ⁵²	Ireland	598	80	51%	Age <70 years, refused, moribund on admission	SHARE-FI	CA
Wallis (2015) ^{53,#}	England	5764	85	56%	Age <75 years, non-emergency admission	9-point CFS	CA*
Warnier (2017, 2019) ^{54,55,#}	Netherlands	2581****	79	51%	Age <70 years, not community-dwelling, not admitted to a regular ward, LOS <48 hours, in hospital deaths (for outcomes data)	VMS, MFST-HP	CA, CA

Legend: Age = mean or median age in years. n = number of patients or admissions. # = Routine clinical data study. CA = Clinically administered. CA* = Clinically administered, pre-morbid. CR = Clinical data from chart review. RC = Retrospective coding data from the index admission acquired after discharge. RC* = Retrospective coding data from the index admission and previous admissions. OC = Other coded administrative data. NR = Not reported. *A count of frailty syndromes was only reported for ~34044050 hospital admissions. **n=282091 patients with 674615 hospital admissions. ***n=2691, but outcomes data were only reported for 2581 people who did not die in hospital so this number was used in analyses.

Table 2.2 Included studies of general medicine admissions (n=28 cohorts)

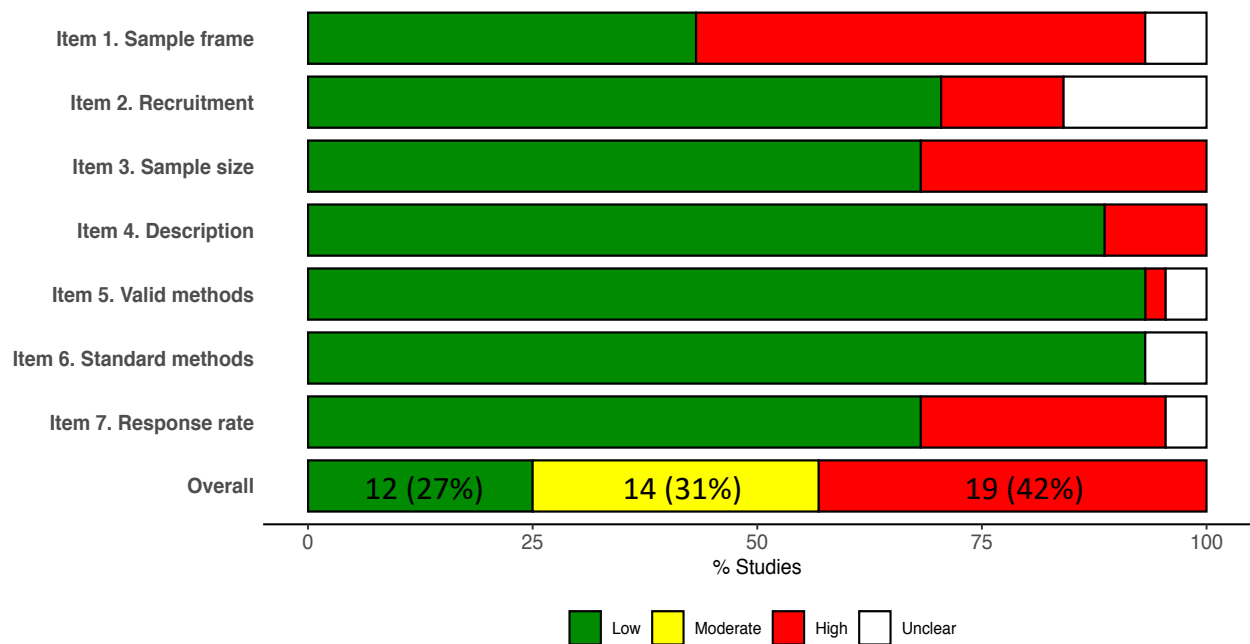
Study	Location	n	Age	% Female	Exclusion criteria (summary)	Frailty Tool	Type of tool
Anani (2020) ⁵⁶	Israel	980	72	43%	Age <55 or >85 years, no consent, advanced illness, bedridden, hospitalized <30 days prior, not admitted via ED	FRAIL	CA
Belga (2016) ⁴⁴⁻⁴⁶	Canada	495	64	51%	Age <18 years, life expectancy <3 months, admitted from long-term care/other hospital, out-of-province, poor English, moderate-severe CI	9-point CFS, Fried, HFRS	CA*, CA, RC*
Bonjour (2021) ⁶⁰	Switzerland	22323	80	52%	Age <65 years	HFRS	RC
Buurman (2012) ⁶¹	Netherlands	639	78	54%	Age <65 years, no consent, too ill to participate, transferred from other ward, LOS or ward transfer <48 hours, poor Dutch	ISAR-HP	CA
Dani (2017) ⁶²	England	710	83	59%	Age <70 years, LOS <48 hours, poor English	FI	U
Eckart (2019) ⁶³	Switzerland	4957	82	51%	Age <75 years, non-urgent admission	HFRS	RC*
Eeles (2012) ⁶⁴	Wales	273	82	NR	Age <75 years, no consent, readmission	FI	U
El-Sharkaway (2005) ⁶⁵	England	200	82	47%	Age <65 years, terminal illness, life expectancy <3 months	CFS	CA
Evans (2014) ⁶⁶	USA	751	84	64%	Age <75 years	FI-CGA	CR
Fitriana (2021) ⁶⁷	Indonesia	266	NR	NR	Age <60 years, died in-hospital, transferred to other hospital	FRAIL	CA
Forti (2014) ⁶⁸	Italy	470	81	53%	Age <65 years, died, terminal illness, coma, LOS or transfer <48 hours, refused, incomplete data	SOF-I	CA

Gregoravic (2016) ⁶⁹	Australia	170	82	49%	Age < 65 years, transferred to specialty unit	9-point CFS	CA
Hernandez-Luis (2018) ⁷⁰	Spain	298	77	53%	Age <61 years, life expectancy <6 months, delirium or impaired consciousness persisting on day two of admission, not admitted via ED	7-point CFS, Fried	CA, CA
Hoogerduijn (2012) ⁷¹	Netherlands	492	78	56%	Age <65 years, too ill to participate	ISAR-HP	CA
Inouye (2003) ⁷²	USA	535	78	56%	Age <70 years, terminal condition, severe dementia, aphasia, coma, intubation, LOS <48 hours, refused	BISEP	CA
Irina (2018) ⁷³	Israel	179	72	46%	Age <18 years, dementia/CI, ALT >40 IU/L, no follow-up, unable to complete FRAIL	FRAIL	CA
Juma (2016) ⁷⁴	Canada	75	81	64%	Age <65 years, palliative or life expectancy <7 days, <1 chronic health conditions and independent ambulation at baseline	9-point CFS	CA
Khandelwel (2012) ⁷⁵	India	250	66	38%	Age <60 years, mechanical ventilation/life support, comatose, neurologic deficits	Fried	CA
Laura (2022) ⁷⁶	Singapore	1507	76	51%	Age <65 years, live in shelter/nursing home, admitted via HDU, ICU or non-medical unit, no consent, died in hospital, transferred, discharged against medical advice	9-point CFS	CA
McCrow (2016) ⁷⁷	Australia	44	81	55%	Age <60 years, unstable CHF, severe CKD, nil by mouth on admission, expected LOS <24 hours, poor English	7-point CFS	CA
Nardi (2019) ⁷⁸	Italy	541	80	51%	Age <40 years, <2 chronic diseases	FCS-1, MPI	CA, U
Noro (2011) ⁷⁹	Nordic countries	763	NR	65%	Age <75 years, CCU	MAPLe-AC	CA
Polidoro (2013) ⁸⁰	Italy	140	79	60%	NR	FI	U

Ramdass (2018) ⁸¹	USA	503	80	54%	Age <65 years, refused, died in-hospital, advanced dementia, transferred from other facility, admitted under observation, not living in community	REFS	CA
Rizza (2021) ⁸²	Italy	80	82	46%	Age <75 years, unable to complete CGA, no consent, end-stage cancer or CKD, connective tissue or inflammatory bowel diseases, sepsis	MPI	U
Rose (2014) ⁸³	Australia	133	87	61%	Age <70 years, unable to complete REFS, refused	REFS	CA
Sharma (2022) ⁸⁴	Australia	263	84	52%	Age <65 years, no consent, terminally ill	REFS	CA
Subramanian (2020) ⁸⁵	Australia	1118	NR	NR	Age <80 years, LOS <24 hours	HFRS	RC

Legend: Age = mean or median age in years. CI = Cognitive impairment. n = number of patients or admissions. Age = mean or median age in years. n = number of patients or admissions. # = Routine clinical data study. CA = Clinically administered. CA* = Clinically administered, pre-morbid. CR = Clinical data from chart review. RC = Retrospective coding data from the index admission acquired after discharge. RC* = Retrospective coding data from the index admission and previous admissions. OC = Other coded administrative data. NR = Not reported.

Figure 2.2 Risk of bias



2.3.2 Frailty measurement

Frailty measures and their administration

Twenty-two frailty tools were identified (Table 2.3), of which eight were developed in primary care or outpatient settings, 13 in-hospital and one was unclear. Among the tools developed for use in-hospital use, eight were intended to be prospectively administered (BISEP, VMS, FCS-1, FI-CGA, ISAR-HP, MFST-HP, MAPLe-AC, REFS),^{53,58,59,73-76} three were designed to be applied to administrative data (HFRS, Soong, DF-GFS)^{8,35,36} and two used a combination approach (eFI-AH, MPI).^{77,78} Deficit-accumulation methods, i.e., the HFRS, were the most common among included studies (18/54 prevalence estimates from the 45 cohorts), followed by the CFS (10/54), and phenotype (9/54), multi-dimensional (7/54), brief (5/54) or other (5/54), however, there were differences in the operationalisation of tools. For example, some cohorts calculated the HFRS using the index admission alone

(n=5),^{8,26,47,79} whereas others (n=6) used the index and any other admissions in the previous two years.^{28,29,31,38,44,50,80} Three studies used the CFS to assess frailty status pre-admission (i.e., prior to the acute illness), but in the other seven, it was unclear how the CFS was operationalised.^{33,34,45,81} Frailty assessment was done within 72 hours of admission in 14/27 cohorts using clinically administered tools, and occurred later or was unclear in the remainder.

Domains and data sources

The most common domains covered by the frailty tools identified (Table 2.4) were mobility, balance or falls (n=16), function (n=14) and cognition (n=13 overall, n=7 delirium), but eleven also assessed psychosocial factors. Data sources included administrative data, questionnaires, physical/functional assessments, chart review and data routinely collected as part of clinical care, for example body mass index and nursing assessments (Table 2.5).^{53,59} Cognition was assessed using self/proxy report in two measures,^{42,74} chart review or diagnostic coding in seven^{8,29,35,36,53,59,66} and objective testing in five,^{7,26,30,76,78} using a variety of methods including the Brief Cognitive Six Item Screener, 10-item Short Portable Mental Status Questionnaire, clock-drawing test and Mini Mental State Examination. Delirium/acute confusion was evaluated using self/proxy report in two measures,^{42,74} chart review or diagnostic coding in four^{8,36,53,82,83} and the Confusion Assessment Method in one.²⁶

Table 2.3 Frailty measures identified in review

Frailty Tool	Description of original tool	Cut points	Items (n)	Includes cognition?	Includes social supports?	Relies on retrospective coding data*?	Originally developed for hospital population?*
Burden of Illness Score for Elderly Persons (BISEP) ⁵⁹	An index scored from 0 to 7, which includes dementia, walking impairment, high-risk diagnoses, low serum albumin and high creatinine.	Risk group I (0-1), II (2), III (3), IV (≥ 4)	5	Yes (Alzheimer's, organic brain syndrome, or chronic cognitive impairment in medical record)	No	No**	Yes
CSHA Clinical Frailty Scale (7- or 9-point CFS) ⁹	7-point scale ranging from 1 (very fit for their age) to 7 (completely dependent, or terminally ill).	Not frail (1-3), apparently vulnerable (4), mildly frail (5), moderate-to-severely frail (6-7)	1	N/A	N/A	No	No
Developed by author (Soong et al. 2015) ³⁵	Frailty syndromes identified from ICD-10 diagnostic codes	Not frail (0), frail (≥ 1 or ≥ 4)	7	Yes (ICD-10 codes for delirium, dementia and senility)	No	Yes	Yes

Dr Foster Global Frailty Score ³⁶	Prediction model developed from administrative data. Includes demographic information, frailty syndromes, comorbidity and previous admissions.	Unclear	11	Yes (ICD-9/10 codes for dementia and delirium)	No	Yes	Yes
Dutch National Safety Management Program (VMS) ^{73,74}	A questionnaire assessing delirium, fall risk, malnutrition (MUST), and functional decline (Katz index).	Frail (≥ 3 aged 70-80 years; ≥ 1 over 80 years)	6	Yes (Self-report of "transient state of confusion")	No	No	Yes
Electronic Frailty Index (eFI) ⁸³	Score derived from 36 equally-weighted deficits coded in primary care read codes in the electronic patients records	Fit (0-0.12); mild frailty ($>0.12-0.24$), moderate frailty ($>0.24-0.36$); severe frailty (>0.36)	36	Yes (read codes for 'Memory and cognitive problems')	Yes (read codes for 'Social vulnerability')	Yes	No
Electronic Frailty Index Acute Hospital (eFI-AH) ⁷⁷	Score consisting of 37 deficits, including dementia, delirium, pressure sore risk, falls risk, speech pathology review, polypharmacy or comorbidities from a variety of sources, including routine screening tools or administrative data.	Robust (eFI-AH < 0.05); prefrail ($0.05 \leq \text{eFI-AH} < 0.25$); frail ($0.25 \leq \text{eFI-AH}$)	37	Yes (Brief Cognitive Screen Six Item Screener)	No	Yes**	No

FADOI-COMPLIMED Score 1 ⁸⁴	Score resulting from the average of Barthel Index (ADLs) and Exton Smith (pressure sores) scores after recalibration such that the scale ranges from 0 (best) to 100 (worst).	NA	2	No	No	No	Yes
Frailty Assessment Measure (FAM) ³⁰	Score is a subset of Frail-PPS and includes age, sex and 12 items assessing physical frailty (i.e., body mass index, mobility limitations, chronic physical conditions and handgrip strength), age and sex.	Robust (<0.38); Pre-Frail (≥0.38-≤0.82); Frail (>0.82)	14	No	No	No	Unclear
Frail-Physical, Psychological, Social (Frail-PPS) ³⁰	Screening tool including physical frailty, age and sex, as well as measures of 'psychologic' and social vulnerability.	Robust (<0.41); Pre-Frail (≥0.41-≤0.83); Frail (>0.83)	31	Yes (10-item Short Portable Mental Status Questionnaire)	Yes (6-item Lubben social network scale)	No	No
FRAIL questionnaire ⁸⁵	5-point questionnaire evaluating self-reported fatigue, resistance (ability to climb stairs), ambulation, weight loss, and ≥5/11 illnesses.	Robust (0 criteria), pre-frail (1-2), frail (3-5)	5	No	No	No	No

Frailty Index; Searle et al., 2008 ⁷	40-item index including deficits that are associated with health status, generally increase in prevalence with age, and do not saturate before old age, for example, presbyopia.	N/A, continuous	At least 30-40	Yes (MMSE score <24, <i>i.e.</i> MCI 21-23, mild dementia 18-20, moderate 10-17 or severe <10)	Yes ("Feel lonely")	Yes	No
FI-CGA ⁵³	55-item index based on data from comprehensive geriatric assessment, including similar deficits to the FI, <i>i.e.</i> those that are associated with health status, generally increase in prevalence with age, and do not saturate before old age.	<0.35, 0.35-0.45, 0.45-0.55, >0.55	55	Yes (As part of CGA)	Yes (As part of CGA)	No	Yes
Fried phenotype ⁶	Phenotype characterised by five physical characteristics measured with standardized criteria: weakness/grip strength, exhaustion, slow walking speed, low activity, weight loss or sarcopenia.	Not frail (0 criteria), intermediate or pre-frail (1-2), or frail (≥ 3)	5	No	No	No	No
Hospital Frailty Risk Score (HFRS) ⁸	Score derived from ICD-10 codes that were at least twice as prevalent in a cohort of individuals with one or more frailty syndromes	Low (<5), intermediate (5-15), or high (>15) risk	109	Yes (ICD-10 codes for dementia and delirium)	No	Yes	Yes

Identification of Seniors at Risk-Hospitalized Patients (ISAR-HP) ⁵⁸	A questionnaire (yes/no) assessing use of walking aids, educational attainment, independence in performing IADLs and traveling.	Scores ≥ 2 indicate high-risk for functional decline	4	No	No	No	Yes

Maastricht Frailty Screening Tool for Hospitalised Patients (MFST-HP) ⁷⁶	A questionnaire (yes/no) assessing physical, psychological and social domains.	Not reported	15	Yes ("Patient is known to have a memory problem," and "disorientation and/or confusion at home or during previous admissions")	Yes ("Patient experiences loneliness")	No	Yes
Method for assigning Priority Levels-Acute Care (MAPLe-AC) ⁷⁵	Algorithm that includes function, cognitive impairment, behavior issues, decline in decision-making, medication management issues, pressure/stasis ulcers, or problems with the environment.	Low, mild, moderate, high or very high-risk.	8	Yes (InterRAI-HC data: "decision making deterioration," "behavioral symptoms," CPS>1-3)	No	No**	Yes

Multidimensional Prognostic Index (MPI) ⁷⁸	An index ranging from 0-1, which includes 8 items (ADLs, IADLs, cognition, comorbidity, nutrition, pressure sore risk, polypharmacy, social support) which were selected from a CGA-like data set.	Low (<0.33), intermediate (0.34-0.66), or high (>0.66) risk	8	Yes (SPMSQ, minor 4-7, major 8-10)	Yes (live alone, with family or in institution)	No**	Yes
Reported Edmonton Frail Scale (REFS) ⁷⁶	Self-reported questionnaire scored from 0-18, including cognition, general health status, function, medication use, social supports, nutrition, mood, continence, and performance.	Not frail (0-5), apparently vulnerable (6-7), mild frailty (8-9), moderate frailty (10-11), or severe frailty (12-18).	18	Yes (errors on clock-drawing test)	Yes ("Can you count on someone who is willing and able to meet your needs?")	No	Yes
Study of Orthopaedic Fractures Index (SOF-I) ⁸⁶	Index consisting of weight loss of more than 5%, inability to rise from a chair 5 times without using arms, and self-reported reduced energy level.	Robust (0 criteria), intermediate (1), frail (2-3)	3	No	No	No	No
Survey of Health, Ageing and Retirement in Europe Frailty Index (SHARE-FI) ⁸⁷	A self-reported screening questionnaire based on the Fried model of frailty. Adjusted for sex.	Not frail, pre-frail, frail (calculator available for scoring)	6	No	No	No	No

*i.e. as opposed to prospectively available clinical data. **ICD codes or administrative data in some form were used in the development or use of the tool (or it was unclear if they were used), but the tool can be used with clinical data. MMSE = Mini-Mental State Examination. SPMSQ = Short Portable Mental Status Questionnaire. CPS = Clinical Performance Scale.

Table 2.4 Domains included in frailty measures

Category	Domain	CFS	Brief		Fried					Deficit/ related					Multi-dimensional				Other				
		CSHA CFS	ISAR-HP*	VMS*	Fried	FAM**	FRAIL	SHARE-FI	SOF-1	HFRS*	eFI	eFI-AH**	FI***	FI-CGA*	REFS*	MFST-HP*	MPI*	MAPLe-AC*	BISEP*	FCS-1*	Frail-PPS**	DF-GFS*	Soong*
Cognitive and sensory	Cognitive									x	x	x	x	x	x	x	x	x	x		x	x	x
	Delirium			x						x		x		x		x						x	x
	Vision/hearing									x	x	x	x	x		x							
	Communication									x		x		x									
Physical function	Function		x	x				x		x	x		x	x	x	x	x	x		x		x	x
	Balance or falls			x			x		x	x	x	x		x		x		x				x	x
	Mobility		x			x	x			x	x	x		x	x	x			x		x	x	x
	Slow walk				x																		
	Low activity				x			x															
	Weakness				x	x	x	x						x							x		
Other physical	Weight				x	x	x		x					x	x	x					x	x	
	Nutrition or appetite			x				x		x				x	x		x						
	Pressure sores									x	x	x	x			x	x	x		x		x	x
	Incontinence									x	x	x	x	x	x								x
	Polypharmacy/medications										x	x	x	x	x	x	x	x					
	Comorbidity					x	x			x	x	x	x	x			x		x		x	x	
Psycho-social or other	Mood									x		x	x	x	x	x						x	x
	Social supports					x				x	x					x	x				x		
	Socio-demographic			x		x		x			x		x								x	x	
	Clinical frailty scale	x																					

Legend: CSHA CFS = CSHA Clinical Frailty Scale; ISAR-HP = Identification of Seniors at Risk-Hospitalized Patients; VMS (Veiligheids Management Systeem) = "Dutch National Safety Management Program; FRAIL = FRAIL questionnaire; SHARE-FI = SHARE-Frailty index; SOF-1 = Study of Orthopaedic Fractures Index; HFRS = Hospital Frailty Risk Score; FI = Searle et al., 2008 Frailty Index; FI-CGA = Frailty index-CGA; REFS = Reported Edmonton Frail Scale; MFST-HP = Maastricht frailty screening measure for hospitalised patients; MPI = Multidimensional Prognostic Index; MAPLe-AC = Method for assigning Priority Levels-Acute Care; BISEP = Burden of Illness Score for Elderly Persons; FCS-1 = FADOI-COMPLIMED Score 1; DF-GFS = Dr Foster Global Frailty Score; Soong et al., 2015 = Developed by author (Soong et al. 2015); *Originally developed for use in hospital settings. **Multiple variations are included in this review.

Table 2.5 Summary of data sources used in frailty measures

Data sources	CFS	Brief		Fried					Deficit					Multi-domain				Other				
	CSHA CFS	ISAR-HP	VMS	Fried	FAM	FRAIL	SHARE-FI	SOF-1	HFRS	eFI	eFI-AH	FI*	FI-CGA**	REFS	MFST-HP	MPI	MAPLe-AC	BISEP	FCS-1	Frail-PPS	DF-GFS	Soong 2015
Administrative codes (ICD-9/10 or other)									x	x	x	x				?		x			x	x
Questionnaire		x	x		x		x							x	x					x		
Physical measurements				x	x			x			x	x								x		
Routine clinical data***			x		x						x	x				x		x		x		
Judgement-based	x										x											
Comprehensive geriatric assessment													x				x					
Standardized scales (e.g. Katz Index)			x ^a								x ^b	x ^c				x ^d			x ^e	x ^f		
Total no. items	1	4	6	5	14	5	5	3	109	36	37	31+	55	18	15	8	8	5	2	31	11	7
Time required to perform (average, in minutes)													25	10		20						

*Multiple variations of the FI were included in this review

**The FI-CGA is considered to be a variation of the FI, but was presented separately here because it relied on a different data source.

*** Routinely acquired data from the patient's chart

a: Includes the MUST (Malnutrition Universal Screening Tool) and Katz Index

- b: May include Brief Cognitive Screen Six Item Screener, Confusion Assessment Method—CAM, Waterlow Scale, Ontario Modified Stratify Falls Risk Screen and speech pathology review.
- c: Includes the MMSE (Mini-Mental State Examination)
- d: Includes the Katz index of independence in activities of daily living, Lawton instrumental activities of daily living scale, SPMSQ (Short Portable Mental Status Questionnaire), Exton-Smith scale, Mini-nutritional assessment and CIRS-CI (Cumulative rating of illness scale--Comorbidity-index)
- e: Includes the Barthel index and Exton-Smith score
- f: Includes the 10-item Short Portable Mental Status Questionnaire and 6-item Lubben social network scale.

Feasibility and related considerations

The total number of items included ranged from 4-6 for brief, 3-9 for phenotype, 8-18 for multidimensional and 31-109 for deficit accumulation tools. The CFS was the only global or judgement-based tool identified. All clinically administered tools required additional assessments by staff or questionnaires, but only three studies reported the time required and none evaluated feasibility or acceptability (i.e., to clinicians, patients or carers) further.^{53,76,88} Of note, hospital-wide frailty screening was done using the CFS (n=2) or MFST-HP (which contains the shorter VMS; n=1) as part of routine patient care in three studies. Between 72-92% coverage of eligible patients was achieved with screening data collected over a 1-year period in all studies.^{33,34,81,89,90}

2.3.3 Prevalence

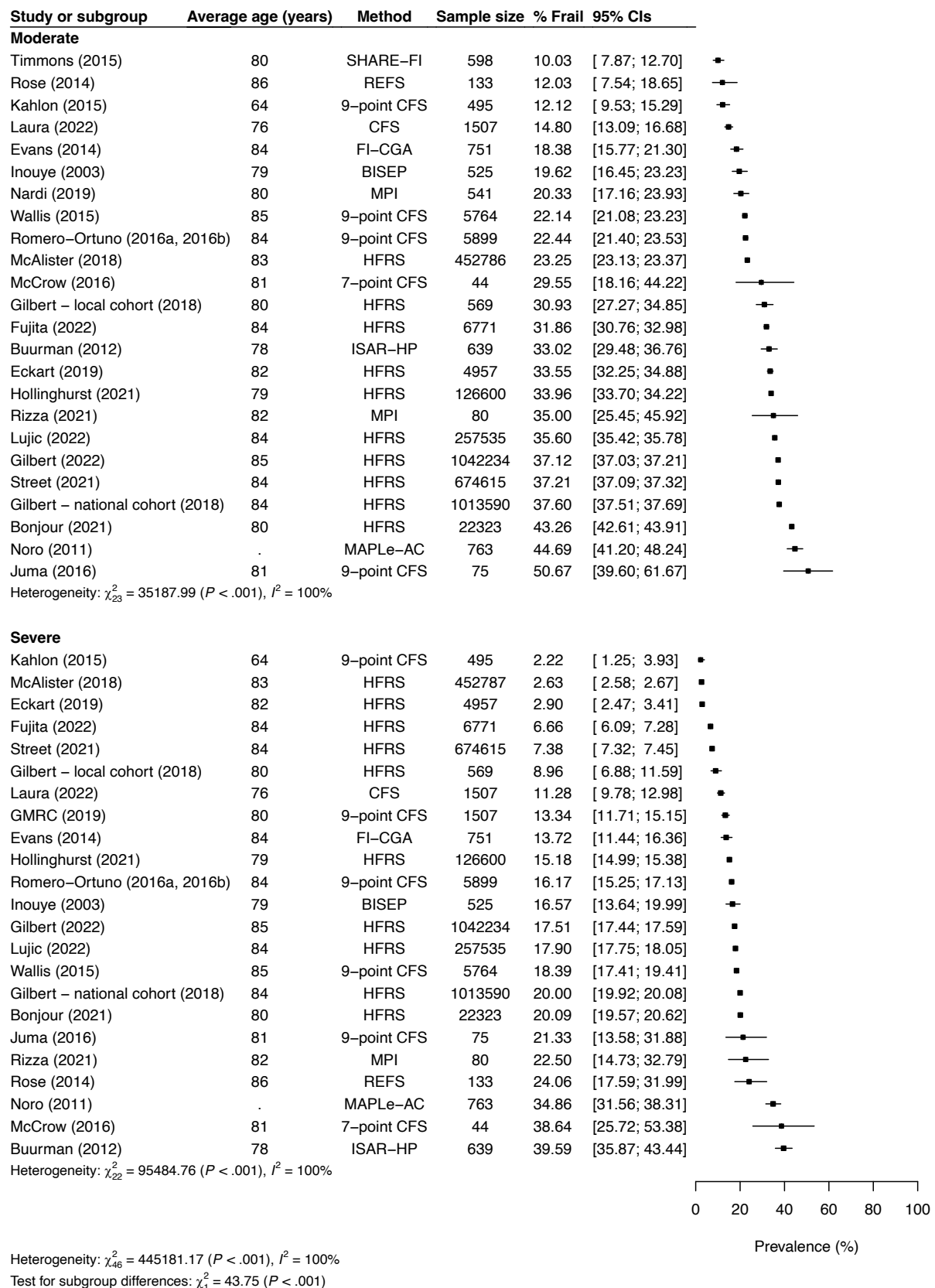
Prevalence of moderate to severe frailty

The median prevalence of moderate/severe frailty was 40.9% (IQR 36.-2-54.2; range 14.3-79.6, N=40 cohorts; n=4,994,931 admissions), with rates <25% in only 3/45 cohorts (n=4 cohorts not reporting moderate/severe frailty were not analysed).

Moderate frailty was about twice as common (31.4% [20.2-36.0%], range 10.0-50.7%, n=24 cohorts) as severe frailty overall (16.6% [10.1-20.7%]; range 2.2-39.6%;

Figure 2.3), although this varied within individual studies (median=1.9 [IQR=1.3-3.2]; range=0.5-11.5%, n=23 cohorts). Prevalence data were not pooled due to heterogeneity, which remained after stratification by study setting, frailty tool, and risk of bias ($p_{\text{het}} < 0.001$) and was not explained by average cohort age in meta-regression (y-intercept=-1.5402, beta=0.0174; $R^2=2.02\%$; $p=0.36$).

Figure 2.3 Prevalence of moderate and severe frailty



Subgroup analyses

Hospital-wide versus general medicine admissions

The prevalence of moderate/severe frailty was similar between hospital-wide (median 40.5% [IQR 38.6-52.8%]; range 16.1-72.6%; N=15 cohorts; n=4,956,548 admissions) and general medicine cohorts (median 41.2% [IQR 36.1-56.0%]; range 14.3-79.6%; N=25 cohorts; n=38,383 admissions) (Figure 2.4).

Type of tool & whether clinically administered or applied to retrospective data

Median prevalence was similar for most tools except for brief measures which had a median prevalence of 66.9% (IQR=53.2-69.9%; range 52.2-72.6, N=5 cohorts; n=4,593) (Figure 2.5). The median prevalence of frailty was 36.9% for the Fried phenotype (IQR=31.9-51.1%, range=22.0-54.0%, N=8, n=3,486), 38.6% for the CFS (IQR=31.6-40.7%, range=26.1-56.0%, N=8, n=14,252), 43.6% for multi-domain tools (IQR=28.3-55.9%, range=16.1-66.5%, N=6, n=4,593), 44.2% for deficit accumulation measures (IQR=38.0-53.9%, range=25.6-77.9%, N=16, n=3,605,463) and 39.4% for other types of tools (IQR=37.8-53.0%, range=36.2-66.5%, N=3, n=1,367,253). Overall, median prevalence was also similar for tools that were designed to be clinically administered (median 38.6% [IQR 30.1-53.1%]; range 14.3-79.6%; N=27 cohorts) versus applied to retrospective coding data (median 44.6% [IQR 39.4-53.5%]; range 25.9-63.3%; N=13 cohorts).

Figure 2.4 Prevalence of moderate to severe frailty by setting

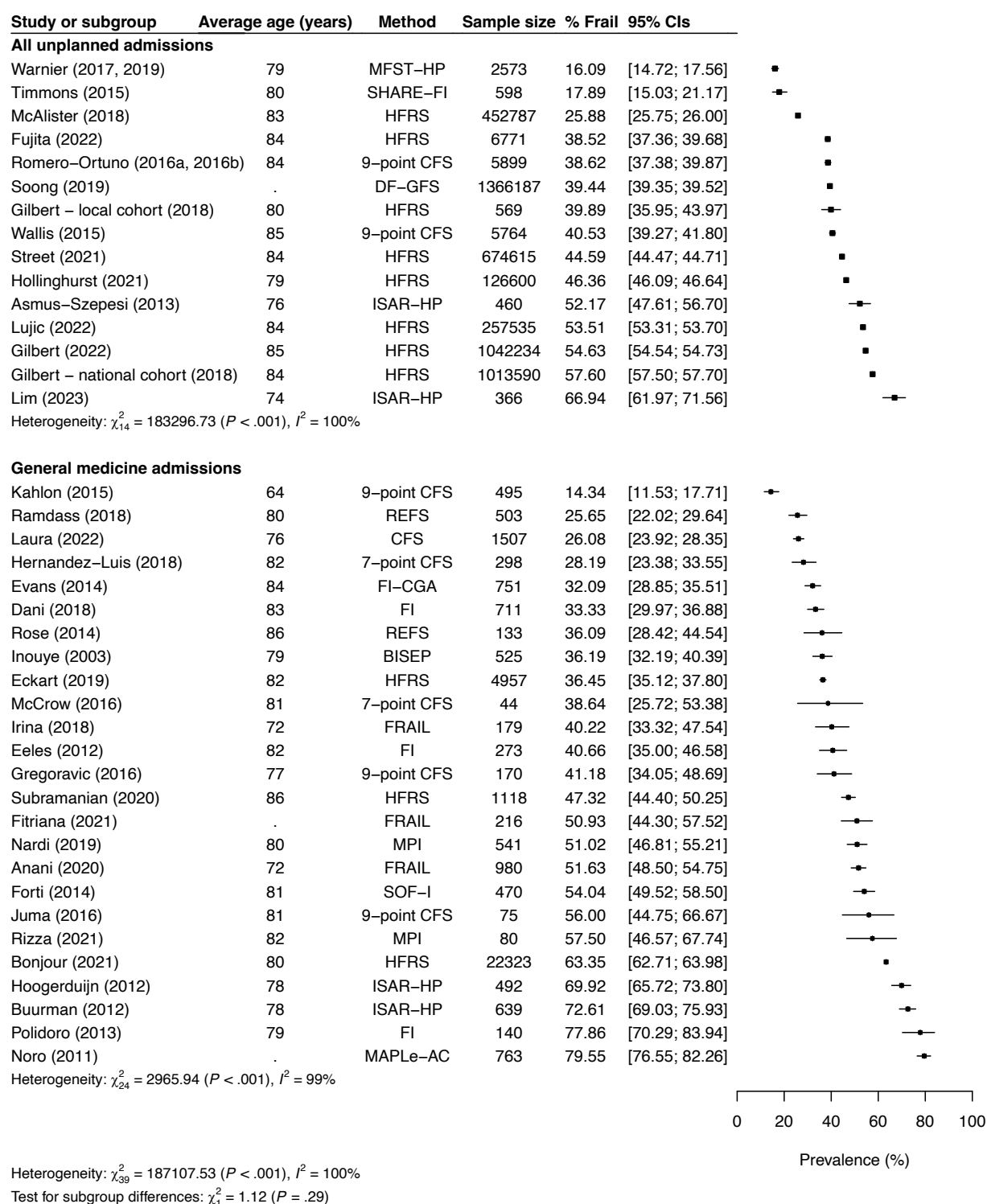
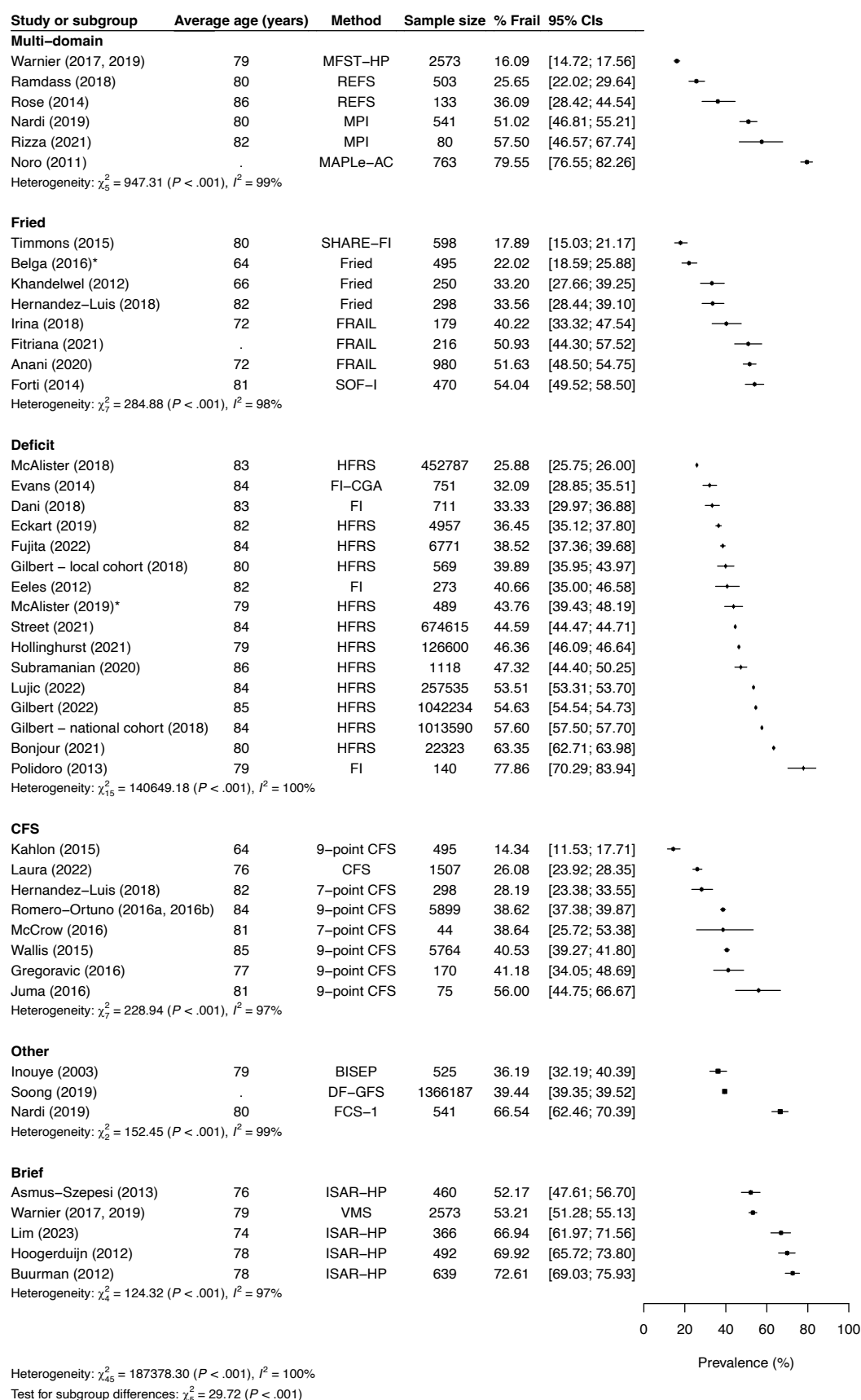


Figure 2.5 Prevalence of moderate to severe frailty by type of tool



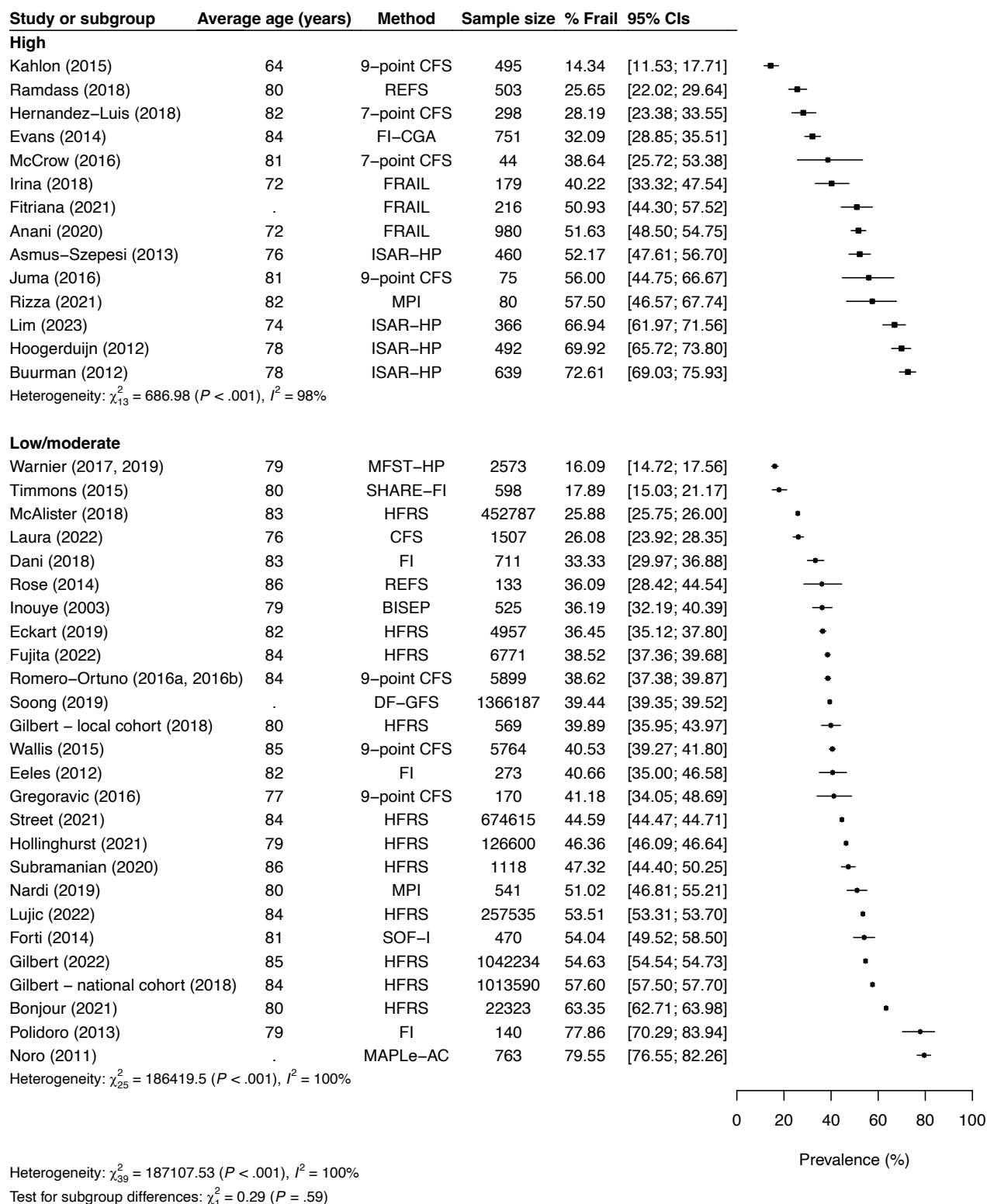
Risk of bias

Median prevalence of low to moderate risk of bias was 40.6% (IQR=36.3-43.7; range 14.3-79.6) in 26 cohorts versus 51.2% (IQR=33.7-57.1%; range 14.3-72.7%) in 19 cohorts with high risk of bias (Figure 2.6).

Stratification of prevalence within studies based on age, sex or cognitive status or care home residence was not possible because few studies reported data.

Additionally, for clinically administered tools, subgroup analysis for prevalence in prospective versus routine clinical data was not done because of the small number of routine clinical data studies identified (n=3) and differences in frailty tools (i.e., CFS versus MFST-HP for which moderate/severe frailty prevalence was only 16%).

Figure 2.6 Prevalence of moderate/severe frailty by risk of bias



2.4 DISCUSSION

Moderate to severe frailty was common in the acute hospital setting with a median prevalence of around 40% and although estimates varied, they were mostly unaffected by type of frailty tool. Despite including a broad range of domains and data sources, all 22 frailty tools identified assessed physical function/performance and most included multiple markers of frailty, regardless of whether they were developed for real-time, clinical use, prospective research studies or application to retrospective administrative data.

Frailty measurement tools

Regardless of whether tools were intended to be clinically administered or applied to retrospective coding data, all included some aspect of physical function/performance and most included additional medical and geriatric comorbidities, providing evidence of commonalities between different methods for operationalising the frailty construct. In contrast to the physical domains, only about 13 measures included cognition. Delirium, which affects 20-30% of older inpatients and is a marker of frailty, was included in fewer than half of tools developed for hospital use (and usually assessed using insensitive or non-validated methods, i.e., ICD codes or self/proxy report) and none for community (e.g., CFS, Fried and FI), where delirium is less common.⁹¹ Although many people with cognitive impairment likely have several manifestations of frailty that would be identified on screening, information on cognition may be beneficial for identifying specific needs and individualising care. Additionally, cognitive impairment may impact outcomes over and above physical frailty (investigated in **Chapter 8**)^{49, 92}

Heterogeneity in frailty prevalence

Variation in frailty prevalence could not be attributed to average age, setting (general medicine versus hospital-wide unplanned admissions) or frailty measure. Differences in eligibility criteria, such as the need to be able to complete questionnaires or give consent will have impacted case-mix and probably frailty prevalence where frailty was clinically measured potentially introducing heterogeneity across studies.⁹³ The proportion of participants who were care home residents or had cognitive impairment varied widely, although definitions varied. Furthermore, regional differences in demographics, health and social services may have had an impact. For example, the number of hospital beds, and access to ambulatory emergency care may reduce inpatient admissions preferentially amongst younger, fitter people.^{80,81}

Differences in the administration/operationalisation of frailty measures might also contribute to heterogeneity in measured prevalence. For example, retrospective, administrative data-based tools depend on the accuracy of diagnostic coding, which is variable and known to be poor for frailty syndromes, particularly cognitive frailty.⁹⁴ The time frame of data included in retrospective studies also varied and likely impacted results: the prevalence of moderate/severe frailty in one UK hospital-wide cohort was 45% (7%) based on coding data from the index admission, but 63% (27%) when all admissions in the previous two years were included because not all conditions are documented during every hospitalisation.³⁸ Administration of the CFS also differed between studies, although it was not possible to determine if assessment of frailty prior to versus during admission or if differences between frailty

measured by trained research staff versus assessments done as part of routine care accounted for heterogeneity.

Comparison to previous studies

Compared with previous studies, frailty prevalence was two-to-four fold higher in the acute hospital setting than in population-based studies, which is consistent with frailty being a risk factor for hospitalization,^{95,96} and 50% higher than in the acute surgical setting (two-to-three fold higher for severe).⁹⁷ However, the median prevalence of frailty (~40%) in my study was lower than the 51% (IQR 35-55%) reported for general medicine studies using both validated and non-validated frailty tools.¹³ I found that prevalence was also mostly unaffected by type of tool, including for deficit accumulation measures (mostly HFRS), but higher frailty prevalence was previously reported for deficit-accumulation measures (mostly FI) in a review of population-based studies, possibly because deficits were documented better in the outpatient setting. In the previous systematic review of frailty in geriatric medicine and/or unspecified acute hospital settings, which included only prospective studies reporting functional decline or mortality, prevalence ranged from 25-97%.¹⁴

2.4.1 Strengths and limitations

Strengths of this review include a comprehensive literature search with detailed synthesis of evidence from many unselected cohorts enhancing generalisability and filling an important evidence gap. This review has several limitations. First, case-mix factors in prevalence estimates could not be accounted for using meta-regression or subgroup analysis because of limitations in reporting. Data on cognition were limited,

so its contribution to/overlap with frailty prevalence could not be evaluated despite the implications for decision-making and patient care.^{49,51} Similarly, prevalence estimates could not be stratified by factors such as age, sex, dementia status or care home residence which may impact estimates. Second, few studies of data from routine global and physical frailty screening were identified, limiting comparison to prevalence estimates obtained as part of prospective research. Third, the impact of type of frailty tool on prevalence could only be evaluated across studies, so differences between samples could confound observations. Fourth, categorisations of moderate and severe frailty were based on accepted cut-offs and author's judgement but were approximations.

2.4.2 Implications for clinicians and decision-makers

My findings provide evidence on frailty prevalence in the acute hospital setting to inform policy and plan services, including frailty screening and CGA. Although there is no consensus on which frailty tool is ideal for use in the acute setting, this review provides preliminary support to current guidance recommending the CFS as a first line screening tool for use in the inpatient setting because it is pragmatic and appears to identify a similar proportion of patients as being frail as more lengthy or complex tools.⁵ Two out of three hospital-wide studies using routine screening data ascertained frailty with the CFS. In both cases, screening was done over a 1-year period suggesting that it was sustainable.^{33,34,81} In 2023 NHS England introduced pay-for-performance (CQUIN) scheme for screening patients 65 years and over attending EDs or same-day emergency care (SDEC) with the CFS.⁹⁸ No CQUIN scheme for inpatient frailty screening with the CFS currently exists, but this review

supports its feasibility as an alternative or adjunct to ED screening where workload, acute illness and rapid discharges home/to inpatient wards pose as barriers to screening.⁹⁹

Other clinically administered tools appeared impractical for routine, first-line use in the acute setting and despite their length, most did not include valid measures of cognition or social risk factors, which are both important drivers of admission.^{81,82,95-98} However, I noted variations in the operationalisation of the CFS, emphasizing the importance of training.¹² Also, because the CFS is a global frailty score, further assessments of frail patients (e.g., CGA) are needed to identify frailty domains to fully individualise care.

I identified several retrospective tools based on administrative data (primarily the HFRS), which could be useful for policy or research purposes. Importantly, retrospective coding frailty tools may incorporate frailty syndromes occurring as complications of admission (e.g., falls, pressure sores) in contrast to prospective clinical tools. In case-mix adjustment for mortality and other acute hospital outcomes, retrospectively acquired frailty measures could therefore conceal preventable safety and quality issues.

2.4.3 Conclusion

In conclusion, frailty is prevalent in older people with acute, non-elective hospital admissions, regardless of method of measurement, supporting the implementation of hospital-wide frailty screening. Most frailty tools identified did not appear practical for

routine clinical use in the acute hospital setting, but the Clinical Frailty Scale appears to be a pragmatic option in line with current guidance and was used for routine hospital-wide frailty screening in two studies.^{5,100} However, cognitive domains of frailty were poorly assessed by existing tools and should be evaluated separately. Future studies could evaluate the use of routinely collected data in hospital electronic patient records (EPRs) to identify specific frailty domains and individualise care, for example based on the presence of cognitive versus physical domains of frailty.

Chapter 3 will review the predictive value of existing clinically administered and retrospective frailty tools and subsequent chapters will focus on the prevalence and outcomes of cognitive domains of frailty using hospital EPR data.

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Chapter 3

Frailty outcomes in adults with unplanned hospital admission: a systematic review and meta-analysis

ABSTRACT

Background: Frailty is prevalent in older people with unplanned hospital admissions as shown in Chapter 2, but previous evidence synthesis on frailty outcomes in the acute hospital setting was limited outside of specialty-specific and elective settings. Therefore, I undertook a systematic review and meta-analysis to determine the association between global and physical frailty and outcomes in adults with unplanned admissions hospital-wide and to general medicine services.

Methods: See Chapter 2. I searched MEDLINE, EMBASE and CINAHL up to 31/01/2023 and included observational studies using validated frailty measures in adult hospital-wide or general medicine admissions. I extracted summary data on outcomes, measurement tools, study setting (hospital-wide vs general medicine), and design (prospective vs retrospective clinical, administrative or other) and risk of

bias (modified Joanna Briggs Institute checklist). I pooled unadjusted relative risks (RR; moderate/severe frailty vs no/mild) for mortality, length of stay (LoS), discharge destination and readmission where appropriate using random-effects models.

Results: Overall, 36 cohorts (median/SD age = 80/5 years; n = 4,993,464 admissions; n=18 frailty measures) were included. Moderate/severe vs no/mild frailty was associated with increased mortality (n = 19 cohorts; RR range = 1.08 to 3.70), more consistently among cohorts using clinically administered tools (n = 11; RR range = 1.63 to 3.70; $p_{het} = 0.08$; pooled RR = 2.53, 95% CI = 2.15 to 2.97) vs cohorts using (retrospective) administrative coding data (n = 8; RR range = 1.08 to 3.02; $p_{het} < 0.001$). Clinically administered tools also predicted increasing mortality across the full range of frailty severity in each of the six cohorts that allowed ordinal analysis (all $p < 0.05$). Moderate/severe vs no/mild frailty was also associated with LoS >8 days (RR range = 2.14 to 3.04; n = 6) and discharge to a destination other than home (RR range = 1.97 to 2.82; n = 4) but was inconsistently associated with 30-day readmission (RR range = 0.83 to 1.94; n = 12). Associations remained significant after adjustment for age, sex and comorbidity where reported.

Conclusions: Frailty was predictive of mortality, LoS and discharge home over with more severe frailty associated with greater risk. Associations were most consistent for cohorts using clinically administered tools supporting current guidance on routine screening using pragmatic clinical tools such as the Clinical Frailty Scale. In the next

section of my thesis, I will investigate the value of routine cognitive screening data in hospital EPRs for measuring cognitive frailty and overlap with physical frailty.

3.1 INTRODUCTION

Frailty is prevalent in older people with acute, non-elective hospital admissions as illustrated in Chapter 2. As discussed previously, guidelines recommend frailty screening for all older inpatients to inform care decisions,¹⁻³ but uptake has been poor with uncertainty about the clinical utility of identifying frailty in acutely unwell patients likely a contributing factor.⁴ Most admissions of older people to hospital are unplanned, predominantly to non-specialist general medicine services, where multi-morbidity and complex care needs are common and additionally, patients may be moderately to severely ill. However, current guidance is mainly based on studies conducted in outpatient and specialty-specific or elective settings where the prognostic value of frailty may differ compared to the hospital at-large. Also, current recommendations do not distinguish between more versus less severe frailty even though care needs are likely to differ significantly.¹⁻³

Large, hospital-wide studies of frailty could be done using retrospective clinical or administrative datasets, however, previous evidence synthesis on frailty outcomes in the acute hospital setting was limited to prospective studies.⁵ A systematic review (published 2019) studied the outcomes of functional decline and mortality after discharge in older hospitalised people in prospective cohorts, but did not include

length of stay (LoS), in-hospital mortality, discharge home or readmission as primary outcomes. The review was also undertaken prior to the development of measures using administrative data such as the Hospital Frailty Risk Score (HFRS) and included a large number of cohorts from geriatric medicine services and unspecified acute settings, for which the prognostic value of frailty might differ.^{6,7} Other reviews have focused on specific settings and populations (e.g., surgery, including elective procedures⁸⁻¹¹, acute coronary syndrome¹²).

Therefore, I undertook a systematic review and meta-analysis to synthesise evidence on the predictive value of frailty for adverse outcomes in unselected adults with unplanned admissions to hospital and general medicine wards in prospective and retrospective studies using clinically administered and administrative coding data tools. Specifically, I aimed to look at associations between frailty, mortality, length of stay in hospital, discharge destination and readmission by degree of frailty and after accounting for potential confounding variables (i.e., age, sex, comorbidity and illness severity).

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Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts.

EClinicalMedicine, 59:101947.

Contributions: See Chapter 2. I developed the protocol and contributed significantly to the methods, including the search strategy and modified risk of bias assessment tool based on Joanna Briggs Institute Critical Appraisal Checklists. I completed all data acquisition (i.e., searches, screening, data extraction and risk of bias assessment), designed and performed the analysis, interpreted data, created tables and figures and drafted the resultant manuscript.

3.2 METHODS

Analyses presented in this chapter are based on a subset of studies included in Chapter 2. Detailed information on searches and eligibility can be found there (see 2.2 Methods, pg. 62), but a summary with additional details specific to data/analyses shown in this chapter is provided below:

3.2.1 Summary of searches and eligibility

See Chapter 2. In brief, I searched MEDLINE, EMBASE and CINAHL from inception to January 31, 2023, without restrictions using search terms related to frailty, geriatric assessment, hospitalization, outcomes and observational study design and reviewed reference lists of included studies. I included observational cohort studies of adults ≥ 18 years with mostly unplanned admissions to hospital or general medicine services that assessed frailty using validated tools. I further restricted analyses in this chapter to studies reporting data on mortality, length of stay, discharge destination and readmissions. I excluded studies conducted in outpatient, emergency department, short-stay, geriatric, rehabilitation and mixed settings.

3.2.2 Screening and data extraction

I completed title-abstract and full-text screening with studies reviewed independently (SP, JG) where eligibility was unclear. The final list of included studies was approved by myself, JG, SS and STP. I extracted and verified data using a standardised pro-forma including study and participant characteristics, recruitment method, frailty measurement tool and adjusted and unadjusted data stratified by moderate and severe frailty where reported. Risk of bias was assessed independently and in duplicate (myself, STP) for cohort outcomes using a modified Joanna Briggs Institute Critical Appraisal Checklists for Cohort Studies (Appendix Table 2.2).^{13,14} Item 5, “were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)” was only evaluated for the outcome “discharge to a location other than home.” We resolved discrepancies through discussion.

3.2.3 Data analysis

I defined frailty categories (none, mild, moderate, severe frailty) using accepted cut-offs for each tool where possible as described in the previous chapter. For the main outcomes analyses, I used data on moderate/severe versus no/mild frailty as this was most frequently reported. I determined the association of moderate/severe frailty vs no/mild frailty with mortality up to one-year, hospital length of stay, discharge to a new institutionalisation and readmission within 30-days. For dichotomous outcomes, I calculated relative risks (RR) from data reported by the authors. For continuous data (e.g., LoS), I calculated the ratio of means (ROM) for moderate/severe versus no/mild frailty. I determined 95% CIs for dichotomous and continuous outcomes from the normal approximation of the mean.

When multiple estimates were reported for the same cohort (e.g., using different frailty measures), I took the estimate judged to have the best validity (i.e., internal, external, construct and conclusion). I also extracted adjusted estimates but did not include them in the main outcomes analyses, because of differences in the reference groups used between studies, and also because I did not have access to individual patient data to calculate adjusted estimates. I performed subgroup analyses based on whether frailty measures were designed for real-time administration by healthcare staff (“clinically administered tools”) or retrospective application usually to administrative data (“retrospective coding tools”).

Potential bias due to the competing risk of in-hospital death

For discharge to a new institution and readmission, I endeavoured to restrict analyses to people alive at discharge because the competing risk of in-hospital death would otherwise result in underestimation of risk. Where not reported by the authors, I subtracted in-hospital deaths from the denominator. In cases where these data were not reported, I estimated in-hospital deaths based on data provided by the study authors (e.g., 30-day mortality including in-hospital deaths) or excluded the study from analysis. I performed sensitivity analyses using denominators as reported by the authors (e.g., including deaths during admission; see Appendix 3, pg. 364).

Random effects models and assessment of heterogeneity

I pooled data using a random-effects (DerSimonian and Laird) model with inverse-variance weights. I did not pool data where important unexplained heterogeneity was present, which I evaluated based on differences between populations, measurement

tools, setting, and study design; and by assessing differences in the direction of effects, and testing for statistical significance with the Chi² test.¹⁵ Where it was not possible to perform meta-analysis, I narratively synthesised results and tested for evidence of an overall effect using the exact binomial (sign) test.¹⁶

Assessing for trends in effect size with frailty severity

To assess for a trend in effect size (dose response effect) with increasingly severe frailty, I plotted outcomes stratified by degree of frailty in individual studies on forest plots and performed the Cochran-Armitage test for trend for each cohort. I also assessed the discriminative performance of categorical versus dichotomous frailty scores by calculating the apparent c-statistic to evaluate the prognostic value of differentiating between varying degrees of frailty.

Meta-regression for measured prevalence and risk of death

Given differences in the likely sensitivity of different frailty measures and their operationalisation between studies (e.g., accuracy of administrative coding), variation in prevalence beyond that attributable to differences in case-mix and population was expected. Therefore, I explored the relationship between measured prevalence and the predictive value of frailty for mortality (log RR of death) in a meta-regression. The analysis was repeated with the addition of mean cohort age as a covariate in the model.

Certainty of the evidence (GRADE)

The certainty of evidence on outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach

adapted for prognostic questions by EB with input from SS and STP.¹⁷ Studies were downgraded from high-certainty evidence due to bias, imprecision, indirectness, unexplained inconsistency in the direction and magnitude of effects.^{18,19}

Software

I performed statistical analyses in R version 3.6.3 (R Project for Statistical Computing)²⁰ using the packages *meta*, *DescTools* and *pROC*.²¹⁻²³

3.3 RESULTS

3.3.1 Description of included studies

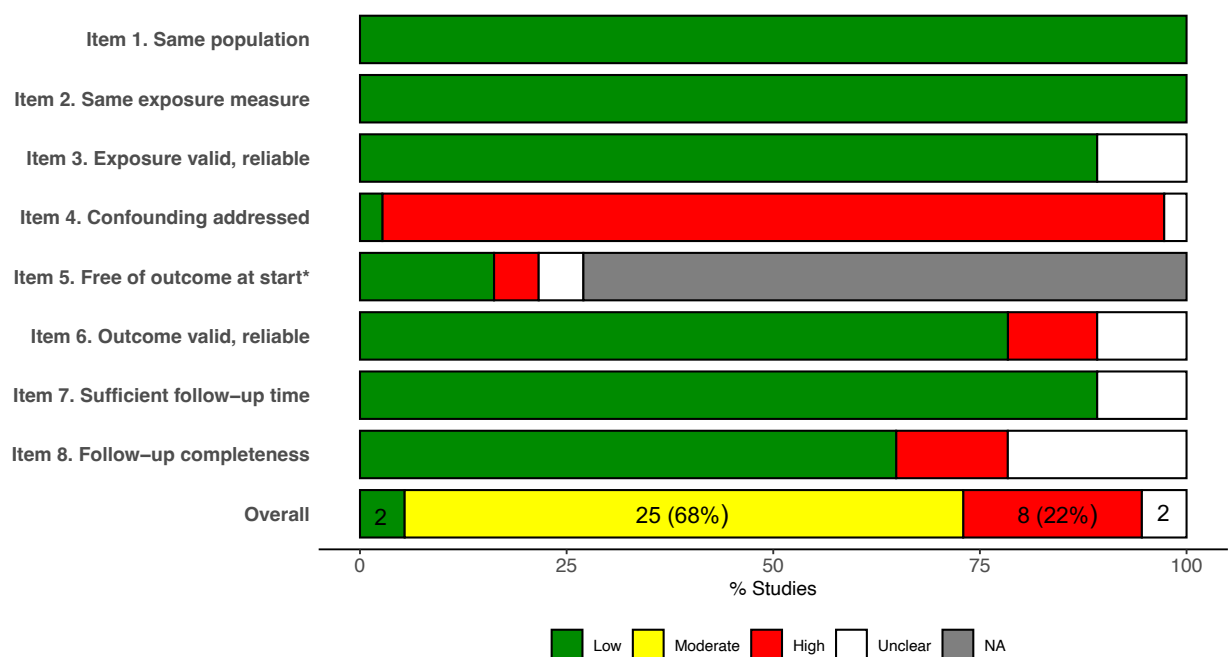
Of the 45 cohorts^{7,24-71} eligible for inclusion in the review overall (see Chapter 2), 37 (n=4,993,464 admissions) reported one or more outcomes and were included in analyses.^{7,24,26,28,31-35,37-42,44,46-61,65-67,72-78} The mean/SD age of this subset of studies was 80/5 years (range=64-86 years; 33 cohorts) and minimum age for inclusion was ≥ 65 years in 29/37 cohorts. Eighteen tools were used to measure frailty in these studies, of which, 11 were designed for real-time administration by healthcare staff (“clinically administered tools”), three were intended for retrospective application to administrative data and four were unclear. The most common tools used were the HFRS (12/37 studies) and CFS (7/37 studies).

3.3.2 Quality and risk of bias

Risk of bias for outcomes was low-moderate for 27/37 studies (Figure 3.1), with common sources of bias related to sample frame and coverage, for example due to

restrictive eligibility criteria (Appendix Table 3.4 & 3.5). There was no evidence of publication bias in funnel plots or according to Egger's test ($p=0.652$ for clinically administered tools and $p=0.867$ for retrospective coding tools; Appendix Figure 3.2). The certainty of the evidence for each outcome was evaluated according to GRADE and is shown in the summary of findings table (see at the end of the Results).

Figure 3.1 Summary of risk of bias across studies



Legend: Risk of bias was assessed with a modified version of the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies. Percentages may not add up to 100% due to rounding.

3.3.3 Mortality

Consistent associations with mortality, LOS and discharge to a location other than home were found across all levels of frailty. Moderate/severe frailty was associated with an increased risk of death up to one year after hospital admission in 20/21 cohorts for which data were available ($n=3,486,819$; p for test of binomial proportions <0.001) but study estimates were not pooled due to heterogeneity in the absolute size of the effect ($p_{het}<0.001$) (Figure 3.2). When restricted to studies using clinically administered measures heterogeneity was not significant ($p_{het}=0.08$) and the pooled RR was 2.53 (95% CI 2.15-2.97; $n=17,337$; $N=11$) (Figure 3.3), whereas data for retrospective coding measures were not pooled due to heterogeneity ($n=3,469,157$; $N=8$ cohorts, RR range=1.08-3.02, $p_{het}<0.001$). When studies reporting no events per group were included, heterogeneity remained insignificant ($p_{het}=0.05$; Appendix Figure 3.3).

Increasing severity of frailty was associated with a stepwise increase in the risk of death up to one year after hospital admission for all six studies using clinically administered (CFS, brief and multidimensional) tools and four of six using retrospective coding tools (p for test of binomial proportions=0.039) suggesting a dose response effect (Figure 3.4). Outcomes for moderate or severe frailty versus no/mild frailty were analysed using data from all studies (Figure 3.5). For moderate frailty, heterogeneity was not significant ($p_{het}=0.08$) when data were restricted to studies using clinically administered measures and the pooled RR was 1.99 (95% CI 1.67-2.37; $n=8,797$; $N=7$). For severe frailty, data were not pooled due to heterogeneity ($n=8,248$; $N=7$ cohorts, RR range=1.79-7.40, $p_{het}<0.001$).

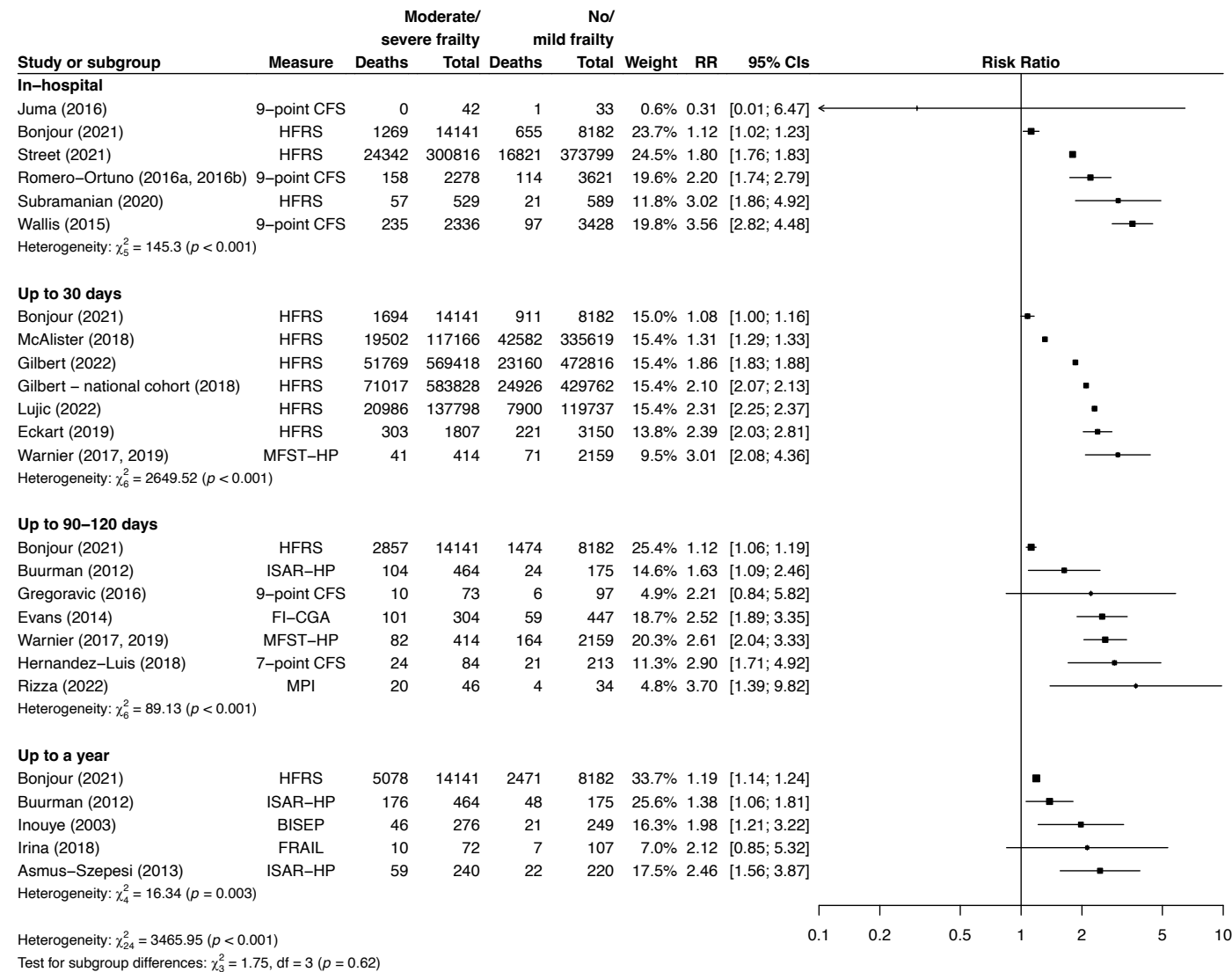
Discrimination (c-statistic) also improved for both types of tools when ordinal instead of dichotomised frailty data were used (Appendix Table 3.8).

Meta-regression of frailty prevalence versus the log RR of death showed that frailty prevalence accounted for over half of the variation in mortality risk (y-intercept=1.0022; $\beta=-0.0069$; $R^2=60.38\%$; $p=0.04$) (Figure 3.6). The addition of average cohort age to the model did not account for any additional heterogeneity (y-intercept=-1.099, $\beta_{\text{frailty}}=-0.0070$; $\beta_{\text{age}}=0.0255$; $R^2=53.42\%$; $p_{\text{frailty}}=0.05$; $p_{\text{age}}=0.16$).

3.3.4 Length of stay

All nine studies examining the risk of a longer LoS by frailty status showed an increase in LOS for moderate/severe frailty ($n=3,454,869$ admissions). Relative risk for a LOS of >8-10 days ranged from 2.43 to 3.04 for six cohorts ($n=3,445,716$) inclusive of inpatient deaths (Figure 3.7A-i), with increasing severity of frailty associated with greater risks in all studies (Figure 3.8A). The ratio of means for LoS in days ranged from 1.19 to 3.07 for moderate/severe frailty ($n=1,051,387$ admissions; $N=5$ cohorts; Figure 3.7A-ii). Sensitivity analyses where inpatient deaths were censored showed similar results (Appendix Figure 3.4).

Figure 3.2 Relative risks of mortality for no/mild frailty versus moderate-to-severe frailty by time-point



Legend: To avoid artificially reducing the standard error, when multiple estimates were reported for the same cohort (i.e. using different frailty measures), the estimate judged to have the best validity was included in the pooled estimate. Estimates not included in the pooled estimate included Warnier et al. (2017, 2019), which reported a RR for 30-day mortality of 8.97 (95% CI 4.71 to 17.10) and 90-120 day mortality of 4.53 (3.26 to 6.30) with the VMS, Hernandez-Luis et al., (2018) which reported a RR for 90-120 mortality of 3.26 (1.88 to 5.67) with the Fried phenotype.

Figure 3.3 Unadjusted relative risks of mortality for moderate/severe versus no/mild frailty by type of measure (excluding studies with no events in either group)

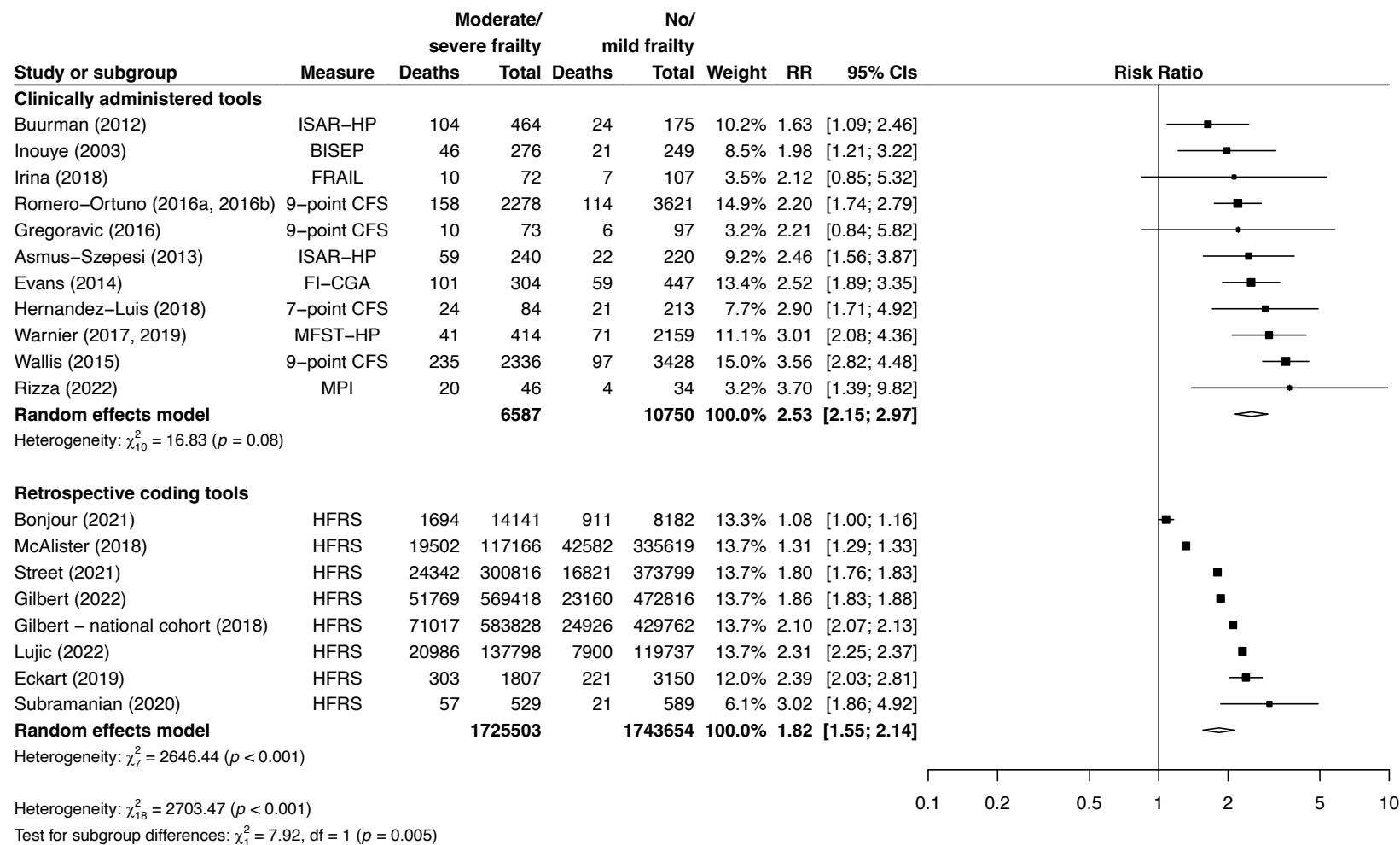
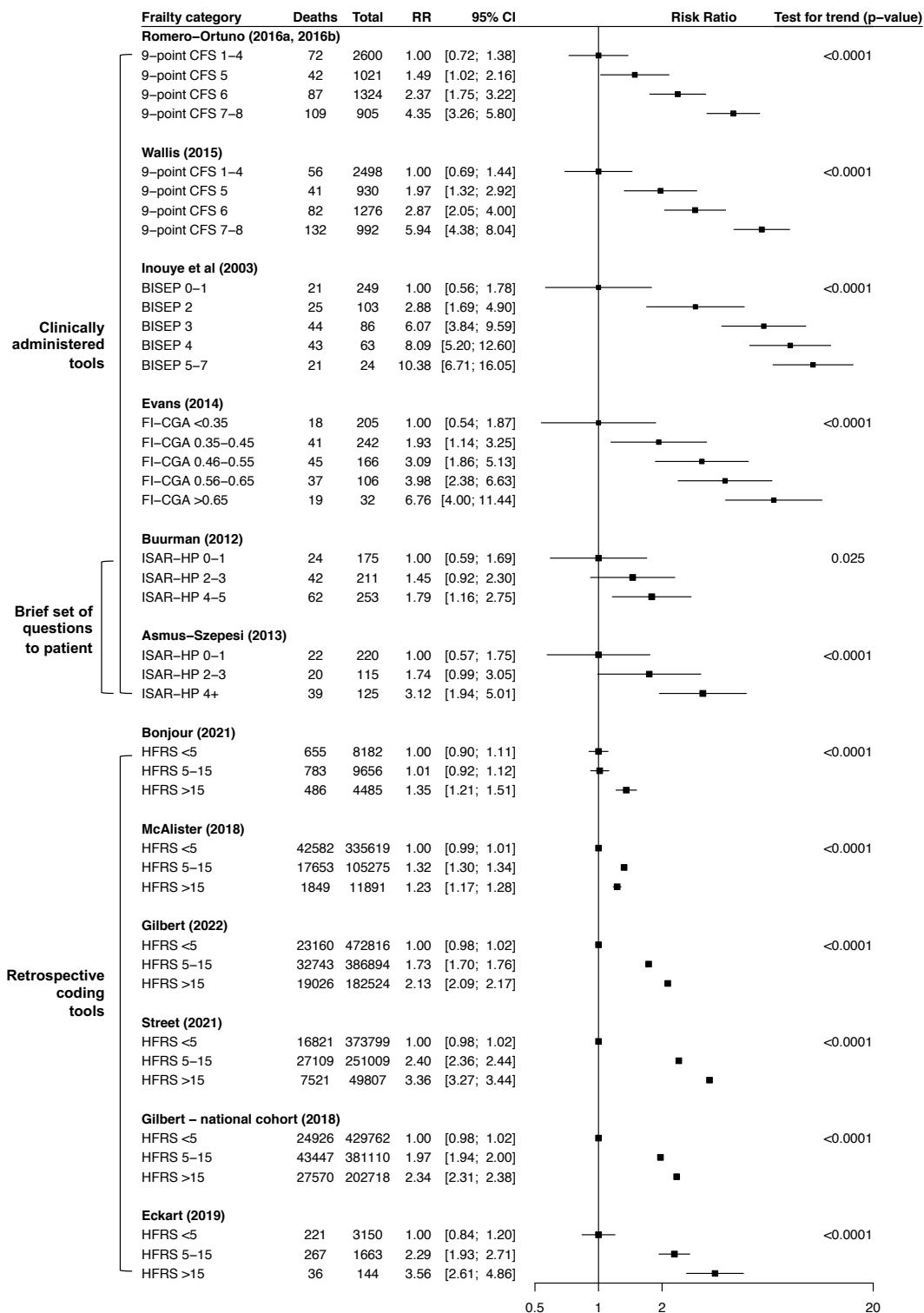


Figure 3.4 Unadjusted relative risks for mortality up to one year after discharge across ordinal categories of frailty & two-sided Cochran Armitage test for trend



Legend: Unadjusted relative risks for death up to one year after discharge by degree of frailty. Studies with >5 events per cell were included. Romero-Ortuno et al. (2016a, 2016b) only reported data for people with CFS 1-8. Dani et al. (2018) (not shown) reported data on mortality up to 3 years and found 48% mortality in the first FI tertile, 51% in the second and 60% in the third (n~237 per group).

Figure 3.5 Unadjusted relative risks of mortality (clinically administered tools only) for moderate and severe versus no/mild frailty (stratified)

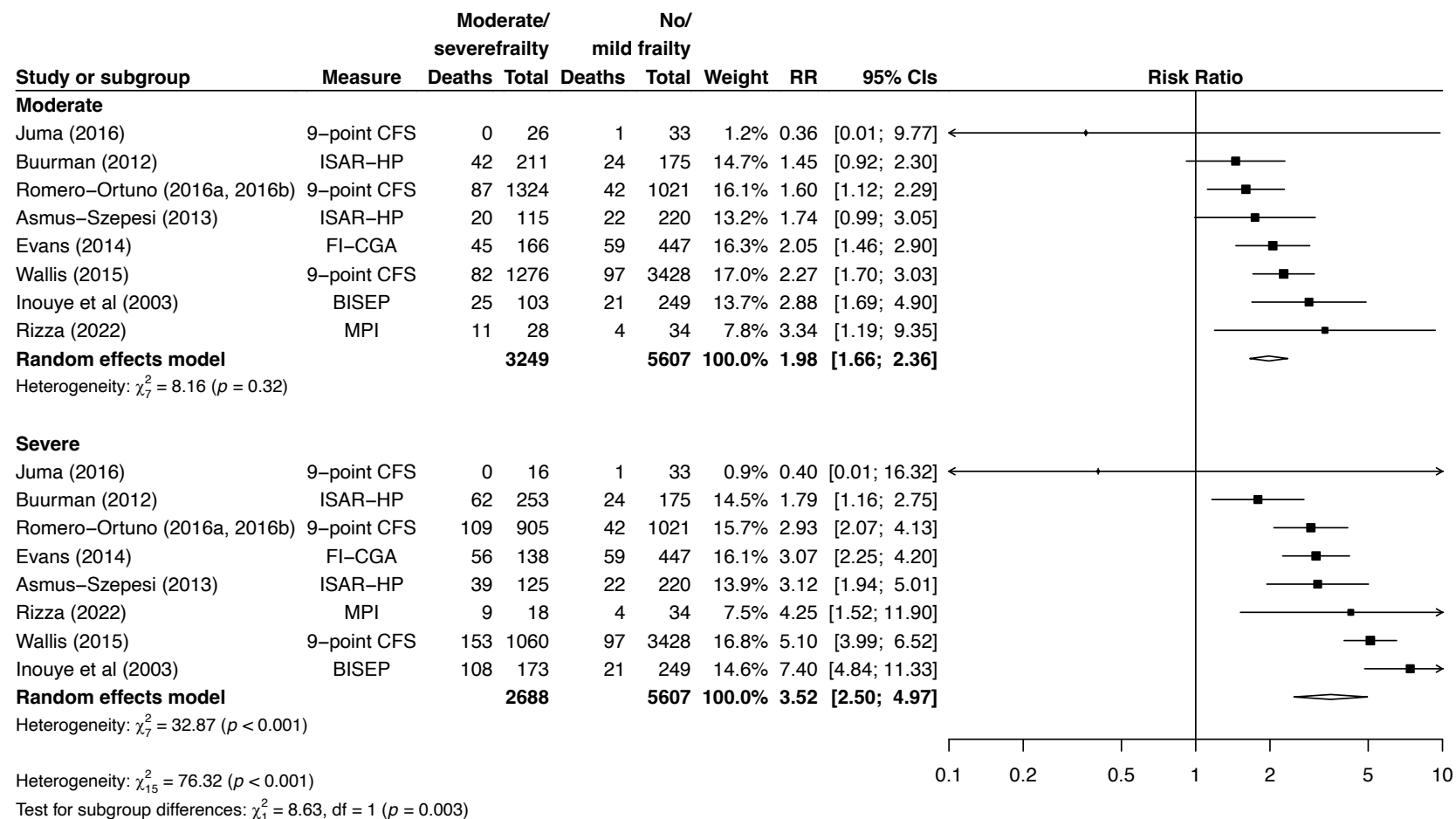
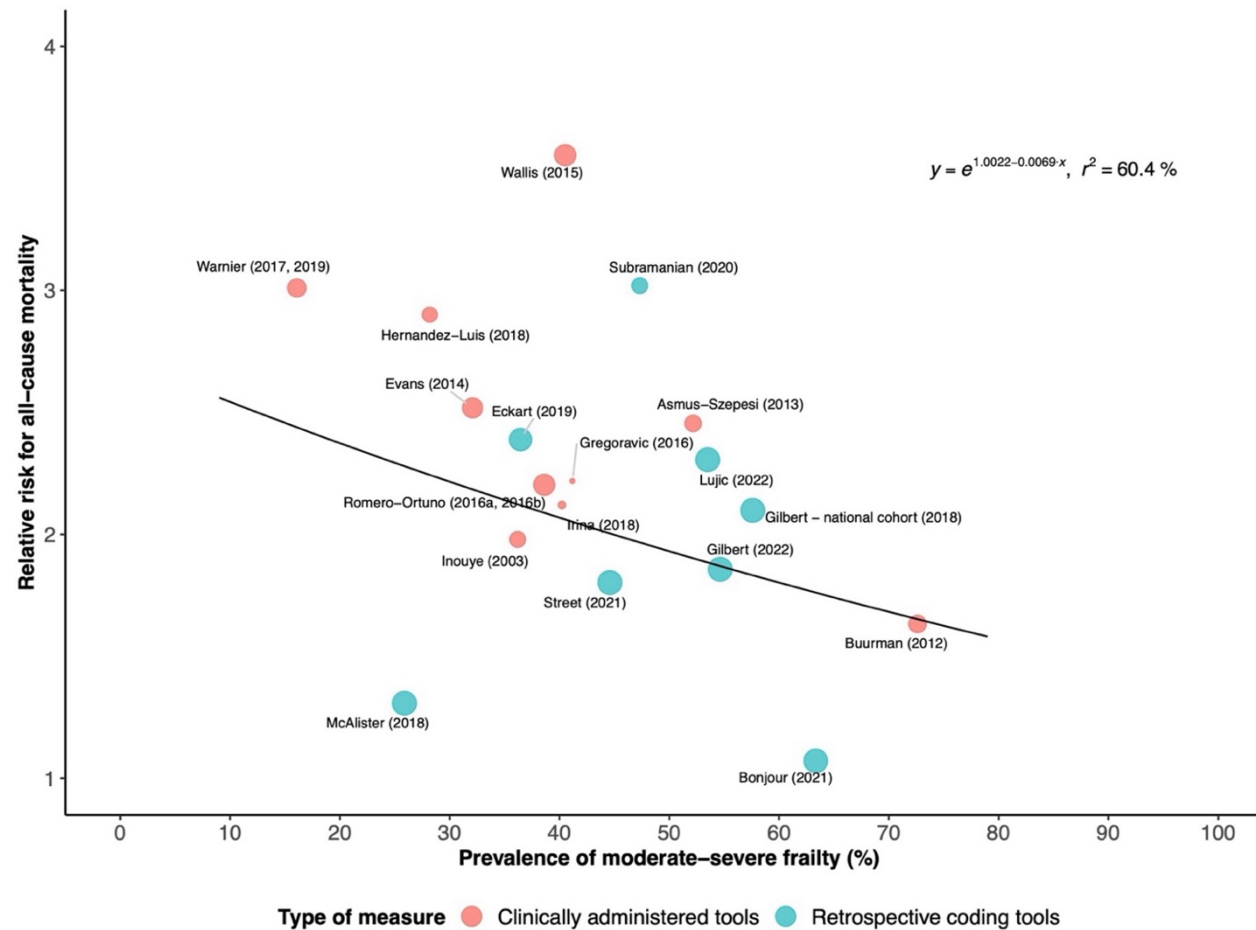


Figure 3.6 Bubble plot for meta-regression of moderate/severe frailty prevalence versus the log of the relative risk for all-cause mortality



Legend: Point size is proportional to the random-effect weight of each study. Khandelwal et al. (2011) is not shown, because no events were reported for the robust-to-mild frailty group.

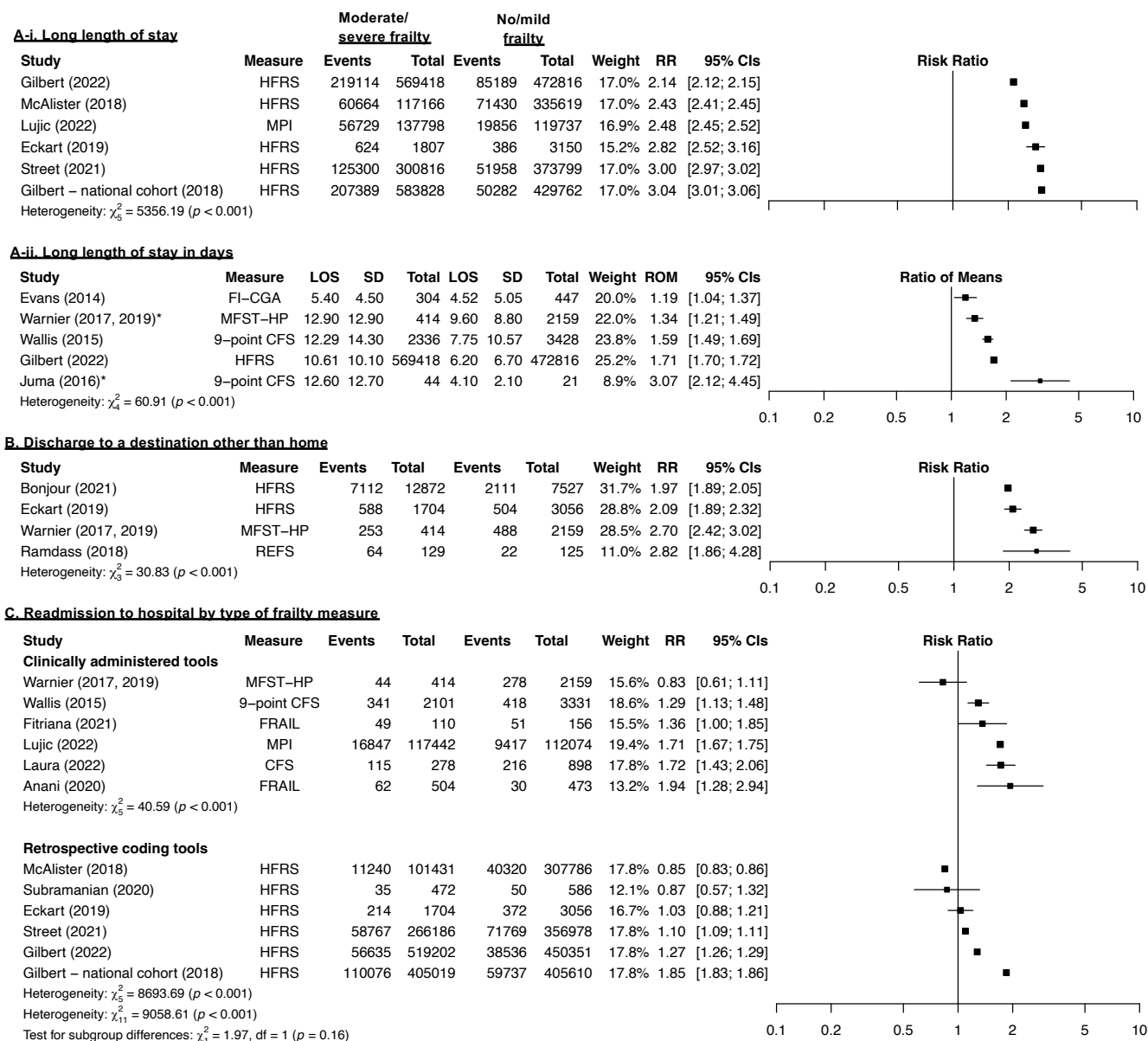
3.3.5 Discharge Destination

All four studies examining discharge to a destination other than home found reported increased risks for moderate/severe frailty. In participants alive at discharge (n=27,986), the relative risk for discharge to a destination other than home ranged from 1.97 to 2.82 (Figure 3.7B), with increasing severity of frailty associated with greater risks in 3/3 studies (Figure 3.8B). Similar results were obtained using the denominators reported by the authors (e.g., including patients who died during admission, Appendix Figure 3.4).

3.3.6 Readmissions

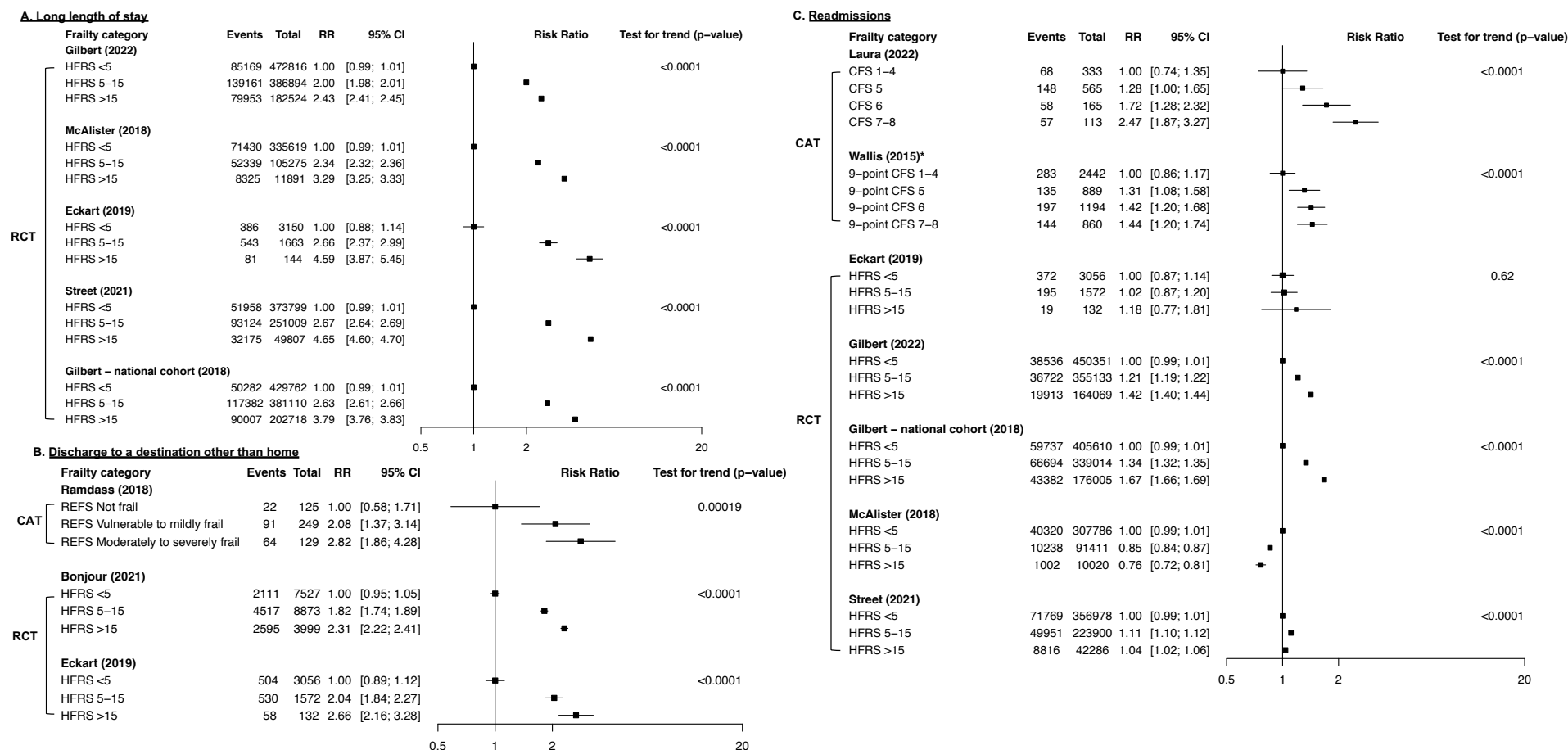
The risk of 30-day readmissions in moderate/severe frailty showed conflicting findings with variation in the direction of effect in participants alive at discharge (n=3,055,748; N=12 cohorts). RRs ranged from 0.83 to 1.94 with 7/12 cohorts showing an increased risk of readmission and 4/12 reduced or unchanged risk. Conflicting findings were not explained by stratification by study setting (Appendix Figure 3.5) or clinically administered versus retrospective coding tools (Figure 3.7C). Similar results were obtained using the denominators reported by the authors (e.g., including patients who died during admission, Appendix Figure 3.4).

Figure 3.7 Unadjusted relative risks of moderate/severe versus no/mild frailty for (A) LOS >8-10 days and ratio of means in days, (B) discharge other than to home in survivors and (C) 30-day readmissions by type of frailty measure in survivors



Legend: Unadjusted relative risks of moderate/severe versus no/mild frailty for (A-i) LOS >8-10 days with (A-ii) ratio of means for LOS in days, (B) discharge to location other than home (i.e., nursing home or post-acute care facility) in survivors and (C) 30-day readmissions stratified by type of frailty. For LOS, Forti (2014) was not shown because it excluded in-hospital deaths (relative risk of 1.35, 95% CI 1.11-1.64). In-hospital deaths were estimated for Gilbert (2018) by multiplying the number of 30-day deaths after the date of admission (including in-hospital deaths) for each frailty category by the % of overall deaths that occurred in hospital and McAlister (2018) by using the n and % of survivors with readmissions and may be subject to rounding errors. In-hospital deaths were assumed to be absent from Anani (2020).

Figure 3.8 Unadjusted relative risks across ordinal categories of degree of frailty and two-sided Cochran-Armitage test for trend for (A) long LOS, (B) discharge destination other than home in survivors and (C) readmissions in survivors.



Legend: CAT = Clinically administered tools. RCT = Retrospective coding tools. Unadjusted relative risks by degree of frailty for (A) long LoS, (B) discharge destination other than home in survivors and (C) readmissions in survivors. Studies with >5 events per cell were included. P-values for the two-sided Cochran-Armitage for trend (increasing or decreasing) are shown.

3.3.7 Adjusted outcomes

Regarding adjusted analyses for outcomes, five individual studies adjusted for a minimum of age, sex and comorbidity and also reported unadjusted estimates (Appendix Tables 3.6 & 3.7). Eleven studies variably adjusted for multiple covariates including multi-morbidity (and did not report unadjusted estimates), but nevertheless found clinically important associations of frailty with death. The risk of death remained significant after adjustment or stratification for illness severity (i.e. NEWS, MEWS) scores on admission in two studies.^{33,49} Adjusted estimates for moderate and severe frailty are shown in forest plots in Appendix 3 where reporting allowed, but most are from studies using retrospective coding tools and could not be pooled due to differences in reporting and statistical heterogeneity (Appendix Figure 3.6 & 3.7).

Table 3.1 GRADE Summary of findings table for main study outcomes

Outcomes	Range of anticipated absolute effects		Relative effect	No of participants (cohorts)	Certainty of the evidence (GRADE)	
	No/mild frailty	Moderate to severe frailty			Direction of the association	Magnitude of the association
All-cause mortality						
Clinically administered*	0 to 14 (per 100)	0 to 43 (per 100)	RR ranged from 0.31 to 16.06; pooled 2.53 [95% CI 2.13 to 3.00]	17,662 (13 cohorts)	⊕⊕⊕⊕ HIGH	⊕⊕⊕○ MODERATE ^a
Retrospective coding data tools*	4 to 13 (per 100)	8 to 17 (per 100)	RR ranged from 1.08 to 3.02	3,469,157 (8 cohorts)	⊕⊕⊕○ MODERATE ^a	⊕⊕○○ LOW ^{ab}
Long length of stay (>8-10 days)**	12 to 21 (per 100)	35 to 52 (per 100)	RR ranged from 2.14 to 3.04	3,445,716 (6 cohorts)	⊕⊕⊕○ MODERATE ^a	⊕⊕⊕○ MODERATE ^a
Discharge to NH or SNF (incl. rehab)**	16 to 28 (per 100)	33 to 56 (per 100)	RR ranged from 1.97 to 2.82	27,986 (4 cohorts)	⊕⊕⊕○ MODERATE ^a	⊕⊕⊕○ MODERATE ^a
Readmission Up to 30 days	6 to 33 (per 100)	7 to 45 (per 100)	RR ranged from 0.83 to 1.94	3,055,748 (12 cohorts)	⊕○○○ VERY LOW ^{ab}	⊕○○○ VERY LOW ^{ab}
RR: Relative risk; NA: Not applicable *Where multiple time-points were reported, I used the estimate closest to up to 30 days post-discharge. **In those who survived to discharge.						

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Risk of bias. b. Inconsistency. c. Indirectness. d. Imprecision. e. Other

3.4 DISCUSSION

Despite the unexplained variation in prevalence described in the last chapter, moderate to severe frailty remained an independent predictor of mortality up to one-year, longer LoS in hospital and discharge to a care home, although the evidence on readmission risk was conflicting. Additionally, I found that more severe frailty was associated with worse outcomes, suggesting a dose response effect. Associations were strongest and most consistent across studies using clinically administered tools, but a large proportion of statistical heterogeneity in mortality risk ratios was also accounted for by variation in measured frailty prevalence.

Heterogeneity and identification of a group at risk

Associations between frailty and poor outcomes held irrespective of the frailty tool administered, indicating that all measures identified a group at risk. Studies with higher frailty prevalence generally reported weaker associations with mortality possibly because these studies operationalised frailty in a more inclusive way, identifying some individuals as frail who would have been classed as fit in other studies (e.g., the CFS which is based mainly on function compared to the HFRS which mostly counts acute diagnoses and comorbidities), with differences in case-mix (as discussed in the previous chapter) possibly contributing to remaining variation.^{43,79} The strength of association between moderate frailty and mortality were similar, but varied widely for severe frailty across studies, even after the analysis was restricted to clinically administered tools. Eligibility criteria such as the need to be able to complete questionnaires or give consent could have preferentially

excluded patients with cognitive frailty, many of whom may be among the most severely frail and/or ill and contribute to variation in estimates of risk.^{48,50,80}

Mortality

Mortality risk ratios for moderate to severe frailty measured with clinically administered tools appeared quantitatively similar. However, mortality risk ratios for retrospective coding tools varied widely even though these measures included data acquired up to the end of the admission. The accuracy of administrative coded data and differences in operationalisation are likely contributing factors. More severe frailty was consistently associated with worse outcomes, supporting the construct of 'frailty' as a spectrum rather than a dichotomous state. Future studies may therefore reasonably assume a linear relationship between frailty within the limits of reported categories and mortality as recently described specifically for frailty indices.⁸¹ Associations between frailty and mortality remained clinically significant after adjustment for multimorbidity and also severe illness where reported, which are prevalent in the acute hospital population.^{33,49}

Length of stay, discharge destination and readmissions

Moderate to severe frailty was associated with LoS and discharge destination in all studies reporting data, again with a stepwise increase in effect size with greater degrees of frailty. However, the strength of associations varied, possibly because these outcomes are dependent on healthcare system factors such as availability of hospital beds, admission avoidance and early discharge strategies or impacted by the prevalence of cognitive frailty.^{85,86} In contrast to other outcomes, results for frailty

and readmission risk were conflicting. Readmission risks were mostly unchanged in patients with cognitive frailty and reduced in those in a general medical setting, with access to a multi-disciplinary team care and advanced care planning,⁸² so I expected to see unchanged or reduced readmission risk for 'global' frailty in this study.⁸³ However, readmission risk did not appear to be explained by setting, type of tool or the competing risk of death where reported. A broad range of factors impact hospital readmission rates including socio-demographic factors and discharge planning, which may be of particular relevance in older patients with frailty.^{84,85,86}

Adjustment for confounding

Associations between frailty and adverse outcomes in individual studies remained significant after adjustment for age, sex and also co-morbidity where reported, suggesting that frailty is predictive over these other prognostic indicators. This is consistent with the observation that most individuals with frailty have multi-morbidity, but that people with multi-morbidity are not necessarily frail.^{87,88} The inclusion of additional variables (illness severity, socioeconomic status, hospital variation and others) further attenuated risks, indicating some amount of residual confounding. The effects of acute illness and premorbid frailty should be distinguished to improve prognostication and are important for the individualisation of care,⁸⁹ but only two included studies considered illness severity, with conflicting results.^{33,49} Assessment with the CFS or other tools for the retrospective assessment of premorbid frailty avoids confounding by illness severity, but misses acute indicators of frailty, such as delirium or sudden changes in frailty status. These issues could be mitigated by performing a "triple" assessment including the CFS, delirium and illness severity as

recommended by GIRFT.⁹⁰ In Chapter 8 the impact of concurrent cognitive and physical frailty on outcomes will be investigated, including after adjustment for illness severity.

Comparison to previous studies

My findings are broadly consistent with the two-to-four fold greater mortality risk reported in surgical, acute coronary syndrome, critical care and geriatric medicine/acute service patients and the two-fold greater risk in population-based samples.^{14,16,18,20,90,91} Specialty-specific studies also found similar associations with LOS and discharge destination.^{18,20,89} Stepwise increases in risk of death were reported by Cunha and colleagues for 'pre-frailty' (two-fold increase compared no frailty) and frailty (3.5-fold increase) measured with clinically administered tools.¹⁵

3.4.1 Strengths and limitations

As stated in Chapter 2, strengths of this review include a comprehensive literature search with detailed synthesis of evidence from a large number of unselected cohorts which fills an important gap in the evidence for frailty. Additionally, I compared clinically administered and recently developed retrospective coding frailty tools, examined degrees of frailty and accounted for a proportion of statistical variation in outcomes. This review has limitations. First, associations between frailty and readmission risk were inconsistent and again could not be explained by setting, tool or the competing risk of death.³⁹ This finding was not unexpected, however, because a broad range of healthcare system factors are known to impact readmission risk.^{84,85} Second, I could not account for the impact of case-mix factors,

asides from average age, on effect size using meta-regression or subgroup analyses because of limitations in reporting. Data on cognition were limited, so its impact on outcomes could not be evaluated despite the implications for decision-making and patient care.^{35,50} Additionally, it was not possible to compare outcomes for prospective studies versus those using routine clinical data due to the smaller number of routine clinical data studies identified. Third, for the outcome discharge destination other than home it was not possible to disaggregate data by destination or determine long-term disposition after discharge, for example, the likelihood of returning home after a temporary stay in a community hospital or care home for rehabilitation. Fourth, the applicability of results to people <65 years is again uncertain since they were excluded from most studies.

3.4.2 Implications for clinicians and decision-makers

My findings provide evidence of the prognostic value of frailty for mortality, LOS and discharge destination in the acute hospital setting, supporting the robust implementation of frailty screening in acute hospitals to inform decision making and the target interventions, such as CGA.¹¹ Frailty should inform clinical care through an understanding of likely outcomes but should not be used in isolation to direct clinical decisions. Future guidelines, policy documents and health economic analyses should also differentiate between varying degrees of frailty. My findings support current guidance recommending the CFS as a first line screening tool since it is pragmatic as described in Chapter 2, but nevertheless identifies a group at-risk as reliably as more lengthy and complex tools.⁵ Box 3.1 identifies several ways in which

large-scale, hospital-wide data on the burden of frailty can be useful for informing policy, planning and care.

Box 3.1 Examples of how data on the burden of frailty can be used to inform policy, service-planning and care.

Policy

- Staffing levels and skill mix
- Frailty training requirements
- Resourcing and service design

Service planning

- Frailty care pathways
- Resources required for Comprehensive Geriatric Assessment and multidisciplinary team care
- Case-mix evaluation

Clinical care

- Communication tool for handover and transfers
- Individualisation of acute treatment according to frailty status
- Risk-stratification for further needs assessment or specialized frailty care
- Enhanced discharge planning and strengthening post-discharge care
- Improved patient and caregiver experience, i.e., counselling about prognosis
- Initiate discussions on advanced care planning and power of attorney
- Inform discussions on readmission avoidance strategies

Several retrospective tools based on administrative data (primarily the HFRS) were included in analyses. Despite including information collected over the entire course of the admission (versus prospective ascertainment of frailty), the predictive value of these tools was highly variable. However, they may still be useful for policy or research purposes, particularly where high-quality coded data are available and/or validation studies have been done.

3.4.3 Conclusion

Frailty is an important independent prognostic factor in older people with acute, non-elective hospital admissions, with a dose response effect. My findings support robust implementation of hospital-wide frailty screening using clinically administered tools, particularly the Clinical Frailty Scale, in line with current guidance.^{5,7} Future guidelines and studies should differentiate between varying degrees of frailty to improve prediction and personalisation of care for patients. Additionally, research on the impact of cognitive frailty domains on outcomes may help individualise care decisions and target resources more precisely. Subsequent sections of the thesis will focus on cognitive frailty domains, including their predictive value for outcomes (**Chapter 7**) and interactions with physical frailty (**Chapter 8**) using routinely collected clinical data in hospital electronic patient records.

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Chapter 4

Methods: The Oxford Cognitive Comorbidity, Frailty, And Ageing Research Database- Electronic Patient Records (ORCHARD-EPR)

ABSTRACT

Background: Hospitals are increasingly caring for older, multimorbid and frail patients as the population ages. However, as shown in Chapter 2, measures of ‘global’ frailty poorly capture the cognitive domains of frailty. Additionally, most existing studies of cognitive frailty prevalence and outcomes are small, selected prospective cohorts or administrative data which only partially capture the complexity of this population and are insensitive for cognitive frailty. Electronic patient records (EPRs) allow routinely collected data to be curated for research at relatively low cost and without selection. The Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records (ORCHARD-EPR) was created to exploit EPR-embedded cognitive and clinical data to enable large-scale research of cognitive frailty in older people with unplanned admissions.

Methods: ORCHARD-EPR includes pseudo-anonymised EPR data on all patients ≥ 65 years admitted to one of four general hospitals in Oxfordshire, serving a catchment area of 800,000 (2015-). Data collected include cognitive screening (mandatory for ≥ 70 years) comprising existing dementia diagnosis, delirium diagnosis (informed by the Confusion Assessment Method—CAM), and 10-point Abbreviated Mental Test; together with nursing risk assessments, frailty, diagnoses, comorbidities, observations, illness acuity, laboratory tests and brain imaging. Outcomes include length of stay, delayed transfers of care, discharge destination, readmissions and death.

Conclusion: ORCHARD-EPR is a large and rich data resource that will enable studies on the burden and impact of cognitive and physical frailty in-hospital, with relevance to the design and delivery of clinical services and understanding of healthcare resource use hospital-wide and by specialty. In the next chapter, I will validate cognitive data in ORCHARD-EPR against prospectively collected audit data.

4.1 INTRODUCTION

Data on the burden of cognitive and physical frailty are needed to plan services for older people with unplanned admissions, and also develop policy and guidelines.^{1,2} In previous chapters, I reviewed the evidence base for global frailty in this population, finding that cognitive domains were poorly assessed by global frailty tools (Chapters 2 & 3). I also reviewed the evidence base specifically on cognitive frailty (i.e., delirium and dementia; see Introduction chapter) finding that most prospective studies had limitations including small sample sizes, restrictive eligibility criteria or inappropriate sampling methods which might limit their generalisability to the hospital population at-large or introduce bias. For example, delirium often co-occurs with dementia, but few studies identify both using valid methods and some dementia cohorts excluded patients with delirium.³⁻⁵ Several retrospective studies based on administrative data (i.e., ICD-10 codes) were also done, but are limited by poor coding accuracy.⁶⁻⁸

Routinely acquired clinical data in hospital EPRs could have advantages for measuring cognitive and physical frailty over existing prospective and retrospective study designs by combining large, unselected samples with detailed, accurate ascertainment as explained in the Introduction chapter. Only one hospital-wide study using routine cognitive screening data was identified probably because uptake of cognitive screening is not widespread despite being recommended in national guidelines. The Oxford University Hospitals NHS Foundation Trust (OUHFT), however, has mandated that all older hospital patients be screened for cognitive disorders using a standard paper clerking pro-forma from 2013-2015 and with an

EPR-embedded form from 2015-present.⁹ The Oxford Cognitive Comorbidity, Frailty, and Ageing Research Database-Electronic Patient Records (ORCHARD-EPR) was subsequently created to exploit these cognitive screening data with other pseudo-anonymized OUHFT EPR data for audit and research purposes. The primary aim of the database is to collect data to provide reliable estimates of the prevalence, complications and outcomes of cognitive and physical frailty in unselected, consecutive adult acute care episodes for research and quality improvement purposes. Therefore, I used ORCHARD-EPR as the primary data source to study the value of EPRs for determining the prevalence and outcomes of cognitive and physical frailty in my thesis.

This chapter describes ORCHARD-EPR data and analysis methods. Subsequent results chapters using ORCHARD-EPR data include chapter 5 which compares cognitive data in ORCHARD-EPR data to prospectively acquired audit data; Chapter 6 which estimates the prevalence of cognitive frailty hospital-wide and by specialty; Chapter 7 which determines outcomes of cognitive frailty and Chapter 8 which investigates the overlap of cognitive and physical frailty and impact on outcomes.

Work in this chapter has been published in the following journal article:

Boucher E, Jell A, Singh S, Davies J, Smith T, Pill A, Varnai K, Woods K, Walliker D, McColl A, Shepperd S, Pendlebury ST. (2024). Protocol for the Development and Analysis of the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database - Electronic Patient Records (ORCHARD-EPR). *BMJ Open*, 14(5):e085126.

Contributions: I assembled and cleaned the ORCHARD-EPR data including sense-checking, removing non-inpatient care episodes, deriving comorbidity, frailty and illness severity scores and outcomes, identifying care home residents and patients with a primary diagnosis of infection and extracting delirium/dementia data from the cognitive screen and merging it with relevant ICD-10 codes data. I also created tables/figures and drafted the manuscript.

4.2 METHODS

4.2.1 Study design

ORCHARD-EPR contains routine (i.e., “real-world”) pseudo-anonymized clinical data extracted from the OUHFT EPR for inpatients with unplanned admissions and same day emergency care (SDEC) patients. ORCHARD-EPR includes data from the OUHFT cognitive screen which is mandatory for inpatients ≥ 70 years (see below, 4.2.6). Data were available from January 2015-present (2017 with full coverage of all clinical areas), including during the COVID-19 pandemic, with data added every six months. The structure of ORCHARD-EPR is shown in Figure 4.1.

Figure 4.1 Structure of ORCHARD-EPR and flow of data including observations/labs, cognitive screen results, nursing assessments and prior audits

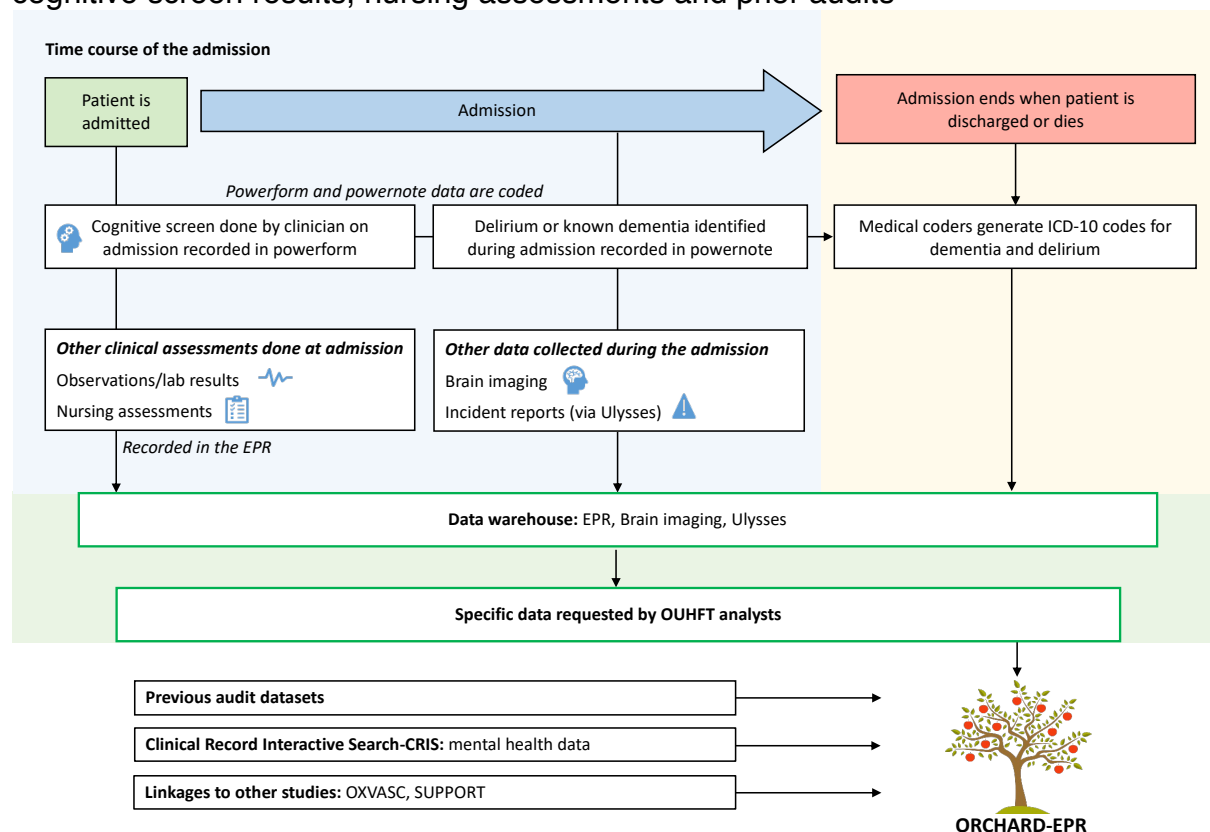


Figure adapted from Boucher E, et al. BMJ Open 2024;14:e085126. This article has been accepted for publication in BMJ Open following peer review and can also be accessed online at <https://doi.org/10.1136/bmjopen-2024-085126>.

4.2.2 Setting

The OUHFT is a large teaching and research trust consisting of four NHS hospitals (John Radcliffe Hospital, Nuffield Orthopaedic Centre and Churchill Hospital in Oxford, and the Horton General Hospital in Banbury) providing all acute hospital care to a catchment area of >800,000 people in Oxfordshire, UK and neighbouring counties. The Oxfordshire population is older and less deprived than England on average but still includes several of the 10-20th percentile of most deprived regions in England.¹⁰

4.2.3 Eligibility

Inclusion: ORCHARD-EPR includes all consecutive, unselected OUHFT inpatients and SDEC patients ≥ 65 years and those < 65 years with a completed cognitive screen, in addition to adult outpatients seen in memory/cognitive disorder clinics and vascular specialty services for which data have been collected as part of OUHFT-approved audits (more detail in Boucher et al., 2024).¹¹

Exclusion: Patients < 65 years without a completed cognitive screen or test. Individual consent is not obtained for inclusion of pseudonymised data in the database, but patients are permitted to opt-out with information provided via the OUHFT website and posters.

Unless otherwise stated, I further limited eligibility for my thesis to:

- **Age ≥ 70 years:** Cognitive screen completion rates were 15% in people < 70 years for whom screening was not mandatory versus 73% in those ≥ 70 years.
- **Admission start date between January 1st, 2017 and December 31, 2019:** This period was selected because full coverage of all clinical areas was achieved in 2017 (see 4.2.6 below) and to prevent the 2020 COVID-19 pandemic from impacting results.⁸
- **Length of stay (LoS) ≥ 1 day on an inpatient ward:** SDEC/ambulatory care patients, those who were transferred to another trust or triaged without admission and those admitted to virtual wards or care-home beds in the community (e.g., hospital-at-home) were also excluded to limit heterogeneity.

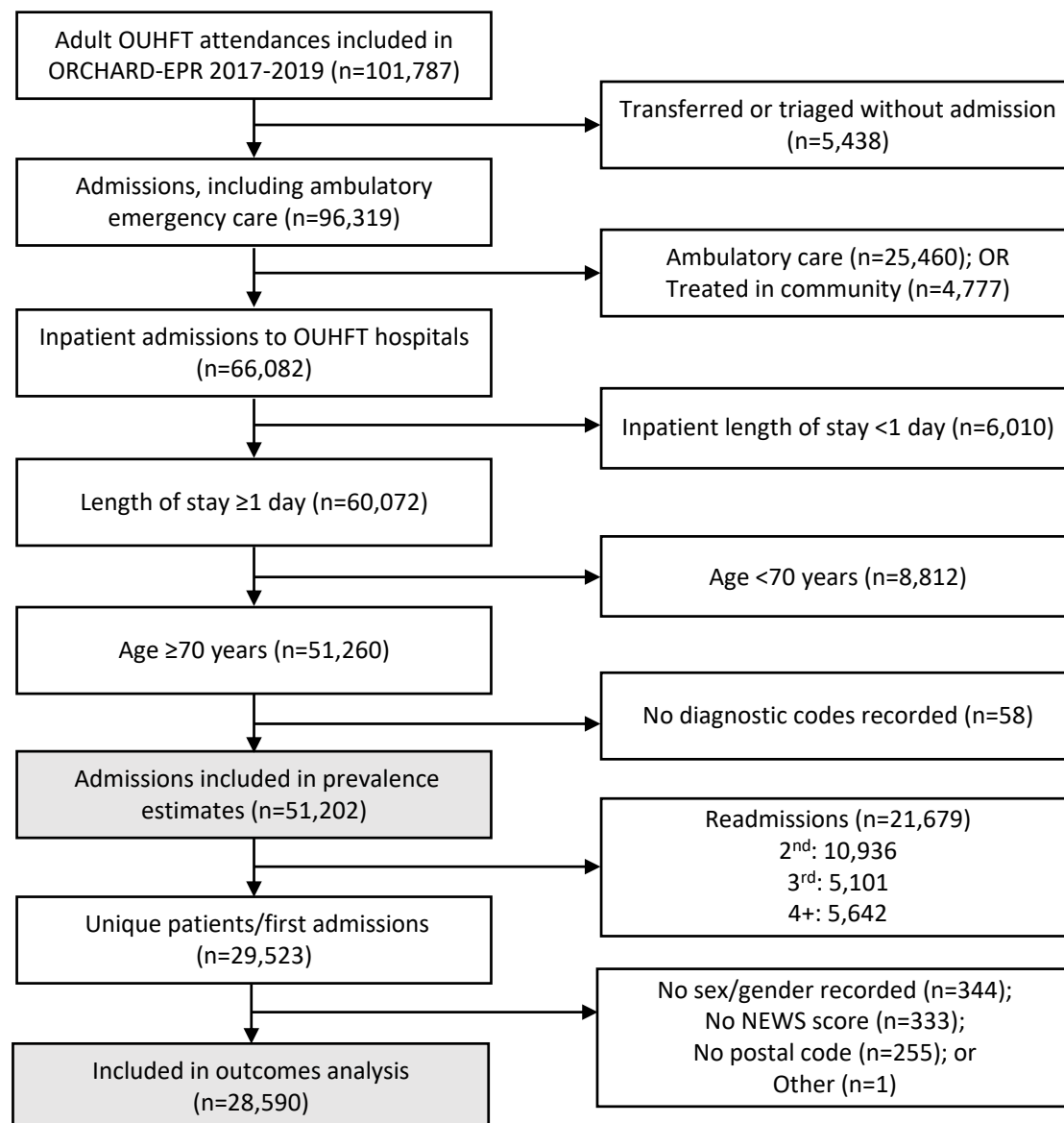
- To apply this criterion to the dataset, I cross-referenced ward names in ORCHARD-EPR with treatment function and the LoS of individuals on each ward. This was necessary because some wards provided multiple clinical services during the study. For example, some individuals with “Emergency Medicine” as their treatment function had “Emergency Assessment Unit” (an acute general medicine unit) as their ward, because part of the Emergency Assessment Unit was used by the Emergency Department temporarily. STP reviewed eligibility.
- **Age and ≥ 1 ICD-10 code reported:** Missing age data or ICD codes might indicate an error in the admission record (i.e., it would be unusual for a patient to be admitted to hospital and not have any diagnoses or comorbidities recorded).

Additional analysis-specific eligibility criteria are given in the relevant chapters (outcomes analyses were generally limited to first admissions with no missing covariates, i.e., sex/gender, illness severity, postal code).

4.2.4 Cohort size

A total of 101,787 unplanned hospital admissions episodes and ambulatory care assessments were included in ORCHARD-EPR (2017-2019). After I excluded patients <70 years of age, those with a length of stay of <1 day and missing age, sex or ICD-10 codes, 51,202 eligible inpatient admissions remained, comprising 29,523 unique patients (Figure 4.2).

Figure 4.2 Eligibility for inclusion in this thesis



4.2.5 Procedures and data

All ORCHARD-EPR data are obtained from assessments completed by medical, nursing, allied health and administrative staff as part of normal patient care. Data were obtained from the EPR by OUHFT Information Analysts or manually for audits. Individual patient records were assigned an ORCHARD-EPR study number by the OUHFT Information Team and patient identifiers (e.g. name, date of birth, hospital medical reference number—MRN, NHS number, etc.) were removed before transfer

to the database. A summary of data fields included in ORCHARD-EPR is shown in Table 4.1 and compared to the data available for a widely used hospital administrative database—the NHS Hospital Episode Statistics-Admitted Patient Care Activity (HES-APC) and other routine clinical data studies reporting data on dementia and/or delirium prevalence and outcomes.¹²⁻¹⁶ Data fields extracted included demographics, postal codes, treating specialty, diagnoses, cognition, nutrition, falls and pressure sore risk, observations, laboratory analyses and outcomes.

Extensive cognitive phenotyping data were obtained by OUHFT clinicians through routine cognitive screening done on admission and supplemented with ICD-10 codes (see Sections 4.2.6 & 4.2.7). Physiologic measures, nursing assessments, and laboratory investigations were also extracted by the information team from the EPR. Free text entries are not currently extracted. Radiology reports and raw images from brain and other imaging, are extracted separately from the OUHFT picture archiving and communications system (PACS) and linked to the ORCHARD-EPR electronic data. Additional data linkages include local mental health trust data (Oxford Health-Clinical Record Interactive Search), the OUHFT incident reporting database (Ulysses) and other studies (i.e., OxVasc and SUPPORT) although none of these datasets were analysed in this thesis. Data were iteratively checked by the ORCHARD-EPR PI (STP) with the OUHFT Information Team including identification of correct data fields, completeness of data items and sense checking.

Table 4.1 Data items available in ORCHARD-EPR vs HES-APC and other routine clinical data studies reporting cognitive frailty.

Note : a = Anand et al. 2022, b = Reynish et al. 2017/2021, c = Romero-Ortuno et al 2017.

Category	ORCHARD-EPR Variable	Multiple time-points	Available in HES?	Reported in previous published routine clinical data studies
Demographic	Age, gender	-	✓	a,b,c
	Postcode, deprivation	-	✓	b
Admission	Presenting complaint [#]	-	x	x
	Method (i.e. GP, ED), source	-	✓	x
Vitals	HR, BP, RR, SpO2, tympanic temp, AVPU	✓	x	x
Illness severity	NEWS, SIRS	✓	x	b (ED-MEWS)
Cognitive screen	AMTS, MMSE, MoCA, ACE	✓	x	a
	Reason for cognitive untestability	✓	x	x
	Delirium diagnosis	✓	Limited*	screening only: a,b,c***
	Delirium on admission (prevalent) and arising de novo during admission (incident) [#]	-	x	x
	Pre-admission dementia diagnosis	-	Limited*	b,c
Multimorbidity	Charlson, Elixhauser indices	-	✓	b,c

Frailty	HFRS	-	✓	b,c
	Clinician's impression of frailty [#]	-	x	c (CFS)
	Dr Foster Global Frailty Score	-	✓	
	Frailty Markers, including vision and hearing	-	Limited*	x
	Long-term catheter (medical/nursing notes [#])	-	x	x
	Catheter insertion during admission (medical/nursing notes [#])	✓	x	x
Functional status	Nursing risk assessments	✓	x	b (ADLs)
Nutrition	Malnutrition universal screening tool (MUST)	✓	x	x
Pressure sore risk	Braden scale (pressure sore risk), including sensory perception, moisture, activity, mobility, nutrition, friction & shear	✓	x	x
Falls risk factors (based on NICE)	Orthostatic hypotension, appropriate footwear, safe walking unaided/with an aid, urinary incontinence or urgency, vision problems, fall history, fear of falling, environment (hazards, lighting, call bell), confusion/agitation/cognitive impairment	✓	x	x
Mental Capacity	Documented mental capacity assessment yes/no, decision assessed [#] , outcome of decision [#]	✓	x	x
Course in hospital	Ward	-	x	b
	Specialty (i.e. Treatment Function, Main Specialty)	-	✓	Limited: a,c

	Procedures, including radiologic imaging	✓	✓	x
	Incidents in hospital	✓	x	x
Diagnoses	ICD-10 codes	-	✓	b,c
	Clinician working diagnosis and final diagnosis [#]	-	x	x
Disposition	Residence [#]	-	x	b
	Care needs/care package [#]	-	x	x
	Increased care needs at discharge: new care home, rehabilitation bed, intermediate care, increased care package [#]	✓	x	x
	LoS in hospital, critical care, palliative care, rehabilitation,	-	✓	a,b,c
	Delayed transfer of care, reasons for delayed transfer	✓	x	c
	Discharge destination	-	✓	b
	Death during admission (via National Office of Statistics)	-	✓	a,b,c
Labs	Haemoglobin, white cell, neutrophil and lymphocyte counts, albumin, C-reactive protein, creatinine, eGFR, glucose, HbA1c, lactate, pH, sodium, thyroid stimulating hormone, urea	✓	x	x
Brain imaging	Brain imaging reports, raw brain scan images	✓	x	x

Mortality	On follow-up	-	✓	a,c
Long term cognitive/mental health outcomes	Dementia and mild cognitive impairment from mental health services assessment	-	Limited**	x
	Cognitive test scores	-	x	x
	Depression and mental illness	-	Limited**	x
CRIS uses artificial intelligence to extract data from free text. *Only available via clinical coding that is known to be insensitive. **Only available for patients readmitted to hospital in whom a corresponding ICD-10 diagnosis was recorded by the coders. ***Screening for “acute confusion” was only done in people with known dementia. #Only available in manual audits. ACE, Addenbrooke’s Cognitive Examination; ADL, Activities of Daily Living; AMTS, Abbreviated Mental Test Score; AVPU, Alert, Voice, Pain, Unresponsive Scale; CRIS, Clinical Record Interactive Search; eGFR, Estimated glomerular filtration rate; HbA1c, Hemoglobin A1C; LOS, Length of stay; MMSE, minimental-state examination; MoCA, Montreal Cognitive Assessment; MUST, Malnutrition Universal Screening Tool; NEWS, National Early Warning Score; NICE, National Institute for Health and Care Excellence; ORCHARD-EPR, Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records; SIRS, Systemic Inflammatory Response Syndrome.				

Table adapted from Boucher E, et al. BMJ Open 2024;14:e085126. This article has been accepted for publication in BMJ Open following peer review and can also be accessed online at <https://doi.org/10.1136/bmjopen-2024-085126>.

4.2.6 Cognitive screen

The OUHFT cognitive screen has been mandatory to complete on admission for all in-patients ≥ 70 years of age or younger in-patients at high-risk (see 4.2.3 Eligibility; repeat assessments were not required to be completed) since 2013 via a paper proforma and 2015 via an EPR-embedded proforma which is shown in Figure 4.3 and includes:

- The 10-point Abbreviated Mental Test Score (AMTS), which is a standardised assessment of cognition, including short- and long-term memory, orientation and attention.¹⁷ If not completed, the reason must be given as free-text.
- “Does the patient have a known diagnosis of dementia?” (Recorded as yes/no/uncertain).
- “Does the patient have delirium?” (Recorded as yes/no/uncertain). Informed by the Confusion Assessment Method (CAM) which has a sensitivity and specificity of $>90\%$.¹⁸ Individual CAM items were displayed on the screening proforma to inform the screening clinician but were not individually recorded.¹⁹

Junior doctors were provided with training in delirium diagnosis using the CAM and Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-4) criteria as part of in a multicomponent intervention. The intervention also included reporting of screening rates at hospital governance meetings, trust-wide education for clinicians and awareness raising and training of the coding team as described previously.⁸

Figure 4.3 The OUHFT cognitive screening EPR powerform

Cognitive Screen - ZZZXXBERENDT, ANTHONY

Performed on: 05/07/2013 1749 BST By: Berendt, Anthony Robert

Cognitive Screen

Is AMTS feasible? ☒ Yes ☐ No Reason AMTS not done ☐ Too unwell ☐ Uncooperative ☐ Dysphasic ☐ Language barrier ☐ Other:

Age ☒ Yes ☐ No

Year ☒ Yes ☐ No Date of birth ☒ Yes ☐ No

Time (nearest hour) ☒ Yes ☐ No Year of 2nd WW (start or end) ☒ Yes ☐ No

Now ask patient to remember this address: 42 West Street

Location ☒ Yes ☐ No Monarch ☒ Yes ☐ No

Recognise 2 people (eg doctor, nurse) ☒ Yes ☐ No Count backwards (from 20 to 1) ☒ Yes ☐ No

Recall 42 west Street ☒ Yes ☐ No

AMTS score 10

Does the patient have a known diagnosis of dementia? ☐ Yes ☒ No ☐ Uncertain

Aid to identify delirium (CAM)

1. Acute onset and/or fluctuating confusion/ altered behaviour
2. Inattention (unable to do 20-1 or distractable)
3. Altered conscious level (agitated or sleepy)
4. Disordered thinking (rambling)

Delirium exists if patient satisfies conditions: 1 + 2 + (3 or 4)
but note that CAM sensitivity is not 100% particularly for hypoactive (SLEEPY) delirium, so if patient has clinical diagnosis of delirium, even if CAM negative, select "yes".

Does the patient have delirium? ☒ Yes ☐ No ☐ Uncertain

Forgetfulness in the last 12 months ☒ Yes ☐ No ☐ Not assessable

Have you/has the patient been more forgetful in the past 12 months to the extent that it has significantly affected you/their daily life?

In Progress

Legend: The last question (i.e., “Forgetfulness in the last 12 months” was removed from the screen prior to 2017). Image provided by STP.

The cognitive screen design was previously evaluated/validated in prospective audits including against other cognitive tests including the Mini Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).^{8,20-23} In Chapter 5, I will compare cognitive data in ORCHARD-EPR to prospectively collected audit data to further evaluate data quality and completeness.

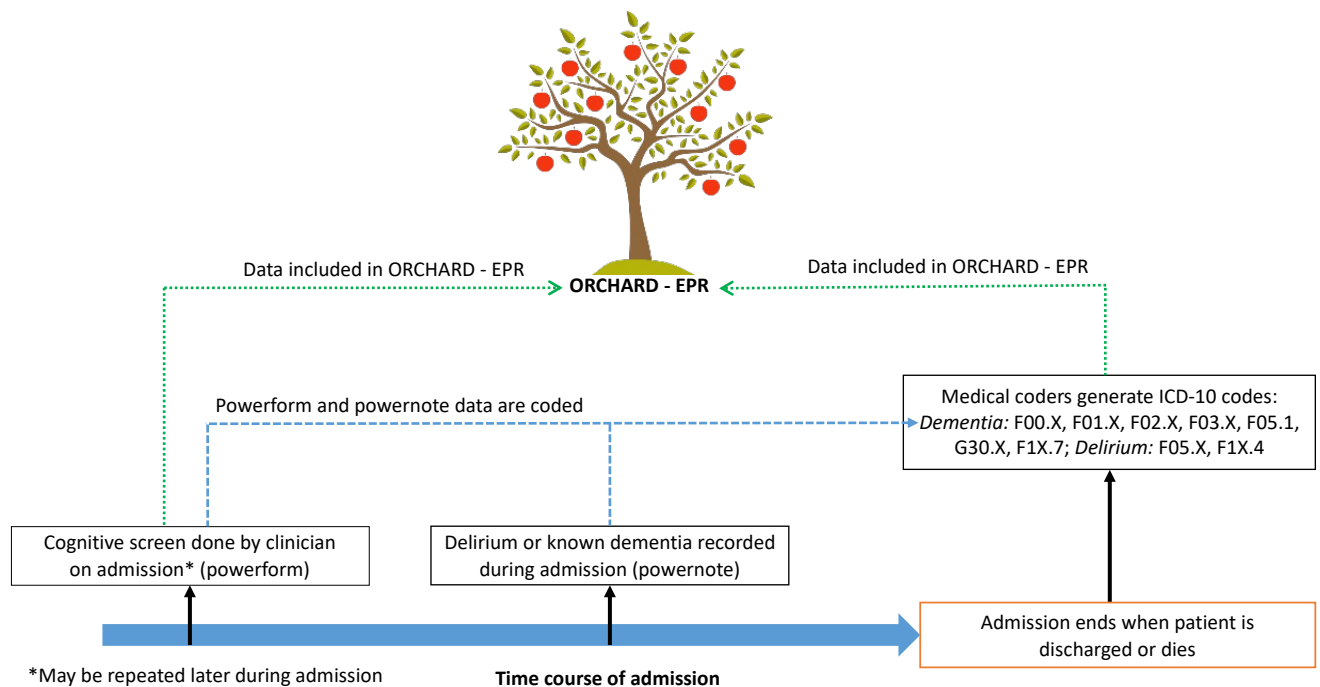
4.2.7 Supplementation of cognitive screen with ICD-10 codes

Cognitive frailty identified after completion of the initial cognitive screen was recorded as free text in patient charts and/or subsequent cognitive screening proformas which were not included in the ORCHARD-EPR dataset used in my thesis.²⁴ ICD-10 codes allocated by trained medical coders based on these records were available, however. Therefore, I used dementia and delirium ICD-10 codes to supplement the cognitive screen and maximise the sensitivity of delirium and dementia ascertainment (Figure 4.4).⁸ To identify codes for dementia and delirium, I hand-searched the ICD-10 code book and cross-referenced results with coding in ORCHARD-EPR to determine which codes were present in the dataset.²⁵ Using this code list, I defined known dementia based on the cognitive screen and ICD-10 codes (F00.X, F01.X, F02.X, F03.X, F05.1, G30.X, F1X.7; '*X*' indicates any whole number value) and delirium based on a positive delirium screen and or the presence of one or more ICD-10 codes for delirium (F05.X, F1X.4).

4.2.8 Nursing assessments

ORCHARD-EPR includes data from relevant nursing risk assessments, including the Malnutrition Universal Screening Tool (MUST),²⁶ Braden Scale for pressure sore risk,²⁷ and a multifactorial falls risk assessment based on National Institute for Health and Care Excellence (NICE) guidance reported by nursing and allied health staff.²⁸ These include data on functional status, vision and continence (see Table 4.1).

Figure 4.4 Cognitive data included in ORCHARD-EPR



Note: Only the cognitive screen done on admission was mandated. Figure adapted from Boucher E, et al. BMJ Open 2024;14:e085126. This article has been accepted for publication in BMJ Open following peer review and can also be accessed online at <https://doi.org/10.1136/bmjopen-2024-085126>.

4.2.9 Derived scores

Laboratory test results and physiologic measures, including heart rate, blood pressure and temperature, from routine patient observations on admission were linked from the existing OUHFT System for Notification and Documentation (SEND) database by the OUHFT Information Team allowing for the calculation of derived variables. I performed “sense-checking” to identify extreme values in these data before using them for analysis.

I calculated measures of illness severity using SEND data including the:

- National Early Warning Score (NEWS) version 1;²⁹
- Systemic Inflammatory Response Syndrome (SIRS) criteria,³⁰ (which has been used in the geriatric setting previously³¹);

Additionally, I calculated measures of comorbidity and frailty using ICD-10 codes:

- Charlson Co-morbidity Index (CCI), which was calculated based on NHS Summary Hospital-level Mortality Indicator (SHMI) weights;³²
- Hospital Frailty Risk Score (HFRS), which was calculated as described by Gilbert et al (2018).³³

I also identified patients with a primary diagnosis of infection using ICD-10 codes. I generated a code list by hand-searching the ICD-10 code book for codes related to infection and cross-checked the list against one independently created by RL for missing codes.²⁵ I used this list to identify patients with any infection ICD-10 codes and a primary diagnosis of infection, i.e., the first code recorded for their admission was an infection code (not including codes describing symptoms). See Appendix 4 for code lists and variable weightings (Appendix Table 4.1-4.4).

4.2.10 Geographic data

Postal codes are collected as part of admission demographics and were used to obtain information on the living conditions of ORCHARD-EPR patients which was not reported in NHS data or ORCHARD-EPR. Examples include:

- The English Index of Multiple Deprivation (IMD) to obtain percentiles of deprivation (calculated by RL based on the 2019 version of IMD);³⁴
- Identification of patients living in care homes prior to admission.

Identification of patients living in care homes prior to admission.

To identify patients living in care homes prior to admission, I cross-referenced postal codes against a list of postal codes of nursing and residential homes providing services for older people and people with dementia registered with the Care Quality Commission (CQC) using similar methods to those described previously.³⁵ It was not possible to distinguish care homes versus nursing homes because many homes offered both services. I created a list of care homes active during the study period by merging care directory data for active and inactive care homes from the CQC website and filtering to limit the list to homes active during the study period (and additionally confirmed that the homes were registered during a given admission). All adult and social care providers are required to be registered, therefore the CQC database is comprehensive.³⁶ I used unit postcodes where reported to identify care homes, which are the most specific and generally represent a group of properties (e.g., a street). I manually spot-checked a sample (n=100) of the care home variable against the list of CQC-registered care homes.

4.2.11 Outcome measures

The following outcomes were available from ORCHARD-EPR and analysed:

- **Death:** Analysed as time-to-event (i.e., based on date of death provided by the Office of National Statistics) and a binary variable (i.e., in hospital death).

- **Length of stay (LoS):** Analysed as a count (i.e., number of days) or binary variable.
- **Delayed transfers of care:** Delayed transfers of care (DTOCs) indicate when a patient is medically fit for discharge but is still occupying a bed, i.e., delayed discharge. Analysed as a binary variable.
- **Discharge destination:** Reported as a categorical variable, dichotomised into 'usual residence' or other for most analyses.
- **Readmissions:** Readmission within ≤ 30 days of discharge were derived from ORCHARD-EPR and analysed as time-to-event or a binary variable.
- Readmissions were not reported in ORCHARD-EPR, but I created a readmissions variable by using study identification numbers to identify the first admission for each patient in ORCHARD-EPR and subsequent admissions occurring within 30 days of the recorded discharge date. For this reason, binary readmissions data were not available for the last 30 days of the study (i.e., December 1-31, 2019).

4.2.12 Statistical analysis

In this section, I describe statistical methods that I used in multiple thesis chapters. Additional chapter-specific methods are described in the relevant sections.

Descriptive statistics

Descriptive statistics included the mean/standard deviation (continuous data) and n/% (counts). The two-sample t-test or z-test (continuous data, proportions and prevalence) and Pearson's Chi-squared test (counts) were most commonly used to

determine statistical significance. The t-test and z-test assume that observations are independent and from normally distributed populations with equal standard deviations, but these assumptions are less important when sample sizes are large.

Prevalence

Prevalence was calculated as the number of cases of cognitive impairment divided by the *total number of admissions* in the dataset, including admissions without any cognitive data reported. Those without cognitive data were on average, younger with a shorter length of stay and fewer cognitive risk factors than those with cognitive data so were assumed to have low rates of cognitive problems (see Appendix Table 5.1, pg. 429). Wilson's method was used to calculate 95% confidence intervals for binomial proportions.

Outcomes

Outcomes were described using descriptive statistics and measures of association were calculated using regression models. Confounding variables were identified *a priori* based on the literature and clinical knowledge (see **Chapters 7-9**) and included in models. Analyses were based on each patient's first admission.

Binary outcomes for were modelled with logistic regression and reported as odds ratios (ORs) with 95% Wald confidence intervals. When the event rate in the reference group is high (i.e., >10%) and the effect large (i.e., OR>3), odds ratios deviate from relative risk and can no longer be multiplied by a patient's disease risk to predict outcomes. Therefore, relative risks were also calculated using Poisson models as a sensitivity analysis in some situations.^{37,38}

Time-to-event outcomes were plotted on Kaplan-Meier curves and analysed with Cox Proportional Hazards regression. Observations were censored at death or the last date the dataset was updated before analyses were undertaken (May 21, 2021).

Model fit

For regression models, I evaluated *goodness-of-fit*, by plotting binned residuals versus fitted values and evaluating the proportion falling within 95% confidence bounds and their distribution. Additionally, I evaluated linearity by plotting continuous variables against fitted values.

For logistic regression, the Hosmer-Lemeshow test also provides a statistical test for fit ($p < 0.05$) based on the comparison of observed vs expected event frequencies, but I did not use it because the large size of ORCHARD-EPR meant that the test was overly sensitive. For Poisson regression, I evaluated dispersion by dividing deviance by degrees of freedom, with ratios of ~ 1 indicating no dispersion (an assumption of the model). For survival analysis, I checked the proportional hazards assumption by visually inspecting plots of Schoenfeld residuals vs time for each covariate included in the models and performing a Schoenfeld test, which is based on the Chi-squared test.

I evaluated multicollinearity between covariates by including dummy variables in a linear regression model to obtain the variance inflation factor ($VIF > 5$ indicative of multicollinearity).

Software

I performed all statistical analyses in R version 4.2.1.

4.2.13 Training and skill development

I engaged in over 150 hours of training activities during my DPhil degree to develop the skills needed to prepare and analyse ORCHARD-EPR. These activities included courses, self-study and observational experiences.

Courses that I completed included:

- Planning, designing and critically appraising clinical research, Medical Sciences Division, University of Oxford (2020) – 3 hours of instruction
- Statistics for DPhils, Nuffield Department of Primary Care Health Sciences, University of Oxford (2020) – 8 hours of instruction
- Current Biostatistical Methods and Computer Applications, University of Saskatchewan (2021) – 30 hours of instruction
- Epidemiology II - Intermediate, University of Saskatchewan (2021) – 30 hours of instruction
- Introduction to Epidemiology, Department of Population Health, University of Oxford (2022) – 20 hours of instruction
- Observational research: Introduction to epidemiology, real-world data, prognostic models, machine learning, and health economics, Centre for Statistics in Medicine, Nuffield Department of Rheumatology and Orthopaedics, University of Oxford (2022) – 22h of instruction

- Statistical methods for risk prediction and prognostic models, Keele University (2023) – 20 hours of instruction

Self-study included the use of textbooks, academic articles and video/written tutorials, especially those related to R, HES and other routinely collected NHS data, interaction analyses, time-varying covariates and competing risk. I also participated in observational experiences to learn more about the NHS, acute care and older people's medicine. These activities included observing general medicine ward rounds and outpatient memory clinics led by Prof. Sarah Pendlebury at the John Radcliffe Hospital (>20 hours) and shadowing the Chief Medical Officer of OUHFT, Prof. Meghana Pandit (organised as part of Green Templeton College's Management in Medicine programme; 4 hours).

4.2.14 Patient and public involvement

ORCHARD-EPR was developed with input from a patient and public involvement (PPI) group, which includes patients, carers, Alzheimer's society representatives and a retired GP and was led by a researcher with experience in frailty and dementia studies (STP). I additionally had the opportunity to co-lead a PPI group (with KE and SS) which included nine participants from Oxfordshire and five other counties. Key themes that arose from both groups included the need for better information on confusion in hospital as well as prognosis and discharge-planning.

4.2.15 Reporting guidelines

Reporting of study data in this thesis was done according to Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for observational studies.³⁹

4.3 DISCUSSION

ORCHARD-EPR provides detailed phenotyping of cognitive and physical frailty makers in consecutive admissions hospital-wide and by specialty and is unique in terms of its size, inclusiveness and scope (i.e., >100,000 admissions hospital-wide from 2017-2019), differentiating it from existing routine clinical data studies.^{13-16,40}

ORCHARD-EPR also includes a large number of demographic and clinical covariates, allowing confounding and effect-modification by comorbidity, illness severity, deprivation and other variables to be accounted for.

Hospital-wide, EPR-embedded cognitive screen

Cognitive frailty data have direct implications for patient care, service-planning and policy, for example assessment of patients' capacity to consent to procedures.

ORCHARD-EPR exploits OUHFT's cognitive screening programme using a standard EPR-embedded form to obtain rich cognitive frailty data hospital-wide and by specialty. The OUHFT cognitive screen combines clinical assessments with a validated, objective test of cognitive function thus providing more comprehensive cognitive data than previous studies (see Introduction chapter, pg. 39). As described above, delirium was identified with the sensitive and specific (>90%) CAM screening tool to maximise ascertainment.¹⁸ Dementia was recorded if diagnosed prior to

admission with objective cognitive testing with the AMTS also done to identify deficits in people without cognitive diagnoses. The AMTS has acceptable sensitivity for moderate/severe deficits (i.e., MoCA<18) and was feasible for routine use in the acute setting although may miss mild deficits. The AMTS also cannot be done in all patients. Patients who cannot complete the AMTS are more likely to have cognitive problems, so reasons for 'untestability' on the EPR cognitive screening form were also extracted from ORCHARD-EPR.²²

Extensive phenotyping and outcomes data

ORCHARD-EPR also provides rich clinical information on physical frailty markers, diagnoses, illness severity and outcomes that are not available in other routine clinical and administrative datasets currently (for example, Reynish et al 2017, Anand et al 2022 and HES-APC).¹³⁻¹⁵ Data on frailty markers including mobility, malnutrition, incontinence and falls risk could be extracted from subscales from validated nursing assessments. Observation and laboratory test data allow different measures of illness severity to be calculated, although routinely used scores (i.e., NEWS) may have fewer missing data. Postal codes were used to derive IMD and identify patients potentially living in a care home using previously described methods.^{34,36} Longitudinal data on deaths from the Office of National Statistics provides information short- and long-term mortality whereas information on LoS, delayed discharge, discharge destination and readmissions within OUHFT provide valuable information on patient's transition from hospital to home. Collectively, these data will be useful for improving prognostication for cognitive frailty in patient subgroups for which data are limited, for example the severely ill, care home residents and people with varying levels of physical frailty.⁴¹ Not all variables that

might impact cognitive screening rates, prevalence and outcomes were included in ORCHARD-EPR (for example, language, ethnicity and the presence of carers/family) but given the “dynamic” design of ORCHARD-EPR could potentially be included in future iterations of the study.^{42,43}

4.3.1 ORCHARD-EPR compared to other studies

ORCHARD-EPR combines detailed phenotyping of cognitive and physical frailty markers, with inclusion of unselected consecutive admissions hospital-wide. In comparison, existing prospective cohorts of cognitive and physical frailty are mainly small (i.e., a few hundred participants), setting-specific, have restrictive eligibility criteria, for example excluding people with delirium or disturbed behaviour^{3,44} or use non-validated ascertainment methods (see Appendix Table 1.2-1.4, pg. 337-349).⁵ In contrast to prospective cohorts, most retrospective administrative data studies and datasets, such as HES-APC avoid selection bias due to opt-out consent and their non-obtrusive nature. However, these studies may have poor data accuracy, particularly when ICD-10 codes are used in the absence of clinical data, contributing to variation in reported results and are rarely validated.^{41,45} These issues are mitigated in ORCHARD-EPR, which contains rich cognitive data in unselected, consecutive admissions hospital-wide,^{14,46} and is supported by active monitoring of cognitive screening compliance via reporting/feedback mechanisms and other ‘interventions’ to improve data quality.⁸ ORCHARD-EPR is also differentiated from other routine datasets by its rich cognitive phenotyping data and large number of clinically-relevant variables. For example, Reynish et al, Romero-Ortuno et al. and Anand et al. assess delirium using screening tools whereas OUHFT clinicians are

instructed to diagnose delirium. Moreover, Romero-Ortuno et al., the only hospital-wide routine clinical data study identified, only diagnosed delirium in patients with a history of dementia. Anand did not report dementia. Lastly, ORCHARD-EPR is differentiated by its focus on data quality: frontline clinicians and the hospital informatics team were involved in the early development of the dataset and data are periodically compared to reference dataset of prospectively collected audit data (see **Chapter 5**).^{11,13-16}

4.3.2 Strengths and limitations

ORCHARD-EPR fills an important gap among studies of cognition in the acute care setting. However, the data and analyses described in this chapter have several limitations. First, ORCHARD-EPR contains data collected by clinicians who will have different priorities and capabilities when collecting and recording data compared to trained research staff—as is the case in all real-world studies. About 23% of patients in the 2017-2019 cohort did not have cognitive screening or other cognitive data due to service pressures or low clinician engagement. Second, data are from a single NHS Trust providing care in region with relatively low levels of deprivation which may impact generalisability even though the full range of deprivation (i.e., IMD deciles) are represented. Of note, IMD was not significant in preliminary analyses so was not included in the analyses shown in this thesis (data not shown). It is possible that the IMD measure is less applicable to older populations—education and employment account for >1/3 of the index, although the index includes a measure of income deprivation affecting older people.⁴⁷ Third, validated clinical frailty assessments (e.g., the Clinical Frailty Scale) were only introduced during the pandemic so are not

available for my study. Therefore, frailty markers and administrative data scores will be used to measure (physical/global) frailty instead. Fourth, the decision to include people with no cognitive data in the denominator for prevalence will result in underestimation of prevalence although these patients appear to mostly be at low risk of cognitive problems.

4.3.3 Conclusion

In conclusion, ORCHARD-EPR is a valuable research resource for studying cognitive and physical frailty in the real-world acute hospital setting, unique in terms of its size, scope and extensiveness. Analysis of ORCHARD-EPR will allow me to estimate the burden and outcomes of cognitive frailty and physical frailty by age, sex and specialty which will be valuable for patient care, service-planning and policy and overcome some of the limitations of previous prospective and administrative data studies. It will also allow for the exploration of effect-modification, improving estimation and understanding of the impacts of frailty in key patient subgroups for which data are limited thereby filling important gaps in the literature.

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Chapter 5

Validation of dementia and delirium

ascertainment in hospital EPR data:

Comparison of ORCHARD-EPR to a ‘gold-standard’ general medicine cohort

ABSTRACT

Background: Many older people with unplanned admissions hospital-wide have global or physical frailty but good quality data on the burden of cognitive frailty in this population are more limited, with most existing studies being small, selected prospective cohorts or large-scale but insensitive administrative coding studies. Routinely acquired clinical data captured in electronic patient records (EPRs) offers an alternative to existing research methods. Several datasets capture routine cognitive screening data recorded in EPRs, but none have been validated. I aimed to compare cognitive screening data for ORCHARD-EPR to prospectively collected audit data.

Methods: I included general medicine admissions ≥ 70 years with a length of stay (LoS) ≥ 1 day in both cohorts. ORCHARD-EPR (2017-2019) data include a standard cognitive screen comprising existing dementia diagnosis, delirium diagnosis (informed by the Confusion Assessment Method-CAM), and 10-point Abbreviated Mental Test-AMT which is mandated for patients ≥ 70 years. Delirium and dementia questions were answered as yes/no/uncertain by the administering clinician and supplemented with ICD-10 codes to maximise sensitivity. Diagnoses were “certain” if delirium/dementia=“Yes” on the cognitive screen or ICD-10 codes were recorded. Diagnoses were “uncertain” if delirium/dementia=“Uncertain” and no ICD-10 codes were recorded. Comparisons included (i) cognitive frailty prevalence in ORCHARD-EPR vs the audit cohort; and (ii) correlates and outcomes of certain vs uncertain delirium in ORCHARD-EPR.

Results: Of 18,614 general medicine admissions in ORCHARD-EPR (mean/SD age=82.9/7.4 years), 35% (95% CI 34-36; n=6,534) had certain cognitive frailty compared to 50% (95% CI 365/731) in the audit cohort ($p<0.001$). Most of the difference in prevalence was related to delirium: certain delirium was present in 17% of ORCHARD-EPR (95% CI 16-17%; 3,077/18,614) and uncertain in 11% (10-11%; 2,007/18,614) compared to 38% (34-42%; 277/731) based on DSM-IV criteria in the audit cohort. Frailty (Standardised Mean Difference-SMD=0.207) but not comorbid dementia (SMD=0.009) was more common in certain vs uncertain delirium. In-hospital mortality was similar for certain and uncertain delirium vs no delirium (adjusted OR=1.71, [1.51 to 1.94], $p<0.001$ and 1.79, [1.55 to 2.06], $p<0.001$).

Conclusion: ORCHARD-EPR achieved acceptable ascertainment rates for cognitive frailty compared to prospectively collected audit data. Most of the difference in prevalence between the two cohorts was attributable to uncertain delirium diagnoses in ORCHARD-EPR which accounted for 40% of all delirium. Patients with uncertain delirium were also a high-risk group, with similar outcomes to certain delirium. Overall, findings support the use of routine cognitive screening data in hospital EPRs for research. In the next chapters, I will determine the prevalence and outcomes of cognitive frailty in ORCHARD-EPR hospital-wide and by specialty.

5.1 INTRODUCTION

Global and physical frailty was prevalent hospital-wide and associated with worse clinical outcomes in older people with unplanned hospital medicine admissions (Chapters 2 & 3), but there are few reliable, large-scale studies of cognitive frailty in this population (see Introduction chapter).¹⁻³ Reliable estimates of burden of cognitive frailty are needed hospital-wide and by specialty, but existing prospective cohorts are mostly small and limited to specific clinical services and/or selected populations as described earlier.⁴⁻⁶ Widespread adoption of electronic patient records (EPRs) has increased the availability of large-scale routine (also known as *real-world*) clinical data for research. Several large routine clinical datasets reporting on cognitive frailty in hospital are available, including the Oxford Cognitive Comorbidity, Frailty and Aging Research Database (ORCHARD-EPR), which is unique in terms of its size, scope, inclusiveness and detail as described in **Chapter 4**, but none have been internally or externally validated yet.⁷⁻¹¹

Prospective data collection by trained research staff following standard protocols is the gold-standard for observational research, but routine data can fill key knowledge gaps if found to be accurate as outlined in the **Introduction** chapter (see Table 1.1, pg. 42). First, routine data can be obtained at scale and over multiple years at relatively low cost compared to traditional prospective study designs. Second, the use of pseudonymised EPR data can allow for near-complete coverage of the target population thus limiting selection bias. Waiver of consent with the option of opt-out is often appropriate given the non-invasive nature of most routine data studies and is useful for facilitating the inclusion of participants with impaired capacity to consent who might otherwise be excluded, thus avoiding ‘healthy volunteer bias.’ A third related point is that rich phenotypic information can be obtained from clinical data in the EPR without burdening patients and families. Patients who are frail or unwell may not be able to tolerate additional research assessments such as long questionnaires, blood testing and neuroimaging in addition to those performed as part of their routine care.¹²

The incorporation of routine clinical assessments, such as the mandatory Oxford University Hospitals NHS Foundation Trust (OUHFT) cognitive screen, into research databases such as ORCHARD-EPR also offers advantages for research and service-planning over solely administrative datasets, such as Hospital Episode Statistics (HES) as discussed in Chapter 4.^{13,14} However, the value of routine data collection has been debated due concern about the burden of performing assessments on staff and poor data quality,¹⁵ but no studies have validated real-world, routine cognitive screening for accurately identifying delirium, known dementia and objective cognitive test deficits. Therefore, I compared large-scale routinely

acquired cognitive screening data from the OUHFT EPR in ORCHARD-EPR to prospectively collected audit data for general medicine admissions in this chapter.

5.2 METHODS

5.2.1 Study design

I compared data from two different studies conducted in OUHFT hospitals: (i) real-world cognitive data recorded in ORCHARD-EPR 2017-2019 (hereafter 'ORCHARD-EPR') versus (ii) a reference standard of prospectively collected audit data (hereafter 'audit') from consecutive admissions to one acute general medicine team at the John Radcliffe Hospital over six 8-week cycles from 2010-2018 (September–November 2010, April–June 2012, October–December 2015, June–July 2016 and November 2017–January 2018, September–November 2018). Admissions included in audit data from 2017-2018 were omitted from the ORCHARD-EPR dataset to avoid duplication. The ORCHARD-EPR cohort was limited to general medicine patients, which comprised two-thirds of unplanned admissions, to match the audit data for main analyses (audit data were unavailable for other specialties). ORCHARD-EPR was approved by the South Central – Oxford C Research Ethics Committee (REC: 18/SC/0184). The prospective audits were approved by the OUHFT audit team (Datix: 2197) and subsequently approved for inclusion in research studies. For both studies, individual consent was not required, but individuals could request to opt-out.

5.2.2 Setting

The OUHFT consists of four urban hospitals (John Radcliffe Hospital, Nuffield Orthopaedic Centre, Churchill Hospital, Horton General Hospital). The OUHFT general medicine department provides care for all adult general medicine admissions with no separate system for older people.

5.2.3 Eligibility

People admitted to general medicine who were ≥ 70 years with a length of stay ≥ 1 day and age, sex and one or more ICD-10 codes recorded were included in main analyses for both cohorts. Only first admissions were retained to maintain statistical independence between observations.

5.2.4 OUHFT cognitive screen

Since 2015, the OUHFT has mandated that all patients with unplanned admissions ≥ 70 years of age or younger patients at high-risk (e.g., multiple sclerosis, stroke history, altered behaviour) receive a cognitive screen via a proforma embedded in the EPR comprised of:

- The 10-point Abbreviated Mental Test Score (AMTS). A low AMTS suggests a cognitive problem, with an $AMTS < 8$ considered abnormal.¹⁶
 - Where the AMTS could not be completed, clinicians were required to provide a free-text reason.
- “Does the patient have a known diagnosis of dementia?” “Yes/No/Uncertain*”
- “Does the patient have delirium?” “Yes/No/Uncertain*”

Note: the option to select “Uncertain” was only available for ORCHARD-EPR and not the audit dataset.

The cognitive screen was administered to patients in ORCHARD-EPR and the audit cohorts. Further detail on the administration of the cognitive screen in each cohort is provided below.

5.2.5 ORCHARD-EPR 2017-2019

ORCHARD-EPR was described in detail in **Chapter 4**. In brief, ORCHARD-EPR is a research resource including pseudoanonymised routinely acquired data extracted from the OUHFT EPR for all consecutive adult hospital and ambulatory care admissions (aged ≥ 65 years and high-risk younger patients with a completed cognitive screen or test).

The OUHFT cognitive screen was administered to eligible patients (see above) by the admitting clinician, normally a junior doctor. Delirium diagnosis was made with the aid of screening tools (i.e., Confusion Assessment Method—CAM and 10-point AMTS). Clinicians received training in delirium including on the DSM criteria and screening tools (CAM and AMTS) at regular teaching and governance meetings.¹³ Formally diagnosed dementia (i.e., prior to admission) was confirmed with the patient, relatives, and/or by review of medical records.

5.2.6 Audit data 2010-2018

The audit cohort is described in full in Pendlebury *et al* (2015).⁶ All patients admitted to one acute general medicine team at the John Radcliffe Hospital during audit cycles were seen <24 hours of admission by an experienced consultant physician dual-accredited in acute general medicine and geriatrics (STP) every other day until discharge, death, or transfer.

All patients ≥ 70 years received the OUHFT cognitive screen on admission administered by the admitting junior doctor who was trained in its use as described above for ORCHARD-EPR. However, delirium was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) criteria by STP after discussion with the medical team and other members of the multidisciplinary team and review of notes and all available information as appropriate.¹⁷

5.2.7 Cognitive frailty definitions

Cognitive frailty was defined as the presence of one or more of delirium, dementia diagnosed prior to admission or score <8 on cognitive testing with the AMTS.¹⁶ In both ORCHARD-EPR and the audit cohort, I defined cognitive frailty using data from both the cognitive screen **and** ICD-10 codes to maximise sensitivity. ICD-10 codes are reported by professional medical coders at the end of an admission based on the EPR (including free-text records), with dementia and delirium codes shown to have high specificity.¹³ See **Chapter 4** for more detail.

In either cohort, I defined dementia as “certain” if:

- “Yes” was recorded for the dementia question on the EPR proforma; and/or
- One or more dementia ICD-10 codes (F00.X, F01.X, F02.X, F03.X, F05.1, G30.X, F1X.7) were recorded.

Similarly, I defined delirium as “certain” in either cohort if:

- “Yes” was recorded for the delirium question on the EPR proforma; and/or
- One or more delirium ICD-10 codes (F05.X, F1X.4) were recorded.

For the audit data, the dementia/delirium questions were recorded by clinicians as “Yes” or “No” only. For ORCHARD-EPR, in which the cognitive screen was not routinely reviewed by a consultant, the dementia/delirium questions could be recorded as “Yes,” “No,” or “Uncertain” by clinicians.

The “Uncertain” option was provided to enable ascertainment of cases where a cognitive diagnosis was suspected but was difficult for clinicians working under real-world time-constraints and pressures to confirm at the time of assessment, for instance due to fluctuations in the patient’s symptoms or uncertainty about their baseline cognitive function. In the literature, delirium assessment based on the CAM is highly specific (~99%) but less sensitive (~80%).¹⁸ Alternate diagnoses that may be considered include subsyndromal delirium which was added to the DSM-5 but remains an evolving concept, as well as dementia and depression.^{19,20} However, the onset and presentation of delirium, dementia and depression differs and where diagnostic errors are made, delirium is more likely to be misdiagnosed than vice-versa (with one study finding that 28/67 older hospital patients referred to a

psychiatric consultation service for depressive symptoms had delirium).^{17,21} For these reasons, I compared uncertain and certain delirium groups and evaluated the impact of defining cognitive frailty based on uncertain+certain cases on prevalence and outcomes.

5.2.8 Covariates

All other clinical data fields were obtained from assessments completed by medical, nursing, allied health, or administrative staff as part of routine patient care as per Chapter 4. I derived markers of comorbidity (Charlson Comorbidity Index-CCI), illness severity (Systemic Inflammatory Response Syndrome criteria-SIRS, National Early Warning Score-NEWS version 1) and frailty (Hospital Frailty Risk Score-HFRS) for both cohorts as described (see summary in Box 5.1). Of note, the HFRS assigns points for coded delirium (as well as dementia), but medical coders were only able to assign codes if delirium was recorded as “Yes” on the cognitive screen or documented appropriately later during the admission. To mitigate bias related to potential coding differences between the “Yes” and “Uncertain” groups, I used a modified version of the HFRS excluding coded delirium (ICD-10 codes: F05X, F1X4, i.e., mHFRS) in some analyses. Using this approach, missing or absent data was replaced by the mean of available variables.²² Note that for descriptive analyses, the 109-item HFRS was used including coded delirium.²³

Box 5.1 Summary of covariates described in Chapter 4

Illness severity

- **Systemic Inflammatory Response Syndrome (SIRS) score:**²⁴ Available for both cohorts
- **National Early Warning Score (NEWS) version 1:**²⁵ Only available for ORCHARD-EPR
 - NEWS was used to as a secondary measure for comparing illness severity in delirium="yes" vs "uncertain" groups because it includes additional markers not in SIRS

Comorbidity

- **Charlson Comorbidity Index (CCI):**²⁶ Available for both cohorts
 - NHS Summary Hospital-level Mortality Indicator weightings were used for both cohorts²⁷

'Global' frailty

- **Hospital Frailty Risk Score (HFRS):**²³ Available for both cohorts
 - Calculated using ICD-10 codes for each admission as described by Gilbert et al. (2018)²⁸
 - Note: A modified HFRS (mHFRS) excluded coded delirium was used in some analyses

5.2.9 Outcomes

I assessed outcomes including deaths reported by the Office of National Statistics (in-hospital, 30 days post-discharge and from 30 days post-discharge up to 1 year), length of stay (LoS in days and LoS $\geq$ 7 days), delayed transfers in care (DTOC in days and DTOC $\geq$ 2 days), discharge other than to home and readmissions within 30 days of discharge as described in **Chapter 4**. To avoid potential bias in the denominator due to the competing risk of death, delayed transfers of care, discharge destination and readmission were only determined for patients who survived to discharge.

5.2.10 Statistical methods and analysis

I compared real-world (ORCHARD-EPR) and reference standard (audit data) cognitive diagnoses for general medicine admissions using descriptive statistics and hypothesis testing because direct comparison (i.e., in the same patients) was not possible. Additionally, within ORCHARD-EPR general medicine admissions, I compared characteristics and outcomes of certain and uncertain delirium.

Descriptive statistics

I calculated descriptive statistics for demographic, patient characteristics and outcomes as described in **Chapter 4** for both cohorts. I calculated prevalence and 95% confidence intervals using Wilson's method for binomial proportions in both cohorts and compared prevalence using the two-sided, Z-test for proportions.

Prevalence of cognitive frailty in both cohorts

I compared the prevalence of dementia and delirium in the audit data to ORCHARD-EPR according to different case definitions (i.e., certain only versus certain+uncertain). In addition, whether cases were identified from the cognitive screen or ICD-10 codes was reported.

Certain and uncertain delirium in ORCHARD-EPR

I explored the prevalence, characteristics and outcomes of the 'uncertain' delirium group in ORCHARD-EPR. Using the standardised difference, i.e., $|\bar{x}_1 - \bar{x}_2|/s$ as per Flurry and Riedwyl²⁹, I compared means of variables associated with delirium in medical patients, including age, sex, comorbidity, cognitive or functional impairment (i.e., diagnosed dementia or care home resident), uncertain dementia (a proxy for

unknown cognitive baseline), severe illness, hyponatremia, incontinence, frailty (HFRS) and markers of infection for certain vs uncertain delirium.^{6,30} The SMD allows comparison of variables on different unit scales and as per its name, represents the mean difference in standard deviation, with values 0.1-0.2 generally considered potentially significant, 0.2-0.5 small, 0.5-0.8 medium and ≥ 0.8 , large.^{31,32}

I calculated uni- and multivariable odds ratios (ORs) for outcomes for delirium="Yes," and "Uncertain" vs "No" using dummy variables. Wald *p*-values for delirium="Uncertain" vs "Yes" were obtained by repeating the analysis with delirium=yes as the reference group. I sequentially added age, sex, CCI (0, 0-5, >5)²⁷ and NEWS (Low, Low-Medium, Medium, High) to models. Additionally, I investigated the impact of dementia (certain cases) and frailty (HFRS) on delirium outcomes by stratifying data and including interaction terms in models. I assessed linearity between continuous variables, multicollinearity and model fit as per **Chapter 4** (also see example in Appendix Figure 5.1). Inclusion was limited to admissions for which age, sex, CCI and NEWS scores were available in outcomes analyses.

Comparison of ORCHARD-EPR and audit cohorts

I compared the prevalence of dementia and delirium in the audit data to ORCHARD-EPR as described above to validate data and did similar comparisons for the AMT-10. In addition, I compared characteristics for each group with cognitive frailty, i.e., delirium only (certain+uncertain cases), dementia only (certain cases only), delirium on dementia and AMT<8 in the absence of delirium or known dementia, between cohorts to confirm that the patient groups identified as having cognitive frailty in ORCHARD-EPR were similar to those in the audit cohort.

Statistical software

I performed all statistical analyses in R version 4.2.1 using the packages *stats*, *performance* and the *tidyverse*.³³⁻³⁵

5.2.11 Contextualising findings

To provide additional context and support the generalisability of findings to other settings, three additional analyses were included. First, I made qualitative observations of cognitive screening on general medicine wards using overt, non-participant observation (see footnote¹). I recorded unstructured field notes during four general medicine ward rounds over a 12-hour period. A consultant, STP, who is also the OUFT Clinical Lead for Dementia and Delirium and Principal Investigator of ORCHARD-EPR (and my DPhil supervisor) led the ward rounds. I observed two ward rounds on the Emergency Assessment Unit and two on one of four Complex Medicine Units at the John Radcliffe Hospital in 2022 and discussed main findings with the consultant. After the ward rounds, I coded the data in three iterations to identify factors relevant to the completion and accuracy of cognitive screening. Second, in the ORCHARD-EPR dataset, reasons (free-text or drop-down list) were provided when AMT-10 was not feasible (n=2,565). I coded and categorised these data to supplement my ward round observations. Third, to explore the generalisability of findings from general medicine admissions in ORCHARD-EPR to

¹ I initially collected these notes for self-education, but subsequently decided to incorporate them into this chapter. The rationale for this decision was to support hypothesis generation and increase the transparency of the study by presenting information that, in part, informed subjective choices related to data analysis (i.e., grouping uncertain and certain delirium) and provided additional information about the cohort for which quantitative data were not feasible to obtain. I previously received basic training in ethnography by completing two undergraduate courses in medical anthropology.

other acute specialties for which audit data were not available, I calculated the proportion of cognitive screens with “Uncertain” recorded for dementia/delirium or “Not feasible” for the AMTS for each specialty.

5.3 RESULTS

5.3.1 Characteristics of ORCHARD-EPR and audit cohorts

Among 31,281 general medicine admissions in ORCHARD-EPR, 78% (n=24,527) had cognitive data recorded (i.e., cognitive screen and or ICD-10 codes for dementia or delirium). Of these, 18,614 were first admissions of unique patients (mean/SD age at first admission: 82.9/7.4 years) and 12,667 were repeated admissions (mean/SD age 83.5/7.2 years). Patients missing cognitive data were on average younger, with lower CCI scores and fewer frailty markers than those with completed cognitive screens or dementia/delirium codes. They also had shorter stays and lower in-hospital mortality (all $p < 0.001$; Appendix Table 5.1). Cognitive screen data were available for all 893 general medicine admissions in the audit cohort, of which 731 (82%) were unique patients. Demographic and clinical characteristics of the two cohorts were mostly similar (Table 5.1), including age, sex and SIRS with about 10% of first admissions ending in in-hospital death in either cohort ($p = 0.7$). CCI and HFRS scores, which are derived from ICD-10 codes, were higher in ORCHARD-EPR than in the audit cohort, but when data were restricted to more recent years (i.e., >2015, n=514 patients in the audit cohort), these differences were no longer significant ($p = 0.5$ for CCI and $p = 0.3$ for HFRS).

Table 5.1 ORCHARD-EPR 2017-2019 versus Audit 2010-2018 admission characteristics

	First admissions (N=18,614)		
Characteristic	ORCHARD-EPR 2017-2019, N = 18,614 ¹	Audit 2010-2018, N = 731 ¹	p-value ²
Age	82.9 (7.4)	82.7 (7.1)	0.6
Female sex	9,774 / 18,614 (53%)	389 / 731 (53%)	0.7
CCI	10.5 (10.4)	10.7 (10.7)	0.9
Frailty markers			
HFRS	7.9 (6.3)	6.9 (6.0)	<0.001
Fall history	6,306 / 15,065 (42%)	333 / 730 (46%)	0.045
Incontinence	3,471 / 15,097 (23%)	231 / 729 (32%)	<0.001
Braden score	17.9 (3.6)*	17.9 (3.6)*	>0.9
Observations and labs			
SIRS $\geq 2^{**}$	7,146 / 18,331 (39%)	189 / 496 (38%)	0.7
Low oxygen saturation	5,374 / 18,585 (29%)	147 / 513 (29%)	0.9
CRP >6 mm/L	13,077 / 16,994 (77%)	396 / 538 (74%)	0.07
Serum Na <135 mm/L	5,768 / 18,394 (31%)	184 / 581 (32%)	0.9
Length of stay (days)	3 (1, 9)	4 (2, 10)	0.066
In-hospital death	1,815 / 18,614 (9.8%)	74 / 731 (10%)	0.7

¹Mean (SD); n (%); Median (IQR) for length of stay

²t-test; Pearson's Chi-squared test, Fisher's exact test or Wilcoxon rank sum test (length of stay)

³Significant p-values bolded (<0.01)

*N audit=483, N ORCHARD-EPR=16,751

**P-values for each criterion: abnormal tympanic temperature (0.2), WBCC (white blood cell count; <0.001), HR>90 (heart rate; 0.5) and RR>20 (respiratory rate; 0.7)

5.3.2 Prevalence of cognitive frailty in both cohorts

Prevalence of certain cognitive frailty

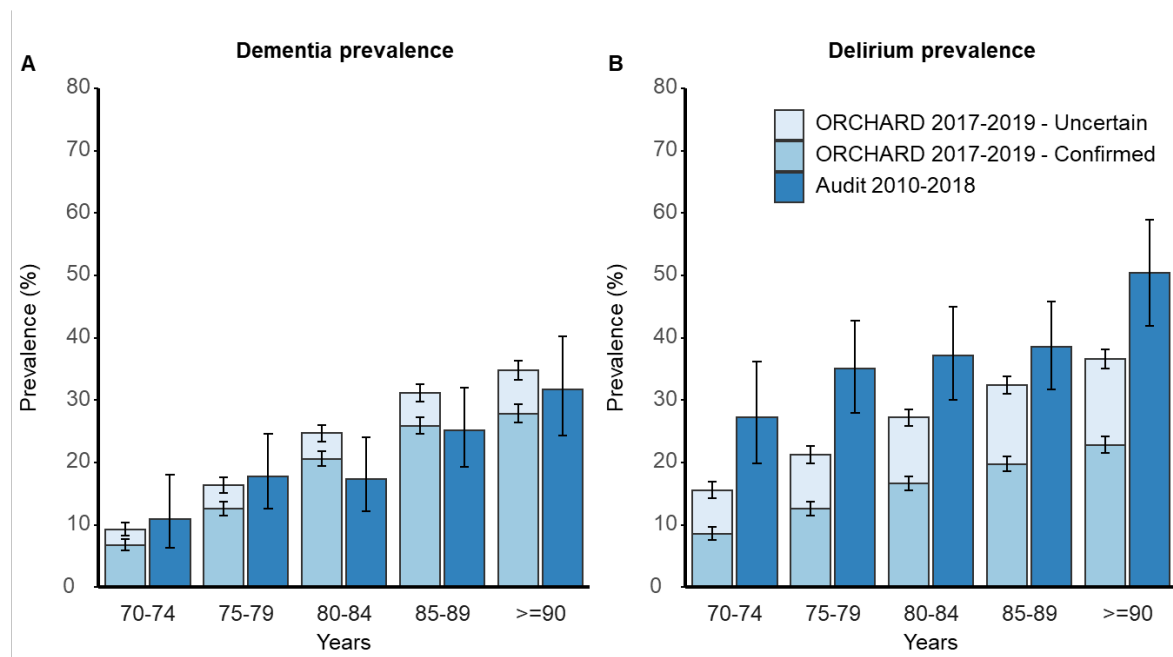
Overall, 35% (95% CI 34-36%; n=6,534) of ORCHARD-EPR general medicine patients had cognitive frailty when restricting the analysis to certain cases only (i.e., certain dementia, certain delirium, and/or AMTS<8) compared to 50% (95% CI 46-54%; n=365) of the audit cohort. There was little difference in the prevalence of dementia in the audit cohort (21%, [95% CI 18-24%]; n=153) compared to ORCHARD-EPR when restricted to certain cases (20%, [95% CI 19-20%]; n=3,637; $p=0.4$). The prevalence of delirium was 38% (95% CI 34-42%; n=277) in the audit cohort compared to 17% (95% CI 16-17%; n=3,077) when restricted to certain delirium in ORCHARD-EPR ($p<0.001$). Of note, about 60% of certain dementia (n=2,180/3,637) and delirium (n=1,783/3,077) in ORCHARD-EPR were identified through cognitive screening. The remainder of certain dementia/delirium cases were identified from ICD-10 codes (Appendix Table 5.2). About 19% of those recorded as having uncertain dementia/delirium on their initial cognitive screen had dementia/delirium ICD codes (dementia 204/1,068; delirium=473/2,480) compared to 4-5% who screened negative (dementia 403/9,415; delirium 431/8,400). About 14% (n=850/5,951) with missing cognitive screens had ICD codes for dementia and 6.6% (n=390/5,951) had ICD codes for delirium. Most commonly, the type of dementia or delirium coded for was unspecified (Appendix Table 5.3).

Prevalence of certain+uncertain cognitive frailty

In ORCHARD-EPR, an additional 864 patients had uncertain dementia (4.6%, [95% CI 4.3-5.0%] of cohort) and 2,007 had uncertain delirium (11%, [95% CI 10-11%]) in

the absence of coded dementia/delirium. Uncertain delirium accounted for about 40% of all delirium (i.e., certain+uncertain) in ORCHARD-EPR. Patients with uncertain delirium were younger (mean/SD age 84.5/7.1 years vs 85.1/7.0; $p<0.003$), with lower frailty scores (mean/SD HFRS 9.9/6.1 vs 13.6/6.7; $p<0.001$) and shorter hospital stays (median/IQR 5/2-13 days vs 7/3-16; $p<0.001$) compared to those with certain delirium (see Table 5.2). The prevalence of certain versus certain+uncertain delirium and dementia by age is shown in Figure 5.1. The prevalence of dementia in ORCHARD-EPR was 3% higher than that in the audit cohort when certain+uncertain cases were included (24%, [95% CI 24-25%]; $n=4,501$; $p=0.04$). The prevalence of delirium was 27% (95% CI 27-28%; $n=5,084$) when uncertain+certain cases were included, i.e., 11% lower than in the audit cohort ($p<0.001$).

Figure 5.1 Prevalence of (A) diagnosed dementia and (B) delirium in ORCHARD-EPR 2017-2019 vs audit data 2010-2018 by age and definition



Note: N for age groups in ORCHARD-EPR 70-74 years=3,089, 75-79=3,364, 80-84=4,124, 85-89=4,244, ≥90=3,793 vs audit datas 70-74 years=110, 75-79=157, 80-84=156, 85-89=179, ≥90=129.

5.3.3 Correlates of certain and uncertain delirium

Delirium diagnosis in people with certain dementia in both cohorts

Diagnosis of delirium may be challenging in patients with pre-existing cognitive impairment. About one-third of patients in either cohort had dementia and delirium concurrently (Figure 5.2). In ORCHARD-EPR, certain dementia did not impact the certainty of delirium diagnosis ($\chi^2=0.0861$; $p=0.8$; $df=1$): 39% of all delirium in those with certain dementia was uncertain ($n=773/1,972$; 95% CI 37-41%) compared to 35% in those without ($n=846/1,972$; 95% CI 33-37%). However, most delirium was uncertain in the group with uncertain dementia (58%, 388/666; $\chi^2=122.9$; $p<0.001$; $df=2$ compared to the no dementia group). AMTS scores for patients by delirium and dementia status are shown in Figure 5.3.

Figure 5.2 Concurrent dementia and delirium in (A) Audit 2010-2018 and (B) ORCHARD-EPR 2017-2019 cohorts

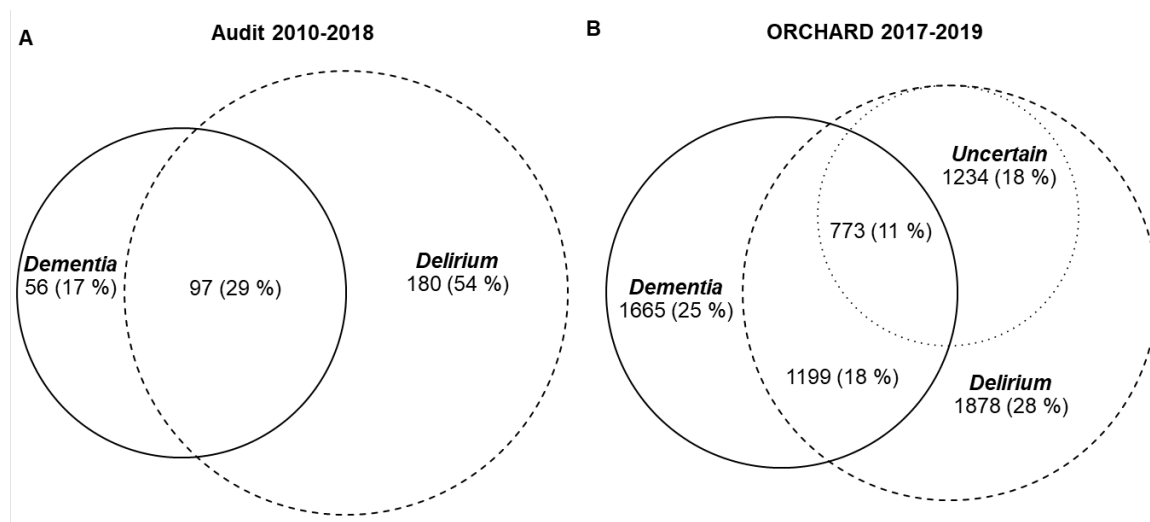
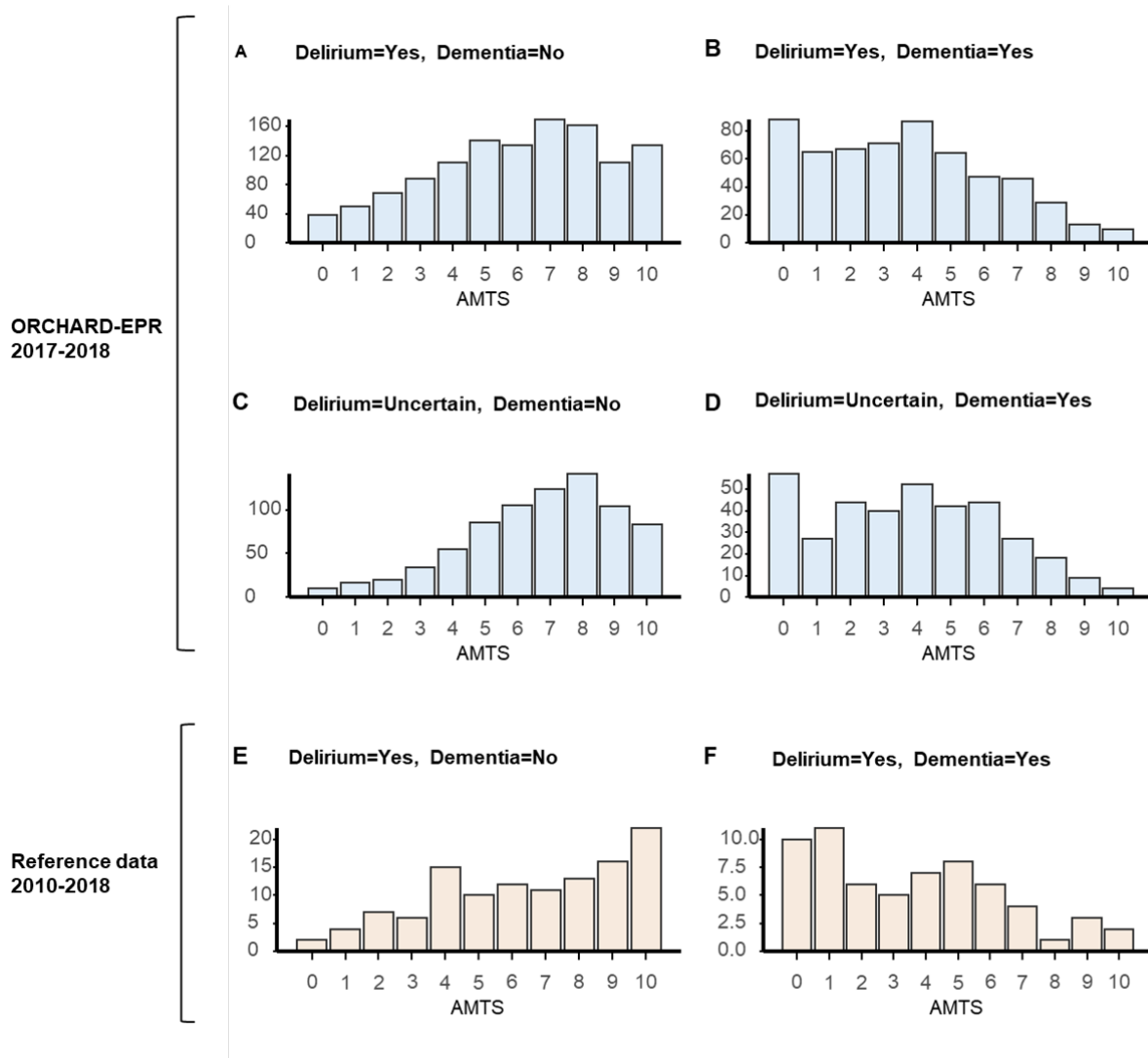


Figure 5.3 Histograms showing distribution of AMTS scores in ORCHARD-EPR and audit cohorts by delirium and dementia status

For ORCHARD-EPR, AMTS scores for certain **(A, B)** and uncertain delirium **(C,D)** in the absence **(A, C)** and presence **(B, D)** of dementia are shown. For the audit (a.k.a., reference data), AMTS scores for delirium in the absence **(E)** and presence of dementia **(F)** are shown. Lower scores suggest greater impairment.



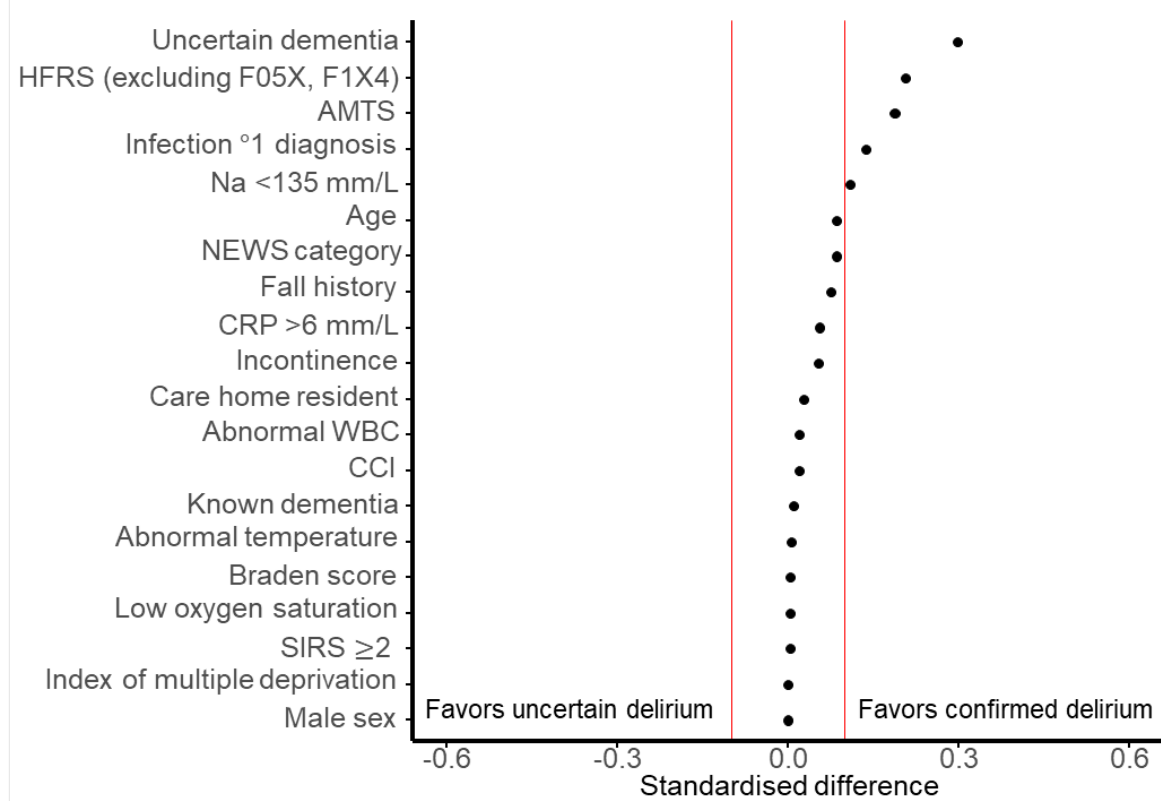
5.3.4 Additional correlates of certain vs uncertain delirium in ORCHARD-EPR

To further investigate patient characteristics associated with the certainty of delirium diagnosis, I calculated SMDs for uncertain vs definite delirium groups (see Figure 5.4). SMDs provide a standardised measure of the difference between two groups. Dementia, discussed above, had SMDs of 0.298 for uncertain dementia compared to 0.009 for certain for certain delirium groups. The HFRS (excluding coded delirium) had a SMD=0.207, with 46% (428/925) of delirium in the low-risk frailty group (HFRS<5) classified as uncertain compared to 40% (1,188/2,976) in the moderate group (HFRS 5-15) and 33% (391/1,183) in the high-risk group (HFRS≥15). Several other variables had SMDs >0.1 including the AMTS (SMD=0.187), infection as the primary diagnosis (0.136) and hyponatraemia (Na <135 mm/L; 0.109).

5.3.5 Outcomes of certain and uncertain delirium in ORCHARD-EPR

Delirium, whether certain or uncertain, was associated with a broad range of adverse health outcomes in ORCHARD-EPR, including after adjustment for age, sex, CCI, and NEWS in the 18,353 patients for whom NEWS scores were available (patients missing NEWS scores or sex were excluded; Table 5.2, Table 5.3 and full models in Appendix Table 5.5). Patients with delirium, whether uncertain (311 / 1,982; unadjusted OR 2.27 vs adjusted 1.79, 95% CI 1.55 to 2.06; $p<0.001$) or certain (448 / 3,041; unadjusted OR 2.10 vs adjusted OR 1.71, 95% CI 1.51 to 1.94; $p<0.001$) had a greater risk of death in hospital, i.e., ~15-16% ($p=0.6$) compared to 8% (1,019 / 13,330) in those with no delirium. Both uncertain and certain delirium remained associated with death 30 days following discharge and up to one-year later ($p<0.001$ both vs no delirium).

Figure 5.4 Standardised difference for mean values of variables hypothesised to be related to uncertain vs certain delirium diagnosis in ORCHARD-EPR 2017-2019 general medicine admissions



Legend: Vertical red lines mark a standardised difference of ± 0.1 , which indicates that standardised differences may be significant. Missing values were excluded.

Patients with delirium also stayed longer in hospital, with 48% (1,460 / 3,041) of those with certain diagnoses (unadjusted 2.89 vs adjusted 2.62, 2.41 to 2.84 $p < 0.001$), 40% (799 / 1,982) with uncertain (unadjusted 2.11 vs adjusted 1.92, 1.74 to 2.12; $p < 0.001$) and 24% (3,229 / 13,330) with no delirium staying ≥ 7 days. They were more likely to have delayed transfers of care ($p < 0.001$). Of 16,575 people with discharge data, 34% (845 / 2,516) with certain delirium were discharged to a place other than home (unadjusted OR 3.0 vs adjusted 2.7, 2.36 to 2.87; $p < 0.001$) compared to 27% with uncertain (442 / 1,637; unadjusted OR 2.19 vs adjusted 1.95, 1.72 to 2.20; $p < 0.001$) and 14% with no delirium (1,743 / 12,138). Associations

between length of stay, delayed transfers of care and discharge destination were strongest for certain delirium ($p < 0.001$), with these findings hypothesised to be related to frailty and possibly dementia. After dementia (“Uncertain,” “Yes” and “No” groups) was added to models with an interaction term, the strength of association for these outcomes was no longer significantly different for uncertain and certain delirium groups for all outcomes except LoS ($p = 0.008$ for LoS; $p > 0.08$ for all other outcomes; Appendix Table 5.6-5.9), with similar findings for frailty (Appendix Tables 5.10-5.13) and stratification of variables.

Associations between delirium and readmission <30 days after discharge were modest, with 13% with certain delirium readmitted (361 / 2,485; crude OR 1.25 vs adjusted 1.15, 1.02 to 1.31; $p = 0.027$) compared to 12% with uncertain (215 / 1,630; crude 1.11 vs adjusted 1.03, 0.88 to 1.20; $p = 0.7$) and 15% (1,428 / 11,910) with no delirium. Hospital-wide outcomes will be investigated in Chapters 7 and 8.

Table 5.2 Descriptive table of characteristics and outcomes stratified by delirium result on the cognitive screen

Delirium status (N=18,249)					
Characteristic	N at risk ¹	None, N = 13,330 ²	Uncertain, N = 1,982 ²	Certain, N = 3,041 ²	p-value ³
Clinical and demographic*					
Age	-	82.1 (7.3)	84.4 (7.1)	85.1 (7.0)	<0.001
Sex	-	6,879 / 13,330 (52%)	1,092 / 1,982 (55%)	1,677 / 3,041 (55%)	<0.001
CCI	-	9.2 (9.6)	13.8 (11.4)	14.1 (11.6)	<0.001
HFRS**	-	6.3 (5.3)	10.0 (6.1)	13.6 (6.7)	<0.001
Known dementia	-	1,638 / 13,330 (12%)	763 / 1,982 (38%)	1,183 / 3,041 (39%)	<0.001
SIRS ≥2	-	4,982 / 13,157 (38%)	812 / 1,948 (42%)	1,261 / 3,014 (42%)	<0.001
Outcomes					
Death					
- In hospital	18,353	1,019 / 13,330 (7.6%)	311 / 1,982 (16%)	448 / 3,041 (15%)	<0.001
- 30 days PD	16,575	655 / 12,311 (5.3%)	163 / 1,671 (9.8%)	205 / 2,593 (7.9%)	<0.001
- 30-365 days PD	15,552	2,080 / 11,656 (18%)	367 / 1,508 (24%)	587 / 2,388 (25%)	<0.001
LOS (days)	-	3 (1, 7)	5 (2, 13)	7 (3, 16)	<0.001
- >7 days	18,353	3,229 / 13,330 (24%)	799 / 1,982 (40%)	1,460 / 3,041 (48%)	<0.001
DTOC (days)	-	7 (4, 14)	8 (5, 13)	8 (5, 13)	<0.001
- ≥2 days	16,575	1,156 / 12,311 (9.4%)	311 / 1,671 (19%)	636 / 2,593 (25%)	0.3
Discharge to different residence*	16,291	1,743 / 12,138 (14%)	442 / 1,637 (27%)	845 / 2,516 (34%)	<0.001
Readmissions within 30 days PD	16,025	361 / 2,485 (15%)	1,428 / 11,910 (12%)	215 / 1,630 (13%)	0.002

Legend: PD = post-discharge. LOS = length of stay. DTC = delayed transfers of care.¹N at risk: includes either the full cohort, those who survived to discharge or 30 days PD. *Discharge destination information was not known for n=284 admissions.

²n (%); Median (IQR)

³Pearson's Chi-squared test; Kruskal-Wallis rank sum test

^{*}P-values for uncertain vs certain delirium groups were 0.005 (age), >0.9 (sex), 0.5, (CCI), <0.001 (HFRS), 0.8 (dementia) and >0.9 (SIRS).

Table 5.3 Outcomes of uncertain vs certain delirium versus no delirium
Unadjusted and adjusted model (age, sex, comorbidity and illness severity) shown. See Appendix Table 5.5 for full models.

	No delirium (OR=1)	Uncertain delirium					Certain delirium					P-value uncertain vs certain
Outcome	Events/N	Events/N	Crude OR	Adjusted OR	95% CI	p-value	Events/N	Crude OR	Adjusted OR	95% CI	p-value	p-value
Death												
In hospital	1,019 / 13,330	311 / 1,982	2.27	1.79	1.55, 2.06	<0.001	448 / 3,041	2.10	1.71	1.51, 1.94	<0.001	0.6
30 days	655 / 12,311	163 / 1,671	1.93	1.57	1.30, 1.88	<0.001	205 / 2,593	1.55	1.24	1.05, 1.46	0.012	0.034
1 year	2,080 / 11,656	367 / 1,508	1.48	1.24	1.09, 1.41	<0.001	587 / 2,388	1.50	1.24	1.11, 1.38	0.001	>0.9
Other												
LOS >7 days	3,229 / 13,330	799 / 1,982	2.11	1.92	1.74, 2.12	<0.001	1,460 / 3,041	2.89	2.62	2.41, 2.84	<0.001	<0.001
DTOC >2 days	1,156 / 12,311	311 / 1,671	2.21	1.97	1.71, 2.26	<0.001	636 / 2,593	3.14	2.76	2.47, 3.08	<0.001	<0.001
Discharge to different residence	1,743 / 12,138	442 / 1,637	2.19	1.95	1.72, 2.20	<0.001	845 / 2,516	3.00	2.60	2.36, 2.87	<0.001	<0.001
Readmission <30 days	1,428 / 11,910	215 / 1,630	1.11	1.03	0.88, 1.20	0.7	361 / 2,485	1.25	1.15	1.02, 1.31	0.027	0.2

5.3.6 AMT-10 test in both cohorts

The distribution of AMTS scores in ORCHARD-EPR and audit cohorts was similar (**Figure 5.5**; Mann-Whitney test $p=0.003$, and median of the difference in scores between samples from the two cohorts= 4×10^{-5}) and the proportion of correct responses were similar for all components of the AMT-10, except year (ORCHARD-EPR: 73% vs Audit: 66%; $p=0.008$; Appendix Table 5.4). The AMT-10 was not feasible in 14% of ORCHARD-EPR (2,565/18,614) compared to 12% (88/731) of the audit cohort ($p=0.2$). I coded seventeen different reasons for the test not being feasible, with the most common reasons being patient too unwell ($n=1,189$), uncooperative ($n=628$), dysphasic ($n=327$), language barrier ($n=132$) or hearing impaired ($n=70$; Figure 5.6).

Figure 5.5 AMTS scores in ORCHARD-EPR compared to audit data

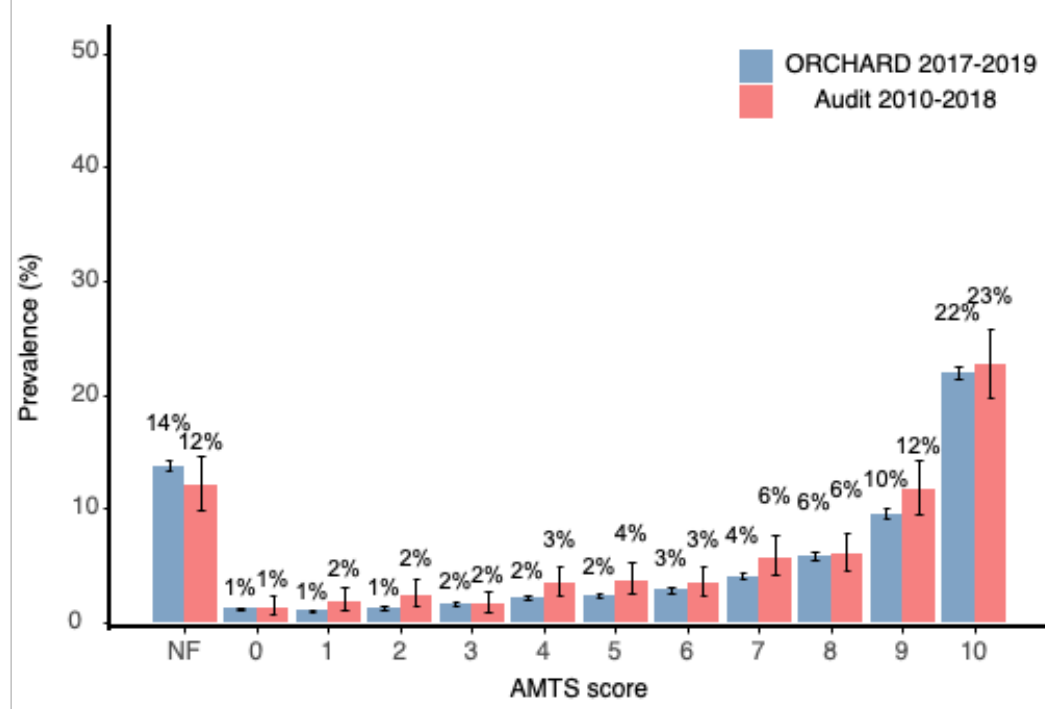
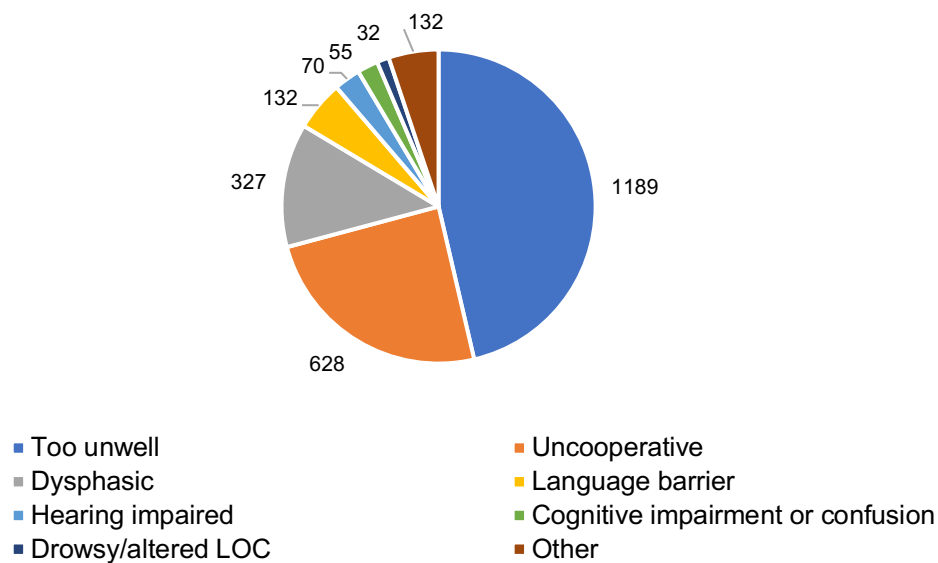


Figure 5.6 Reasons AMTS could not be performed (n=2,565)



Legend: 'Other' included testing was not thought to be required (n=23), communication problem not further specified (n=22), patient absent or sleeping (n=21), not feasible due to other symptoms (n=17), unclear or not reported (n=15), testing was felt to be inappropriate or not a priority (n=15), speech problem (n=8), distress/mental state (n=7), other test performed (n=4). LOC = level of consciousness.

5.3.7 Characteristics of ORCHARD-EPR vs audit cohorts by type of cognitive frailty

To further examine the definitions of cognitive frailty used in ORCHARD-EPR, I provided a table of participant characteristics in ORCHARD-EPR and the audit dataset stratified by cognitive frailty subtype (Table 5.4). Based on the findings above, cognitive frailty was defined as delirium alone (certain+uncertain cases), dementia alone (certain cases), delirium on dementia and AMTS<8 in the absence of delirium or known dementia. Characteristics including age, illness severity, length of stay and mortality were mostly similar between cohorts.

Table 5.4 Characteristics of groups with cognitive impairment in ORCHARD-EPR vs the audit cohort
Dementia was defined as certain cases only. Delirium included certain + uncertain cases.

Characteristic	Dementia only			Delirium only			Delirium superimposed on dementia			AMTS<8 in the absence of dementia or delirium		
	ORCHARD-EPR, N = 2,691 ¹ (8.5%)	Audit, N = 75 ¹ (8.4%)	p-value ²	ORCHARD-EPR, N = 5,515 ¹ (17%)	Audit, N = 215 ¹ (24%)	p-value ²	ORCHARD-EPR, N = 3,778 ¹ (12%)	Audit, N = 130 ¹ (15%)	p-value ²	ORCHARD-EPR, N = 1,078 ¹ (3.4%)	Audit, N = 39 ¹ (4.4%)	p-value ³
Age	86 (81, 90)	85 (80, 90)	0.5	85 (79, 90)	83 (78, 88)	0.072	86 (82, 90)	86 (79, 89)	0.10	86 (80, 90)	83 (76, 88)	0.036
Female	1,484 (56%)	47 (63%)	0.2	2,937 (54%)	127 (59%)	0.12	2,074 (56%)	68 (52%)	0.5	604 (57%)	24 (62%)	0.6
CCI	22 (18, 31)	18 (18, 30)	0.006	9 (0, 16)	7 (0, 14)	0.067	22 (18, 31)	20 (18, 29)	0.012	8 (0, 16)	8 (0, 14)	0.4
HFRS	9.4 (6.0, 14.1)	9.2 (4.3, 13.1)	0.12	10.3 (6.5, 14.8)	8.4 (4.9, 13.8)	<0.001	14 (9, 19)	13 (9, 19)	0.4	8.0 (4.6, 11.8)	5.3 (1.9, 8.7)	<0.001
AMTS	7 (5, 9)	5 (3, 7)	<0.001	7 (4, 8)	7 (4, 9)	0.087	4 (2, 6)	3 (1, 5)	0.4	-	-	
Low SpO2	803 (30%)	14 (25%)	0.5	1,663 (30%)	53 (32%)	0.7	1,064 (28%)	31 (29%)	0.8	307 (28%)	13 (43%)	0.077
Abnormal temperature	684 (25%)	11 (21%)	0.4	1,587 (29%)	44 (27%)	0.5	1,015 (27%)	38 (36%)	0.042	304 (28%)	8 (28%)	>0.9
Abnormal WBC	956 (36%)	22 (30%)	0.3	2,283 (42%)	91 (43%)	0.7	1,517 (41%)	52 (40%)	0.9	371 (35%)	13 (33%)	0.9
CRP >6 mm/L	1,945 (78%)	33 (63%)	0.010	4,453 (84%)	152 (84%)	>0.9	3,000 (83%)	80 (75%)	0.040	823 (81%)	22 (69%)	0.087

Characteristic	Dementia only			Delirium only			Delirium superimposed on dementia			AMTS<8 in the absence of dementia or delirium		
	ORCHARD-EPR, N = 2,691 ¹ (8.5%)	Audit, N = 75 ¹ (8.4%)	p-value ²	ORCHARD-EPR, N = 5,515 ¹ (17%)	Audit, N = 215 ¹ (24%)	p-value ²	ORCHARD-EPR, N = 3,778 ¹ (12%)	Audit, N = 130 ¹ (15%)	p-value ²	ORCHARD-EPR, N = 1,078 ¹ (3.4%)	Audit, N = 39 ¹ (4.4%)	p-value ³
Na <135 mm/L	699 (26%)	12 (20%)	0.3	1,925 (35%)	72 (39%)	0.3	885 (24%)	24 (22%)	0.8	341 (32%)	8 (23%)	0.3
SIRS ≥ 2	993 (37%)	19 (37%)	>0.9	2,344 (43%)	62 (39%)	0.3	1,531 (41%)	47 (45%)	0.5	414 (39%)	12 (41%)	0.8
Braden score	17 (14, 19)	17 (14, 20)	0.4	17 (14, 19)	17 (14, 19)	0.2	15 (13, 18)	16 (13, 18)	0.3	17 (15, 20)	18 (15, 21)	0.2
Care home resident*	1,118 (42%)	28 (37%)	0.5	1,355 (25%)	50 (23%)	0.7	1,835 (49%)	66 (51%)	0.6	274 (25%)	14 (36%)	0.14
Fall history	1,139 (56%)	46 (61%)	0.3	2,326 (51%)	116 (54%)	0.5	1,761 (60%)	96 (74%)	0.002	478 (53%)	22 (56%)	0.7
Incontinence	719 (35%)	39 (52%)	0.002	1,620 (35%)	90 (42%)	0.049	1,513 (50%)	94 (73%)	<0.001	244 (27%)	12 (31%)	0.6
Length of stay	3 (1, 9)	4 (2, 8)	0.4	6 (3, 14)	7 (3, 15)	0.8	6 (2, 15)	6 (2, 16)	>0.9	5 (2, 13)	4 (2, 10)	0.4
In hospital death	259 (9.6%)	8 (11%)	0.8	872 (16%)	35 (16%)	0.9	570 (15%)	21 (16%)	0.7	87 (8.1%)	2 (5.1%)	0.8

¹Median (IQR); n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test

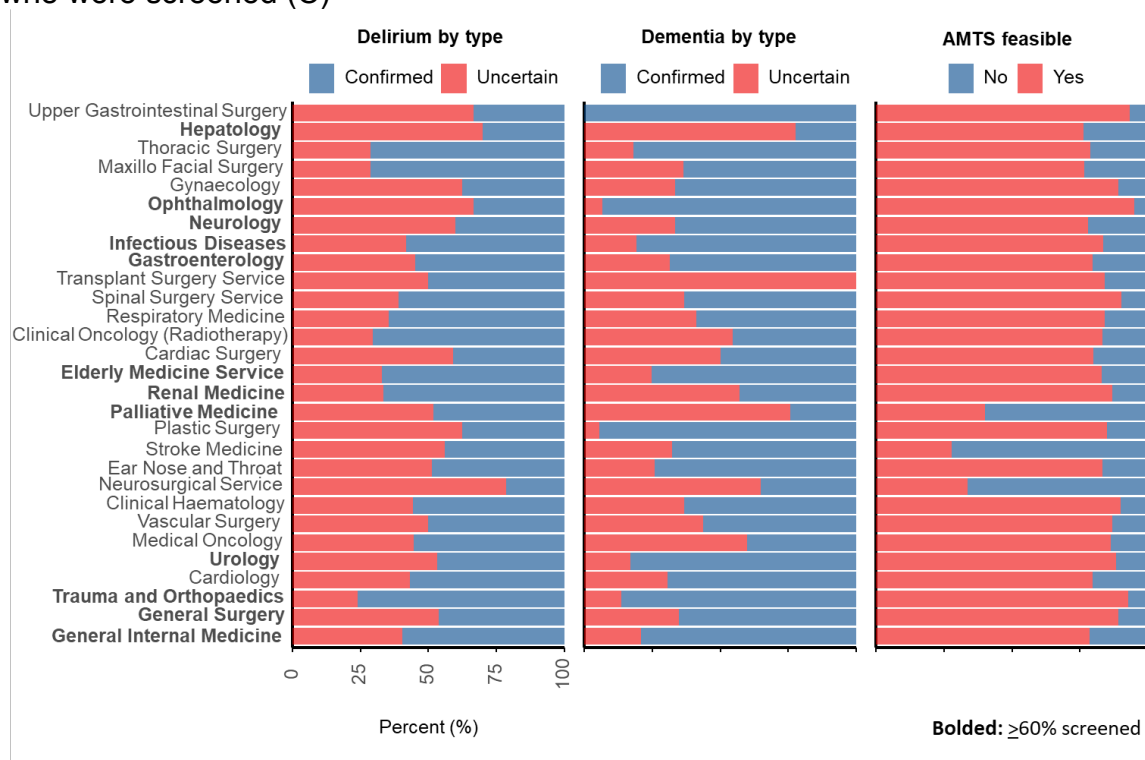
³Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

*Based on postal code

5.3.8 Putting findings into context

I identified several factors relevant to the completion and accuracy of cognitive screening through overt, non-participant observation of general medicine ward rounds. Completion of the screen was challenging in patients with decreased arousal or acute problems (also see Figure 5.6). Delirium symptoms could be subtle, with limited information on patients' baseline cognition also contributing to uncertainty according to the consultant, who was an experienced physician dual certified in geriatrics and general medicine (STP). She noted that even experienced clinicians face uncertainty in diagnosing delirium although most cognitive screening was done by junior doctors. Prioritisation of cognitive screening differed by setting: the consultant and multidisciplinary team encouraged completion of the screen on the Complex Medicine Unit by asking for information on patients' cognitive status, whereas on the Emergency Assessment Unit, cognitive screening was in competition with other priorities including investigations and treatment of 'physical' symptoms (Appendix Table 5.14 & 5.15). Qualitative and audit data were not available for other specialties, but cognitive screening data for general medicine compared to other specialties are shown in Figure 5.7.

Figure 5.7 Summary of cognitive screen results by specialty in ORCHARD-EPR (n=51,202) including the proportion certain vs uncertain on the cognitive screen for delirium (A), dementia (B) and AMT-10 assessments that were feasible in patients who were screened (C)



5.4 Discussion

I found that the prevalence of any-cause cognitive frailty in general medicine admissions was 39% in ORCHARD-EPR based on the combination of delirium="Yes" or "Uncertain" on the cognitive screen and/or diagnostic codes, compared to 50% in audit data from the same setting, with most of the difference attributable to the lower prevalence of delirium reported for ORCHARD-EPR. Overall, 40% of delirium in ORCHARD-EPR was uncertain (even after classifying those with diagnostic codes as "Yes"), with uncertain diagnoses not explained by dementia or other measured variables including age, comorbidity, and illness severity.

I found that the prevalence of any delirium in ORCHARD-EPR was 11% lower than that in the audit data (27% including certain and uncertain cases in ORCHARD-EPR vs 38% in audit), whereas in normal practice (i.e., no mandated screening or multidisciplinary intervention) up to 70% of cases may be missed.^{13,36} About 40% of delirium in ORCHARD-EPR was recorded as uncertain (i.e., about 11% of admissions). Delirium was most often recorded as uncertain in the group with uncertain dementia, which may represent patients with an unknown cognitive baseline but certain dementia was not associated with uncertainty in delirium diagnosis in ORCHARD-EPR. In contrast, a previous study of delirium recognition in nurses reported an association with dementia, possibly because symptoms overlap (in particular in severe or Lewy body disease).^{37,38} Global frailty, a known risk factor for delirium, was associated with certain delirium diagnosis in ORCHARD-EPR including after coded delirium was removed from the HFRS.³⁹ However, in another

study delirium was unrecognised more often in people with frailty measured with the CFS.⁴⁰ Physical frailty was not associated with delirium severity or duration, but may impact the presentation of delirium.⁴¹ hypoactive symptoms are strongly associated with unrecognised delirium (OR=7), but were not recorded in ORCHARD-EPR.³⁷

Delirium, regardless of whether uncertain or certain, was associated with increased death in hospital and up to one year after discharge over and above age, sex, comorbidity, and illness severity on admission, with both groups similarly high-risk as expected. Certain delirium was more strongly associated with longer stays in hospital, delayed transfers of care and discharge to a destination other than home, compared with uncertain delirium and no delirium. Subgroup analysis suggested that this relationship was modified by frailty, measured by the HFRS.⁴² Delirium was not associated with readmission overall, taking into account the competing risk of mortality, which may be a sign of successful post-discharge planning or reflect that 35% (2,534/3,825) individuals with cognitive frailty were admitted from care homes which can be resourced to support people with impaired function returning from hospital.⁴³

Compared to other routine clinical data and prospective studies done in the general medicine and hospital setting, the prevalence of dementia and delirium in ORCHARD-EPR was remarkably similar. Diagnosed dementia was identified in 20% of admissions in ORCHARD-EPR versus 21% in the audit data and 18-62% in three other prospective general medicine and hospital-based studies (and 10-17% in two

routine clinical data studies),^{4,44-47} although the true prevalence may be higher as some cases are undiagnosed at the time of admission.⁵ Delirium, both uncertain (11%) and certain (17%), was present in 27% of ORCHARD-EPR (38% in the audit data) 10-49% in ten other prospective general medicine and hospital-based studies (and 14-25% in two routine clinical data studies).^{36,44,48-57} For comparison studies reliant on diagnostic codes from administrative datasets such as HES reported rates of delirium as low as 0.4-3%,^{58,59} although ascertainment of dementia tended to be better (i.e., 7-26%).^{23,60-63} Associations between delirium and outcomes in ORCHARD-EPR were similar to those reported in the literature.^{64,65}

5.4.1 Strengths and limitations

The main strength of this study is that it fills an important gap in the evidence on the validity of real-world cognitive frailty data by comparing prevalence to prospectively collected audit data in consecutive, unselected general medicine admissions. This study has several limitations. First, real-world and audit data came from different patients, so comparisons were indirect. Additionally, the cohorts covered different but overlapping time periods which could have impacted findings, although most characteristics (e.g., age, illness severity) did not differ between cohorts. Second, cognitive frailty is most likely underestimated in ORCHARD-EPR because 23% of patients did not receive a cognitive screen, although the group that was missing cognitive data tended to have fewer risk factors for dementia and delirium. Third, all data were obtained from one NHS acute care trust which implemented programs to improve the documentation of cognitive diagnoses.¹³ Additionally, suitable audit data

were only available for general medicine, so findings on the validity of data in ORCHARD-EPR may not be fully generalisable to other specialties. Fourth, the qualitative component of this chapter is most appropriately considered for hypothesis-generating due to limitations in data collection.

5.4.2 Implications

My findings demonstrate that routine cognitive screening in the hospital setting can provide useful data for research and audit, with cognitive data available for $\geq 75\%$ of admissions in ORCHARD-EPR and an estimated 95% of known dementia and 70% of delirium identified. Despite the multidisciplinary intervention implemented prior to this study,¹³ about 40% of delirium was recorded as uncertain, illustrating the challenges of real-world diagnosis. Uncertain dementia and frailty appeared to contribute to uncertainty, suggesting that access to cognitive assessments done in the community may improve delirium diagnosis in acute care. Moreover, both certain and uncertain delirium groups were at an increased risk of a broad range of adverse health outcomes including after adjustment for age, sex, comorbidity, and illness severity, with differences possibly accounted for by interaction effects between delirium and frailty or (uncertain) dementia status. This finding provides evidence to support the rule of thumb that “any suspected or uncertain case [...] should be treated as delirium until proven otherwise,” (Inouye et al., 2014; page 916).⁶⁶ Because it is not always possible to reach a definitive diagnosis, the NHS National Clinical Coding Standards allows ‘probable’ and ‘presumed’ diagnoses to be

coded.⁶⁷ If the 'uncertain' response option was changed to 'probable' or 'likely' then additional delirium cases would likely be coded and counted.

5.4.3 Conclusion

I demonstrated that routine cognitive screening achieved reasonable ascertainment rates for cognitive frailty compared to prospectively collected audit data when certain and uncertain cases of delirium were combined. Together with the finding that both certain and uncertain delirium groups were at an elevated risk for a broad range of adverse health outcomes including mortality, long stays in hospital, delayed discharge and discharge to a place other than home, it appears reasonable to define delirium as certain+uncertain cases in main analyses in subsequent chapters.

Overall, my findings support the routine collection of clinical data on cognitive frailty in hospital EPRs and use for research and audit purposes.

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Chapter 6

Prevalence of cognitive frailty hospital-wide and by specialty in ORCHARD-EPR

ABSTRACT

Background: Over one-third of older people with unplanned admissions to hospital are frail as shown in Chapter 2, but data on the burden of delirium, dementia and other cognitive frailty in this population are more limited. Hospital-wide and specialty-specific prevalence estimates are needed for service-planning including understanding the role of non-geriatricians in caring for this population. In this study, I aimed to determine the prevalence of cognitive frailty, i.e., delirium, dementia, delirium on dementia and low abbreviated mental test score (AMT<8) in older people with unplanned hospital admissions hospital-wide and by specialty.

Methods: ORCHARD-EPR includes pseudo-anonymised EPR data for consecutive admissions with a length of stay of >1 day (2017 to 2019) to four general hospitals in Oxfordshire, UK, regardless of specialty. Data include a standard cognitive screen comprising dementia history, delirium diagnosis (informed by the Confusion Assessment Method-CAM), and 10-point Abbreviated Mental Test-AMTS which is mandated for patients ≥ 70 years on admission. I analysed the ORCHARD-EPR data

to determine the prevalence of cognitive frailty (defined as delirium, diagnosed dementia, delirium+dementia or AMTS<8 without delirium/dementia) trust-wide and by specialty (n=29 specialties with >50 admissions).

Results: Among 51,202 admissions (mean/SD age=82/7 years), any cognitive frailty was present in 34.5% (95%CI 34.0-34.9%; n=17,644) of which delirium accounted for 14.6% (n=7,484), delirium+dementia=9.4% (n=4,805), dementia=7.5%, (n=3,821), AMTS<8=3% (n=1,534). The prevalence of cognitive frailty in general medicine, general surgery and trauma/orthopaedics, which accounted for 80% of admissions (n=41,016), was 41% (n=13,879), 21% (n=801) and 35% (n=1,304) in each, respectively. The prevalence exceeded 20% in geriatric (44%; n=133/301), palliative (36%; n=128/356), stroke (29%; n=135/468), infectious disease (27%; n=41/152), and neurosurgery (22%; n=154/702) admissions and was 10-20% in all other specialties except two. Delirium was the most prevalent form of cognitive frailty in 24/29 specialties.

Discussion: Cognitive frailty was common in older unplanned hospital admissions across a broad range of specialties, with delirium accounting for most cases. Findings support the need for hospital-wide and specialty-specific training and service development to reflect the needs of this population and increased emphasis on delirium in research and policy. In the next chapter, I will determine outcomes by type of cognitive frailty in this population, including delirium with versus without diagnosed dementia.

6.1 INTRODUCTION

Specialist services are increasingly providing care to frail, older patients as the population ages in the UK and other countries.¹⁻⁵ There is much evidence on the prevalence of global/physical frailty hospital-wide, as well as in general medicine and several other acute care specialties. However, less is known about the burden of cognitive frailty in representative acute hospital populations and cognitive frailty is poorly captured by global frailty tools as shown in the systematic review in Chapter 2.^{6,7} Reliable estimates of the prevalence of cognitive frailty (i.e., dementia, delirium, delirium on dementia and cognitive test deficits) hospital-wide and by specialty are needed to plan services and guide policy and research to enable the provision of good quality care to this population (see **Box 6.1**).^{8,9}

Most existing cohorts reporting cognitive frailty data ascertained using clinically administered tools are limited to single conditions, populations or services—for example a study of dementia prevalence in medical patients excluded participants with delirium even though delirium is common in inpatients with dementia.¹⁰⁻¹²

Although “big data” retrospective studies have attempted to fill knowledge gaps by achieving near complete coverage of inpatient populations through large-scale hospital EPR data, most ascertain cognitive frailty from diagnostic codes alone.¹³⁻¹⁶

The prevalence of cognitive frailty, particularly dementia and delirium, in the general hospital population was reviewed in the **Introduction** chapter and is revisited below:

Box 6.1 Possible uses of cognitive frailty estimates, hospital-wide and by specialty

Planning clinical services

- Evaluate consent processes;
- Target cognitive screening programmes to relevant services;
- Inform the implementation of mobile versus ward-based frailty teams (i.e., ward-based teams in specialties with a high prevalence of cognitive frailty and mobile teams in specialties with lower prevalence);
- Inform staffing levels and skill-mix.

Health education and training

- Develop cognitive frailty health education curricular objectives;¹⁷
- Inform the development of skills training standards (e.g., Health Education England's Dementia Training Standards Framework).¹⁸

Research

- Inform the choice of funding priorities by identifying the burden of cognitive frailty in a hospital setting;
- Inform research ethics review and consent processes;
- Inform research design including target population, selection criteria and generalisability.

Estimates of the prevalence of dementia

Existing estimates for dementia prevalence hospital-wide in unplanned admissions are limited (see Appendix Table 1.3, pg. 343) with heterogeneity apparently related to variation in sample characteristics and ascertainment method. Most studies have been done on general medicine patients: a systematic review (minimum age across studies ≥ 55 years) reported prevalence rates of 13-63% (n=108-2,000) across

studies identifying dementia with validated criteria (i.e., DSM). Meta-analysis was not done, but prevalence appeared to vary with eligibility and sample characteristics.¹⁹ Hospital-wide, the prevalence of dementia ascertained prospectively using DSM criteria was 18% (≥ 65 years) and 25% (≥ 70 years) in two studies. Estimates for broad specialty categories were also reported, i.e., medical (26%) versus surgical (11%) admissions in one study; and medicine (21%), trauma (20%) and general surgery (13%) in the second.^{10,20} “Big data” studies have reported variable dementia prevalence (e.g., 7% in one study and 26% in a second using ICD-10 codes) likely explained by differences in coding accuracy.^{21,22} One study found that diagnostic coding had only 63% sensitivity compared to mental health records which may also underestimate prevalence.²³

Estimates of the prevalence of delirium

Similar to dementia, estimates of delirium prevalence hospital-wide and by specialty are also limited outside of general (see Appendix Table 1.2, pg. 337) and geriatric medicine. A systematic review of studies that ascertained delirium according to DSM or other validated criteria (minimum age across studies ≥ 66 years), reported a pooled prevalence of 23% (95% CI 19-26%) in mostly medical patients.²⁴ Some variation may relate to whether delirium was ascertained on admission (“prevalent”) only or included cases that developed in-hospital (“incident” or iatrogenic),¹² and also eligibility, sampling method and the need for consent. Delirium ascertained with the 4AT (confirmed with DSM criteria) was identified in 16% of a convenience sample, with estimates reported for acute medicine (18%), geriatrics (28%), stroke (6%), general surgery (9%) and orthopaedics (15%).²⁵ Retrospective data have also been used, but the prevalence of delirium identified varied widely from 0.1-64% using

specific diagnostic terms identified in discharge summaries to 1.5-49% using diagnostic codes, although natural language processing methods are also being explored.^{26,27} Coding sensitivity for delirium was improved from 13% to 60% after implementation of a multicomponent intervention over several years as discussed in **Chapter 4**, but would not be typical of most settings.²⁸

As explained previously, ORCHARD-EPR is a large, pseudonymised research database which includes comprehensive, detailed data from a routinely administered cognitive screen comprising documentation of dementia diagnosis (most commonly pre-existing dementia), delirium diagnosed with the help of the CAM/AMTS, and AMTS scores, supplemented with ICD-10 codes for dementia and delirium.²⁸ No studies report cognitive frailty prevalence (including both delirium and dementia) in unplanned admissions hospital-wide and by specialty. Thus, I aimed to determine the prevalence of cognitive frailty, including dementia, delirium, delirium on dementia and low cognitive test score in the absence of diagnosed delirium or dementia hospital-wide and across acute care specialties in this chapter.

6.2 METHODS

6.2.1 Study design

As per **Chapter 4**, ORCHARD-EPR 2017-2019 (hereafter 'ORCHARD') ORCHARD-EPR is a research database of pseudo-anonymised routine data from the Oxfordshire University Hospitals NHS Foundation Trust (OUHFT) EPR for all consecutive, unselected adult hospital and ambulatory admissions to four urban hospitals. Admissions are eligible for inclusion in the database if patients are aged

≥65 years or <65 if high-risk (e.g., brain injury, vascular disease, multimorbidity).

Individual consent was not required by the ethics committee but individuals could request to opt-out (REC reference: 18/SC/0184).

6.2.2 Eligibility

For this study, I included all unplanned admissions of patients ≥70 years to any specialty were included if they had a length of stay ≥1 day and age, sex and one or more ICD-10 codes recorded.

6.2.3 Cognitive screen and procedures

As described previously, OUHFT mandates that all patients with unplanned admissions ≥70 years of age or younger patients at high-risk receive a cognitive screen via a form embedded in the EPR including the following questions:

- The 10-point Abbreviated Mental Test Score (AMT; score out of 10)
- “Does the patient have a known diagnosis of dementia?” (‘Yes,’ ‘Uncertain,’ ‘No’; confirmed with patient, relatives and/or medical records)
- “Does the patient have delirium?” (‘Yes,’ ‘Uncertain,’ ‘No’; based on the Confusion Assessment Method-CAM)

ICD-10 codes were used to supplement the cognitive screen (see code list in **Chapter 4**). I defined dementia as a response of ‘Yes’ to the dementia question on the cognitive screen and/or one or more ICD-10 codes for dementia. As explained in **Chapter 5**, I defined delirium as defined as a response of ‘Yes’ or ‘Uncertain’ to the delirium question on the cognitive screen and/or one or more ICD-10 codes for

delirium for main analyses. In real-world clinical practice staff may be uncertain if a patient has delirium or not, especially on initial assessment, but delirium is likely missed more often than it is misdiagnosed in hospitals because of its high prevalence and the specificity of the CAM (~99%).²⁹ Lastly, data were reported for people with an AMTS<8 without diagnosed dementia or delirium, which may identify undiagnosed dementia, mild cognitive impairment, subsyndromal delirium or other transient deficits.³⁰

I obtained information on specialty from the 'Treatment Function' variable. Treatment Function is a Hospital Episode Statistics (HES) field which describes the service (department, team or unit) that treated the patient.³¹ I spot-checked treatment Function against ward identifiers for 1000 admissions (~2% of sample) to ensure that the two data fields corresponded. All other descriptors used in this chapter were obtained from assessments completed by clinical or administrative staff as part of routine care or derived as described (details are available in **Chapter 4**).

6.2.4 Analysis

I identified the treating specialty using the treatment function variable and included specialties reporting >50 admissions over the study period. I calculated prevalence by dividing the number of admissions with cognitive frailty by the total number of admissions including those who did not receive a cognitive screen and determined 95% confidence intervals using Wilson's method for binomial proportions. I calculated p-values with Wilcoxon (two groups) or Kruskal-Wallis rank sum tests (more than two groups), or Pearson's Chi-squared test (categorical data and trends) as appropriate.

Software

I performed all statistical analyses in R version 4.2.1 using the packages *stats* and the *tidyverse*.^{32,33}

6.3 RESULTS

6.3.1 Clinical and demographic characteristics

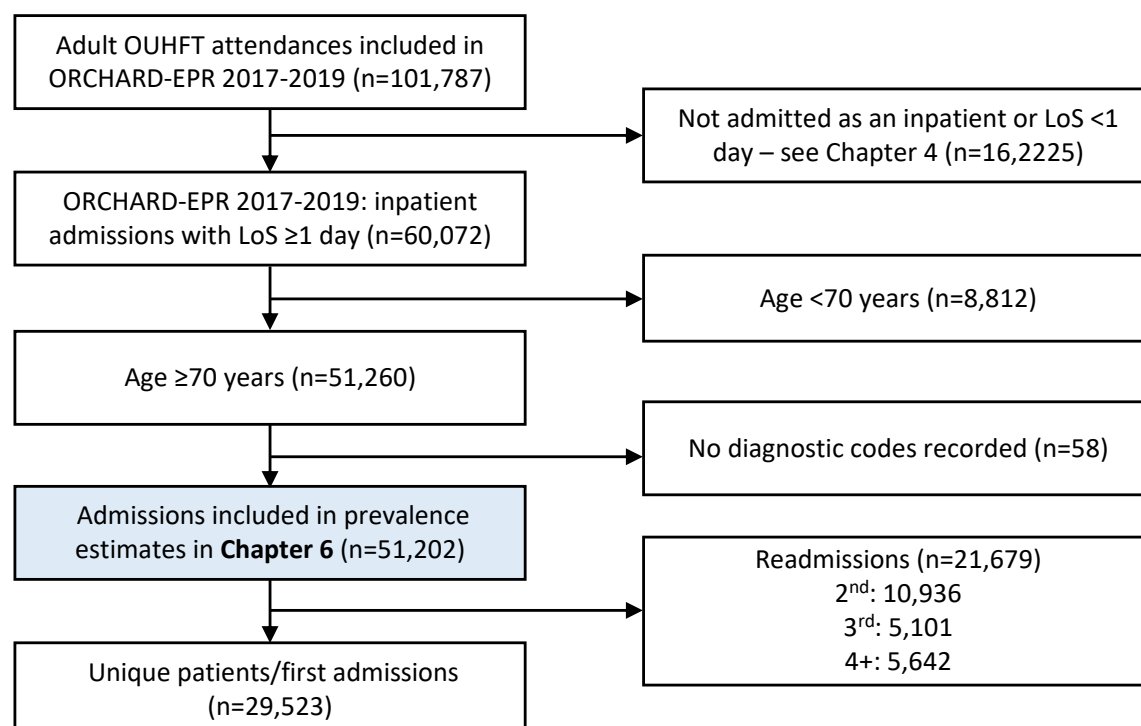
In total 51,202 admissions (mean/SD age of 82/7 years; 51% female) were included hospital-wide (Figure 6.1), of whom two-thirds were admitted to general medicine (n=33,512), with the remainder admitted to general surgery (n=3,819), trauma and orthopaedics (n=3,673) or other specialist medical (n=5,613) or surgical services (n=4,573). About 46% of admissions had moderate frailty (HFRS 5-10; n=23,317), 13% severe (HFRS ≥ 15 ; n=6,890) and 15% were resident in care homes prior to admission (n=7,567). In addition, 28% of the cohort (n=14,083) had an abnormal NEWS score, which is a proxy for illness severity. Cognitive data (i.e., a completed cognitive screen and/or ICD-10 codes for dementia or delirium) were available for 73% overall (78% of general medicine admissions), with missing data associated with younger age and less comorbidity, overall frailty and illness severity ($p < 0.01$; Appendix Table 6.1).

6.3.2 Prevalence of cognitive frailty

Overall, 34.5% (95% CI 34.0-34.9%; n=17,644) of patients with unplanned admissions hospital-wide had at least one cognitive frailty disorder. Patients with cognitive frailty were more likely to be older, live in a care home, and have higher

comorbidity, frailty and National Early Warning (NEWS) scores ($p<0.001$; characteristics by type of cognitive frailty are also shown in **Table 6.1**). Delirium was the most common type of cognitive frailty across all age groups, occurring in 24.0% of admissions hospital-wide. About 14.6% of admissions had delirium alone (95% CI 14.3-14.9; $n=7,484$; certain cases only=8.6%, 8.3-8.8%; $n=4,377$), whereas 9.4% had delirium superimposed on dementia (95% CI 9.1-9.6%; $n=4,805$; certain cases only=5.8%, 5.6-6.0%; $n=2,950$). Dementia in the absence of delirium (certain or uncertain) was also prevalent, with 7.5% (95% CI 7.2-7.7%; $n=3,821$) of admissions known to have a diagnosis prior to admission. A further 3% of admissions (95% CI 2.8-3.1%; $n=1,534$) had objective deficits on cognitive testing (AMTS<8) in the absence of delirium or a known dementia diagnosis.

Figure 6.1 Study eligibility (see Chapter 4 for more detail)



Note: “Treated in the community” includes patients who received treatment in “hub beds” in care homes and community hospitals for further rehabilitation, recovery and needs assessment outside the acute hospital.

Table 6.1 Clinical and demographic characteristics ORCHARD-EPR 2017-2019

Characteristic	Overall, ¹ N = 51,202	Any cognitive frailty, ¹ N = 17,644	Delirium, ¹ N = 7,484	Delirium on dementia, ¹ N = 4,805	Dementia, ¹ N = 3,821	AMTS<8, ¹ N = 1,5341	p- value ²
Age	82 (7)	85 (7)	84 (7)	86 (6)	85 (7)	85 (7)	<0.00 1
Female ³	25,858 (51%)	9,629 (55%)	3,982 (54%)	2,673 (56%)	2,119 (56%)	855 (56%)	0.016
Care home resident	7,567 (15%)	4,492 (25%)	1,369 (18%)	1,750 (36%)	1,090 (29%)	283 (18%)	<0.00 1
CCI	11 (10)	15 (11)	10 (9)	21 (9)	20 (9)	10 (9)	<0.00 1
HFRS	8 (6)	12 (7)	11 (6)	15 (7)	10 (6)	8 (6)	<0.00 1
Abnormal NEWS ³	14,083 (28%)	5,650 (32%)	2,580 (35%)	1,605 (34%)	1,063 (28%)	402 (26%)	<0.00 1

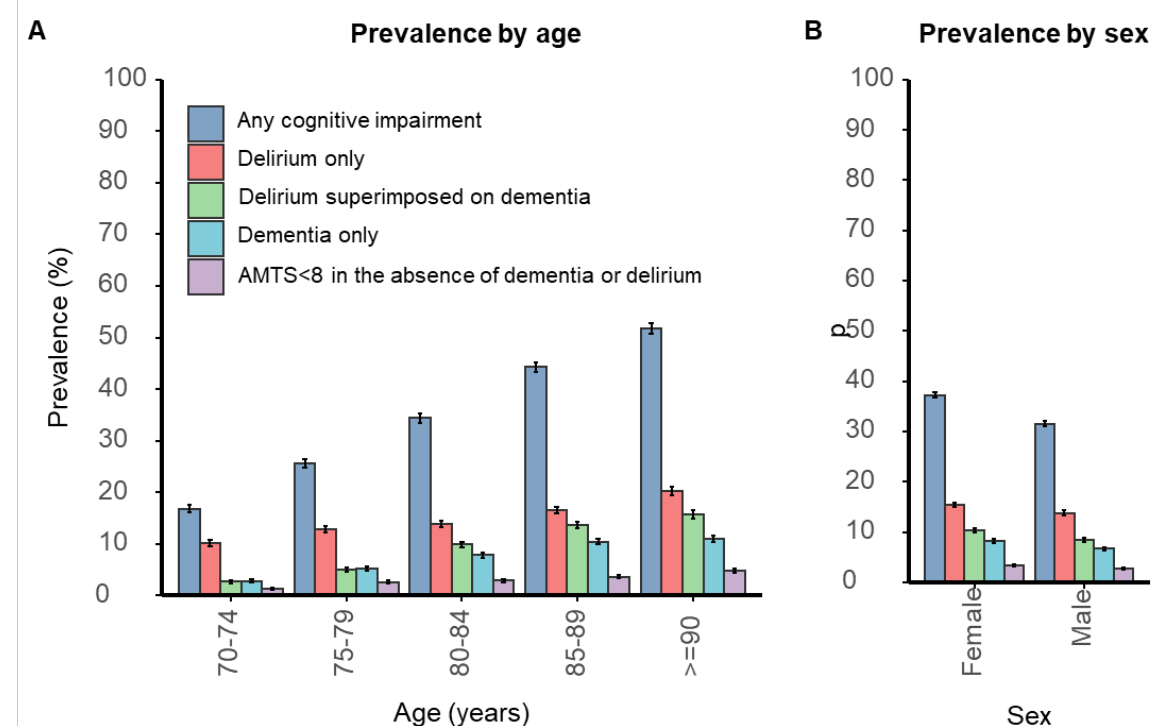
¹Mean (SD); n / N (%)²Wilcoxon rank sum test; Kruskal-Wallis rank sum test; Pearson's Chi-squared test³Sex missing for n=508; NEWS missing for n=961

6.3.3 Age- and sex-specific prevalence

The prevalence of any-cause cognitive frailty tripled from 16.8% of admissions aged 70-74 years (n=1,625/9,675) to 51.7% of those ≥ 90 years (n=4,725/9,140; p trend<0.001; **Figure 6.2** and Appendix Table 6.2). Delirium in the absence of dementia, which was the most common form of cognitive frailty *in all age groups*, approximately doubled from 10.1% (974/9,675) in the 70-74 age group to 20.3% (1,855/9,140) in those ≥ 90 years. Dementia in the absence of delirium was present in 2.8% (271/9,675) in the 70-74 age group, increasing almost four-fold to 10.9% (1,000/9,140) in those ≥ 90 years. Delirium superimposed on dementia increased approximately six-fold with age from 2.7% (260/9,675) in the 70-74 age group to 15.7% (1,434/9,140) in those ≥ 90 years. Low cognitive test score in the absence of any diagnosed dementia or delirium was the least common disorder in all age groups, increasing about four-fold from 1.2% (120/9,675; 53% AMT-10 completion

rate) in those 70-74 years to 4.8% (436/9,140; 79% AMT-10 completion rate) in those ≥ 90 years.

Figure 6.2 Prevalence of cognitive frailty, including subtypes, by age (A) and sex (B)



Note: (A) Any cognitive frailty prevalence by age was: 70-74 years: 1,625/9,675 (16.8%, 95% CIs 16.1-17.6%), 75-80 years: 2,607/10,216 (25.5%, 24.7-26.4%), 81-85 years: 3,925/11,424 (34.4%, 33.5-35.2%), 86-90 years: 4,762/10,747 (44.3%, 43.4-45.3%), ≥ 90 years: 4,725/9,140 (51.7%, 50.7-52.7%). See **Table S6.1** for age-specific prevalence by type of cognitive frailty. **(B)** Cognitive frailty prevalence in females (mean/SD age=83/7.5 years) was 9,629/25,858 (37%) overall and 7,837/24,837 (32%) in males (mean/SD age=81/7.0 years).

6.3.4 Specialty-specific prevalence

Cognitive frailty (any-cause) was identified in all 29 specialties examined, with a prevalence of $\geq 10\%$ in all except for transplant and upper GI surgery for characteristics of each specialty group; mean age ranged from 74-83 years across all individual specialties (see **Figure 6.3**). The prevalence of cognitive frailty was

highest in geriatrics (44.2%, 95%CI 38.5-50%; 133/301), general medicine (41.4%, 40.9-41.9%; 13,879/33,512) and palliative care (36.0%, 31.0-41.2%; 128/356; **Appendix Table 6.3**). However, a large proportion of admissions to trauma and orthopaedics (35.5%, 33.9-37.1%; 1,303/3,685), stroke (28.8%, 24.8-33.2%; n=135/468), infectious disease (27.0%, 20.3-34.9%; n=41/152), neurosurgery (21.9%, 19.0-25.2%; n=154/702) and general surgery (21.0%, 19.7-22.3%; n=801/3,819) also had cognitive frailty although screening rates across specialties varied (range 38-79%). As shown in Figure 6.4, delirium, with or without dementia, was the most common cause of cognitive frailty in 25/29 specialties examined, whereas dementia was predominant in urology, plastics, ear nose and throat (ENT) and ophthalmology.

Table 6.2 Characteristics of ORCHARD-EPR specialty groups

Variable	Overall, ¹ N = 51,202	General Medicine, ¹ N = 33,512	General Surgery, ¹ N = 3,819	Specialty Medicine, ^{1,4} N = 5,613	Specialty Surgery, ^{1,5} N = 4,573	Trauma and Orthopedics, ¹ N = 3,685	p-value ²
Age	82 (7)	83 (7)	80 (7)	79 (6)	79 (7)	83 (8)	<0.001
Female sex ³	25,858 (51%)	17,399 (52%)	1,982 (52%)	2,318 (42%)	38%	67%	<0.001
Care home resident	7,567 (15%)	5,940 (18%)	291 (7.6%)	438 (7.8%)	290 (6.3%)	628 (16%)	<0.001
CCI	11 (10)	12 (10)	7 (9)	11 (9)	8 (9)	9 (10)	<0.001
HFRS	8 (6)	9 (6)	4 (4)	5 (5)	5 (5)	11 (8)	<0.001
Abnormal NEWS ³	14,083 (28%)	11,401 (34%)	520 (14%)	1,196 (22%)	460 (10%)	506 (14%)	<0.001
Data on cognition?	37,478 (73%)	26,097 (78%)	3,003 (79%)	3,040 (54%)	2,468 (54%)	2,870 (78%)	<0.001

¹Mean (SD); n / N (%)

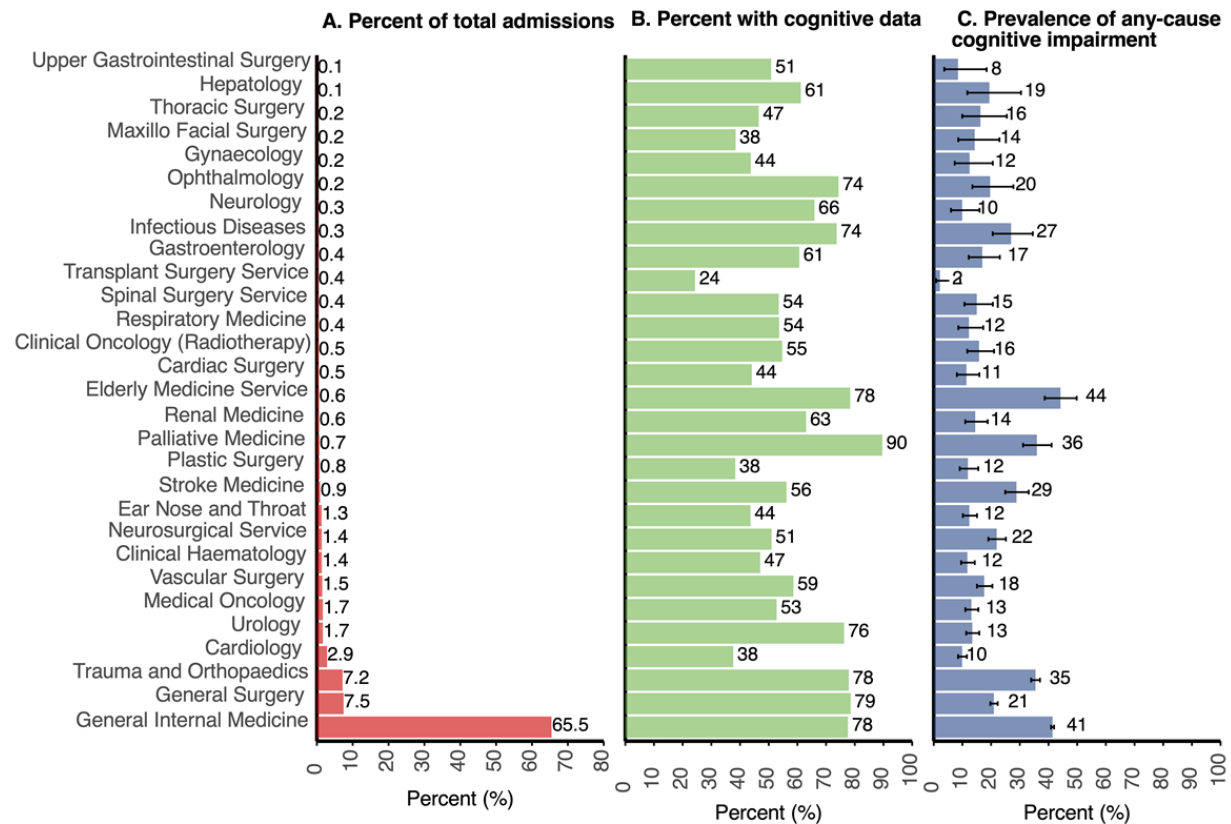
²Wilcoxon rank sum test; Kruskal-Wallis rank sum test; Pearson's Chi-squared test

³Sex missing for n=508; NEWS missing for n=348

⁴ The largest specialty medicine services were cardiology (n=1,462), medical oncology (n=853) and clinical haematology (n=708), which comprised over half of admissions within the group.

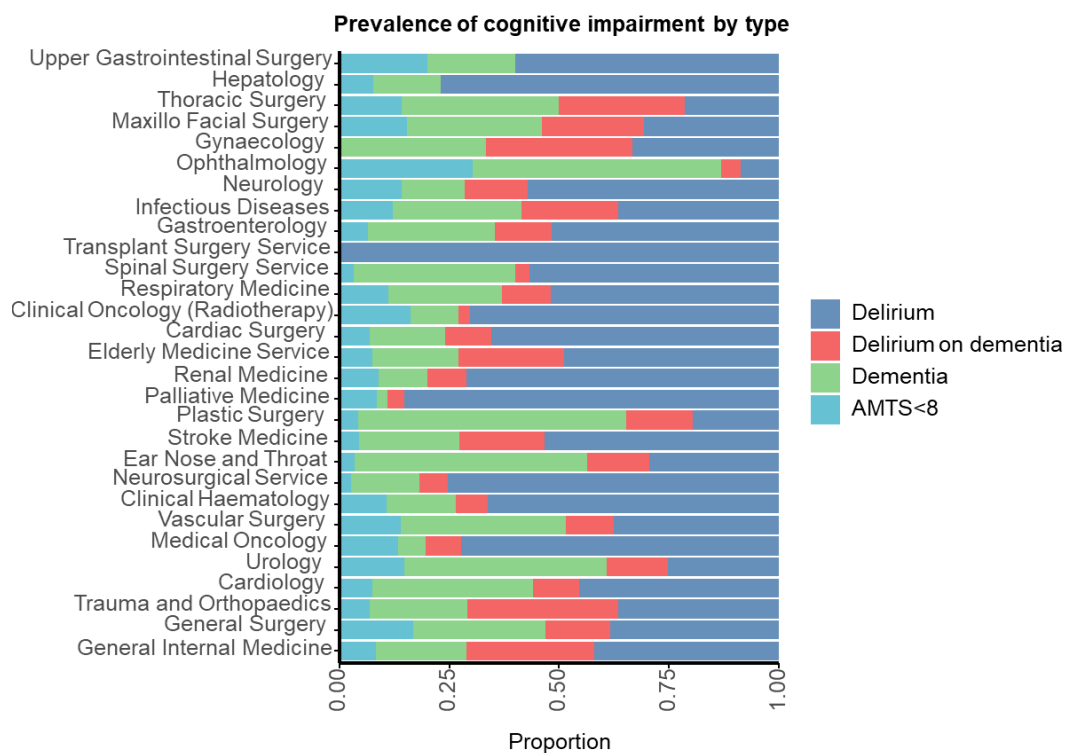
⁵ The largest specialty surgical services were urology (n=856), vascular surgery (n=773) and the neurosurgical service (n=702), which comprised over half of admissions within the group.

Figure 6.3 (A) Percent of total admissions by specialty in ORCHARD-EPR; (B) percent of admissions for which cognitive data (screening tool or ICD-10 codes) were available; and (C) prevalence of any-cause cognitive frailty



Legend: Denominators in panels A-C represent all admissions, whether cognitive data were reported or not.

Figure 6.4 Subtype of cognitive frailty in ORCHARD-EPR by specialty



6.4 DISCUSSION

In this large, real-world, hospital-wide cohort, 35% of patients ≥ 70 years with unplanned hospital admissions were recorded as having cognitive frailty. Delirium, either alone or superimposed on dementia, accounted for 70% of cases of cognitive frailty and was identified in 24% of admissions hospital-wide. Over 75% of patients with cognitive frailty were admitted to general medicine services, but cognitive frailty was present in all 30 specialties examined with variable prevalence (range=2-44%). Cognitive frailty was prevalent hospital-wide as expected, with delirium the most common cause of cognitive frailty across all age groups. Most patients with delirium (60%) in ORCHARD-EPR did not have a dementia diagnosis when admitted although some may have been undiagnosed. In previous studies, up to two-thirds of inpatients meeting DSM criteria for dementia did not have a diagnosis prior to admission, with mild disease the least likely to be documented.^{10,11} Consistent with evidence that dementia is a strong risk factor for delirium, over half (56%) of admitted patients with diagnosed dementia in ORCHARD-EPR had delirium.³⁴ Only 3% of admissions had objective cognitive deficits without delirium or diagnosed dementia, but some patients with unrecognised delirium or dementia might have been missed by the test which has a ceiling effect compared to the lengthier Montreal Cognitive Assessment.³⁵

Although most patients with cognitive frailty were admitted to general medicine, cognitive frailty was ubiquitous throughout the hospital setting. The prevalence of cognitive frailty exceeded 10% in all specialties, except for transplant and upper gastrointestinal surgery. High prevalence rates in specialties that care for large numbers of older, frailer patients including elderly medicine, general medicine and

trauma and orthopaedics gives face-validity to the ORCHARD-EPR data. The data also identified a large burden of cognitive frailty in specialties perhaps less associated with older, frail patients including infectious disease, surgery (neurologic, spinal, ophthalmology and thoracic), hepatology, gastroenterology and radiotherapy.⁶ Delirium, either alone or superimposed on dementia, was the most common cause of cognitive frailty in all specialties but ENT, urology, ophthalmology and plastic surgery in which dementia was predominant which has face validity given that common presentations in these specialties (e.g., epistaxis for ENT and pretibial laceration for plastic surgery) are not typically associated with delirium precipitants such as severe illness.³⁴

Compared to previous studies, ORCHARD-EPR provides comparable or greater coverage of the hospital population and more granular data on cognitive frailty. Hospital-wide, 73% of the >50,000 admissions in this study had cognitive data reported whereas inclusion rates and sample sizes in previous studies ascertaining cognitive frailty using clinically administered tools in hospital-wide and general medicine cohorts (19/25) ranged from 33-100% and n=200-10,014, respectively. Most studies ascertaining delirium using clinically administered tools excluded at least one of (12/17) patients from whom consent could not be obtained (n=6), were terminally ill (n=6) and/or could not complete assessments (n=5), whereas ORCHARD-EPR included consecutive, unselected admissions with an opt-out consenting process and thus may have included a more representative (and high-risk) population.³⁶

Delirium prevalence in ORCHARD-EPR (24%) was most similar to that reported in previous studies of unselected, consecutive admissions evaluated with clinically administered tools (14-20% in n=4 studies vs 5-49% in all 19 studies), including one hospital-wide study (19% ascertained with the CAM and DRS-R-98; n=598) which reported limited specialty-specific data (i.e., general medicine, general surgery, orthopaedics, geriatrics and stroke). Delirium has also been studied in specific populations, for example hip fracture, emergency, elective and cardiac surgery patients (although heterogeneity in methods and case-mix limits specialty-to-specialty comparison between datasets) and mixed acute care settings, but data on unplanned admissions are more limited for other specialty areas.^{24,37-40}

Dementia prevalence in unselected, consecutive admissions varied (9-25% in n=4 vs 7-62% in all 11 studies), but ORCHARD-EPR overlapped with the range reported in hospital-wide (10-25%, n=3 studies), two of which reported specialty-specific data (i.e., medicine, surgery, trauma and combined orthopaedics and geriatrics).^{41,42} Finally, about 5% of acute medicine admissions had AMTS<8 in the absence of diagnosed dementia or delirium in one study, which was similar to 3% in ORCHARD-EPR.¹⁵

6.4.1 Strengths and limitations

The main strength of this ORCHARD-EPR study is that it estimates the prevalence of delirium, dementia and other cognitive frailty hospital-wide and across specialties in a large sample of unselected, consecutive unplanned admissions. Findings from this study fill key knowledge gaps described, including the relative contributions of dementia and delirium to the burden of cognitive frailty in the acute hospital setting

and prevalence across specialties. However, this study has several limitations. First, rates of cognitive screening and documentation varied between specialties, and it is inevitable that some cases were missed although patients missing cognitive data tended to have fewer risk factors for cognitive frailty. Some variation in screening rates may relate to differences in service pressures and the perceived value of screening between specialties. For example, general surgery at OUHFT (79% of admissions had cognitive data reported) is supported by a perioperative physician service and orthopaedics (78% had cognitive data reported) receives a best practice tariff for meeting screening targets. Similar supports/incentives could be used to increase screening rates in other specialties. Additionally, acute symptoms, for example, severe shortness of breath and treatment needs may impact the accuracy of or delay cognitive screening but should not prevent it from being done.⁴³ Nevertheless, data for specialties with lower screening rates mostly appears to have face validity, for example, the high prevalence of delirium seen in palliative care and the most frequent cognitive diagnosis in plastic surgery being dementia.

Second, the delirium data shown in main analyses included both uncertain and certain cases, which could have resulted in overestimation of prevalence. However, certain+uncertain delirium prevalence in general medicine admissions in ORCHARD-EPR underestimated prevalence compared to audit data as shown in **Chapter 5**. The restriction of data to certain cases did not impact the finding that the prevalence of delirium was higher than that of dementia. Additionally, in real-world practice where repeated assessments and lengthy severity rating questionnaires are not practical and it is difficult for clinicians to determine if mild symptoms represent expected fluctuation or evolution of full syndromic delirium

versus subsyndromal delirium.⁴⁴ Outcomes of subsyndromal delirium are normally expected to be intermediate between full and no delirium;⁴⁵ however, in **Chapter 5** survival was similar between certain and uncertain delirium groups (although risk of long length of stay, delayed discharge and discharge to a destination other than home were slightly higher in the certain delirium group before frailty was adjusted for).

Third, some current guidelines recommend screening for cognitive frailty in people aged ≥ 65 years or younger if exhibiting signs of confusion or additional risk factors are present, but routine cognitive screening was only required in the group aged ≥ 70 years in the ORCHARD-EPR cohort.^{46,47} Additional studies may be required in younger age groups although one study in unselected, consecutive general medicine admissions reported delirium prevalence of 11% in patients aged 66-70% and 3% in those < 65 years.¹² Fourth, this study was done in hospitals across one region (Oxfordshire). Although the four hospitals included in ORCHARD-EPR provide all acute services to Oxfordshire's population, generalisability to settings with differing case-mix and strategies for delivering ambulatory and inpatient care (for example, same day emergency care and Hospital-at-Home) may need to be considered.^{48,49}

6.4.2 Implications

My findings have several implications for service-planning, policy and research. First, although this study shows that delirium was the most common form of cognitive frailty in unplanned hospital admissions across age groups, delirium has received comparatively less attention from policymakers and funders than dementia (i.e., National Dementia Strategy and Royal College of Psychiatrists National Dementia

Audit).^{50,51} Compared to dementia which generally follows a predictable course, management of delirium may be more difficult due to its fluctuating course, variable prognosis and risk that the patient develops a new cognitive baseline and increased care needs. **Chapter 7** will investigate outcomes of delirium and dementia in the ORCHARD-EPR cohort. Second, guidance recommending routine screening for delirium and other cognitive impairment in older hospital patients is supported by the finding that cognitive frailty was prevalent in inpatients ≥ 70 years across all specialties, with delirium prevalence 13% in the group aged 70-74 years. The finding that cognitive frailty was concentrated in general medicine but present in all specialties is informative for service-planning and may support the adoption of a mix of mobile (i.e., low prevalence specialties) and ward-based geriatrics teams, which have a stronger evidence-base and may be more cost effective (i.e., high prevalence specialties).⁵² Training non-geriatrician clinicians to provide comprehensive geriatric assessment has also been piloted previously with limited success.⁵³ Third, the finding that delirium in the absence of dementia was the most prevalent form of cognitive frailty across all age groups identifies this population as an important target for dementia prevention research including at the population-level, with most older people having at least one hospital admission.⁵⁴ Emerging evidence that people with a normal cognitive baseline who develop delirium have the most future cognitive function to lose further underscores the importance of developing preventative strategies in this group.⁵⁵

6.4.3 Conclusion

In conclusion, I found that over one-third of patients with unplanned admissions to hospital had cognitive frailty, with delirium the most common subtype. Cognitive

frailty was present across all age groups (70-90+ years) and specialties, with a large proportion of cognitively frail patients admitted to general medicine services. This finding supports a role for both the provision of hospital-wide, mobile frailty teams and centralised resources in specialties with the highest burdens of cognitive frailty to improve access to specialised geriatric care. Over half of patients with delirium were not known to have dementia on admission and may represent an important target for prognosis and dementia prevention research. In **Chapter 7**, outcomes will be investigated to better understand the burden of cognitive frailty in the acute hospital setting and in **Chapter 8** overlap with physical frailty will be studied.

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Chapter 7

Impact of cognitive frailty on death, length of stay, institutionalisation, and readmissions in older people with unplanned hospital admissions in ORCHARD-EPR

ABSTRACT

Background: Cognitive frailty is prevalent in older inpatients as shown in Chapter 6 and hospital-wide data outcomes are needed to inform patient care, policy and research. However, existing evidence is heterogenous with most data from small, selected prospective cohorts with uncertain generalisability or administrative coding studies likely to have poor sensitivity for cognitive frailty. In this chapter I aimed to determine associations between cognitive frailty, i.e., delirium, dementia, delirium on dementia and low abbreviated mental test score (AMT<8) and outcomes in older people with unplanned hospital admissions hospital-wide.

Methods: ORCHARD-EPR (2017-2019) captures routine clinical data from older patients with unplanned hospital admissions in Oxfordshire, UK. Data include a mandatory cognitive screen (AMT, dementia and delirium) for those >70 years. Associations between cognitive frailty and survival, length of stay in hospital (LoS),

delayed discharge, discharge home and readmissions were determined using logistic regression and Cox proportional hazards models adjusted for age, sex, comorbidity (modified Charlson Comorbidity Index-mCCI) and illness severity (National Early Warning System-NEWS score).

Results: Using data from 28,590 inpatient admissions, all cognitive frailty identified through routine cognitive screening was predictive of survival, LoS, delayed discharge, and discharge to a destination other than home over and above age, sex, mCCI and NEWS. Mortality risk was front-loaded for delirium (aORs for in hospital death for delirium alone 2.23, [95% CI 1.98 to 2.50; 558/3,845] vs delirium on dementia 2.14 [1.86 to 2.47; 319/2,352]; both $p < 0.001$ vs no cognitive frailty [1,074/19,453]) but remained elevated over up to four years of follow-up ($p < 0.001$). Only delirium in non-care home residents predicted 30-day readmission (aOR for 30-day readmission for delirium alone 1.18 [1.06 to 1.32]; $p = 0.002$).

Discussion: All cognitive frailty was associated with increased short and long-term mortality, length of stay, delayed discharge and discharge to a place other than home, but only delirium in patients living at home predicted readmission. Findings support guidance on routine cognitive screening hospital-wide, across all specialties and encourage the development of delirium pathways to improve outcomes. In the next chapter, I will look at the overlap between cognitive and physical frailty and impact on outcomes.

7.1 INTRODUCTION

In **Chapter 6** I showed that cognitive frailty was prevalent in older people with unplanned admissions hospital-wide and across specialties. Reliable data on cognitive frailty outcomes hospital-wide are needed to inform guidance, research and services, including cognitive screening, as outlined in the Getting It Right First Time (GIRFT) Geriatrics report.¹ Additional uses of these data may include risk-stratification for care pathways, informing policy objectives, and selection of trial endpoints and sample size calculations for research. Most hospital-based outcomes studies were done in specific populations, for example patients admitted to specialist geriatric wards, receiving elective surgery or with particular diagnoses such as hip fracture.²⁻⁴ However, cognitive frailty outcomes in these populations may not generalise well to the acute hospital at-large because of differences in case-mix. Not all risk factors are known or measured in these population-specific studies, but even when measured may not capture the full range of the characteristics present in the acute hospital population (for example, most geriatric patients will have substantial frailty or dependency), thus residual confounding may impact associations. Concern about the generalisability of findings is underscored by heterogeneity in associations between dementia, mortality and readmissions in studies across a variety of inpatient populations including specialist geriatric, surgical and intensive care patients.^{2,5}

As described in the Introduction chapter, I identified 12 studies reporting cognitive frailty outcomes which were done in hospital and general medicine settings (Appendix Table 1.4 & 1.5, pg. 344). These included six prospective cohorts⁶⁻¹¹ and three routine clinical data studies,¹²⁻¹⁴ one with unclear design, one chart review and

one administrative data study.¹⁵⁻¹⁷ Despite concerns about selection due to requirements for consent, the ability to complete assessments and the exclusion of terminally ill patients in five out of nine prospective and routine clinical data studies,^{6-8,10,18} delirium has been consistently associated with death and longer stays in these studies over and above age, sex, comorbidity and illness severity;^{6-10,18} although data on dementia are more limited, with only one study reporting mortality after discharge.^{13-15,19} High levels of unexplained heterogeneity limit the certainty of the evidence for both conditions: the mean difference in length of stay for delirium ranged from 0.2 days shorter to 13 days longer, mortality risk ratios ranged from 1.9 to 7.3 and there was limited investigation of effect modification to understand variation in outcomes.^{7,10,13} In particular, data on the impact of dementia or pre-existing cognitive impairment on delirium outcomes are limited including for survival which is needed to inform trial design and the need for follow-up after discharge.^{18,20} Also, several studies of delirium outcomes adjusted for dementia; however, this approach to minimising heterogeneity risks biasing estimates towards the null and does not provide useful information on variation in risk across clinical subgroups.^{1,4-6}

I found little evidence for the impact of cognitive frailty, in particular dementia, on outcomes outside of survival and length of stay that are also important to patients, clinicians and decision-makers in the general medical and hospital setting. There are few or no data on delayed transfers of care which may contribute to deconditioning, iatrogenic harm and health service pressures.²¹ Evidence for higher rates of institutionalisation following hospital admission for patients with delirium and dementia is mixed, with one systematic review including acute admissions in medical, surgical and geriatric settings assessing the evidence as being low or very

low quality.¹³ Although policy documents recommend that hospitals track and aim to reduce unnecessary hospital readmissions in frail older people, I found conflicting results on cognitive frailty and readmission risk.^{1,22} For example, delirium was associated with fewer readmissions in patients with 4A's Test scores ≥ 4 (but not scores of 1-3) in one study but increased readmission risk in patients without dementia in another.^{12,13}

Given the limitations in the quality and comprehensiveness of existing data on cognitive frailty outcomes in the literature discussed above, in this chapter I aimed to determine the impact of cognitive frailty on short and long-term outcomes using data from rich, large-scale, data extracted from hospital electronic patient records (EPRs) over and above potential confounding variables and effect modifiers, i.e., age, sex, comorbidity and illness severity. I defined cognitive frailty as delirium alone, delirium on dementia, dementia alone and low cognitive test score and was interested in the outcomes of mortality, length of stay in hospital, delayed discharge, discharge destination and 30-day readmission.

7.2 METHODS

7.2.1 Study design

I used data from the ORCHARD-EPR 2017-2019 (hereafter 'ORCHARD-EPR') database which includes pseudo-anonymized data from the Oxfordshire University Hospitals NHS Foundation Trust (OUHFT) EPR for all consecutive, unselected adult hospital and ambulatory admissions to four urban hospitals serving Oxfordshire and

surrounding areas as described in **Chapter 4**. Individual consent was not required but individuals could opt-out (REC reference: 18/SC/0184).

7.2.2 Eligibility

I included all unplanned admissions of patients ≥ 70 years to any specialty if they had a length of stay ≥ 1 day and age, sex, National Early Warning Score (NEWS) and one or more ICD-10 codes.

7.2.3 Cognitive screen and procedures

As per previous chapters, OUHFT mandates that all patients with unplanned admissions ≥ 70 years of age (and younger patients at high-risk) receive a cognitive screen via a form embedded in the EPR. The form includes three items:

- The 10-point Abbreviated Mental Test Score (AMT; score out of 10)
- “Does the patient have a known diagnosis of dementia?” (‘Yes,’ ‘Uncertain,’ ‘No’; confirmed with the patient, relatives and/or medical records)
- “Does the patient have delirium?” (‘Yes,’ ‘Uncertain,’ ‘No’; informed by the Confusion Assessment Method-CAM)

I considered dementia to be present if ‘yes’ was recorded on the cognitive screen or dementia ICD-10 codes were recorded. I considered delirium to be present if a response of ‘yes’ or ‘uncertain’ was given for the delirium question on the screen and/or at least one ICD-10 code for main analyses (see **Chapter 5**). I also identified people with an AMTS <8 in the absence of diagnosed dementia or delirium.²³

Patients who did not have dementia, delirium or low cognitive test scores as defined

above (including those who did not have a cognitive screen recorded) were assumed to not have cognitive frailty and used as the reference category.

7.2.4 Outcomes and group at risk

I assessed outcomes including death, length of stay, delayed transfer of care, discharge to usual place of residence and readmissions which were defined as per **Chapter 4**.

Specifically, I calculated outcome variables as follows:

- **Mortality:** Time-to-event, in hospital and 1-year after discharge deaths.
- **Length of stay (LoS):** Count and >10 days (about the 75th percentile).
- **Delayed transfer of care (DTOC):** Binary >48 hours.
- **Discharge to different place of residence:** Binary variable for discharge to usual place of residence, including care homes if that was where the patient was living previously versus an alternate destination such as a new care home, rehab facility or community hospital.
- **Readmission:** Time-to-event, within 30-days after discharge.

Mortality data were censored as of May 21, 2021, and follow-up ranged from 0-1,601 days (median, interquartile range-IQR=796, 317-1189 days; e.g., 0 representing patients who died in hospital) via the Office of National Statistics. Only patients who survived to discharge were included in odds ratio (OR) analyses for 30-day and 1-year mortality after discharge, delayed transfers of care, discharge destination and 30-day readmissions to avoid bias due to the competing risk of death. Binary

analyses of 30-day readmissions were also limited to those with a minimum of 30-days of follow-up.

7.2.5 Covariate measurement and choice

Other data fields were obtained from assessments completed by clinical or administrative staff as part of routine patient care as described in Chapter 4 or derived from other fields. I identified age on admission, sex, comorbidity and severe illness as important confounders. Age is associated with delirium and acute care outcomes may differ by sex.^{9,24} Severe illness is a precipitating factor for delirium and predictor of death.^{25,26} I used the NEWS version 1 as a proxy for illness severity as a categorical variable (low, low-medium, medium and high risk groups) in regression analyses and dichotomous variable (low/low-medium and medium/high, i.e., scores of $<$ or ≥ 5) for stratification.²⁷ Comorbidity may predispose to delirium and is a known predictor of mortality.^{25,28} I used ICD-10 codes to calculate Charlson comorbidity Index (CCI) using the NHS Digital Summary Hospital-level Mortality Indicator (SHMI) weightings.²⁹ I performed sensitivity analyses using a modified version of the CCI (mCCI) that did not include coded dementia to mitigate bias related to double-counting dementia as an exposure (cognitive frailty) and confounder (comorbidity). In this approach, the mCCI was replaced by the mean of all other variables.¹⁸

7.2.6 Statistical analysis

I used each patient's first admission in ORCHARD-EPR to meet the statistical assumption of independence and maximise follow-up time. General analytical

considerations are discussed in **Chapter 4**; however, additional details relevant to this chapter are included below:

Descriptive statistics

I calculated descriptive statistics for demographic/clinical characteristics on admission, including by cognitive status using mean/standard deviation or n/% as appropriate, in addition to performing statistical tests as described in Chapter 4.

Outcomes

I described outcomes were using descriptive statistics and modelled them using regression. I identified covariates *a priori* based on the literature and clinical knowledge and included them in models to control for confounding.

Binary outcomes were modelled with logistic regression and reported as odds ratios with 95% Wald confidence intervals. When the event rate in the reference group is high (i.e., >10%) and the effect large (i.e., OR>3), odds ratios deviate from relative risk and can no longer be multiplied by a patient's disease risk to predict outcomes. Therefore, in such situations, I also calculated relative risks using Poisson models.^{30,31}

Time-to-event and count outcomes were plotted on Kaplan-Meier curves and analysed with Cox proportional hazards regression to obtain hazard ratios (HRs). Observations were censored at death or the last date the dataset was updated. See notes on competing risk below under "Special Considerations." Length of stay was

modelled as a count using negative binomial regression to account for overdispersion, i.e., a large proportion of patients having a length of stay of one day.

I reported both unadjusted models and models sequentially adjusted for confounders: age & sex, mCCI (continuous) and NEWS categories (a proxy for illness severity). I hypothesised that illness severity was an effect modifier for in hospital death, and care home residence (it was not possible to distinguish residential and nursing homes) was an effect modifier for readmissions, so I stratified data by these variables.

Model fit

For regression models, I evaluated goodness-of-fit by plotting binned residuals versus fitted values and evaluating the proportion falling within 95% confidence bounds and their distribution, i.e., visually. For Poisson regression, I evaluated dispersion by dividing deviance by degrees of freedom, with ratios of ~ 1 indicating no dispersion, which is an assumption of the model. For survival analysis, the proportional hazards assumption was checked by visually inspecting plots of Schoenfeld residuals vs time for each covariate included in the models and performing a Schoenfeld test, with models with a global p -value of <0.05 considered non-proportional and tests for individual variables used to identify variables contributing to the non-proportionality. I evaluated multicollinearity and the linearity of continuous covariates versus outcomes as described in Chapter 4.

Special considerations

For mortality, violation of the proportional hazards assumption was handled by reporting HR estimates for specified time periods and also calculating time-by-covariate interaction for covariates that violated the proportional hazards assumption. I chose these strategies because they allow estimation of change in mortality risk over time, unlike other approaches, e.g., stratification by the time-varying variable, choosing an accelerated failure time model or interpreting the Cox HR as a weighted average of the true HR over the follow-up period.

For 30-day readmissions, I handled the competing risk of death using two complementary methods as recommended: cause-specific and subdistribution hazard models.³² Cause-specific HRs were obtained from standard Cox regression by censoring individuals who died without being (i.e., *before having the chance to be*) readmitted.^{33,34} The resultant HRs represent a “hypothetical setting in which the competing event cannot occur,”^{33(p.43)} but may overestimate risk, especially where the competing event is common. Subdistribution HRs were calculated using the Fine-Gray method. These models are based on the Cumulative Incidence Function which retains individuals who died in the dataset (despite no longer being at risk).³⁵ The resultant HRs therefore provide an estimate of *overall* readmission risk, i.e., for the purpose of prediction, but are more difficult to interpret aetiologically because both outcomes are considered in the model.³³

Software

I performed all statistical analyses in R version 4.2.1 using the packages *stats*, *performance*, *survival*, *survminer*, *tidycmprsk* and the *tidyverse*.³⁶⁻⁴⁰

7.2.7 Sensitivity analyses

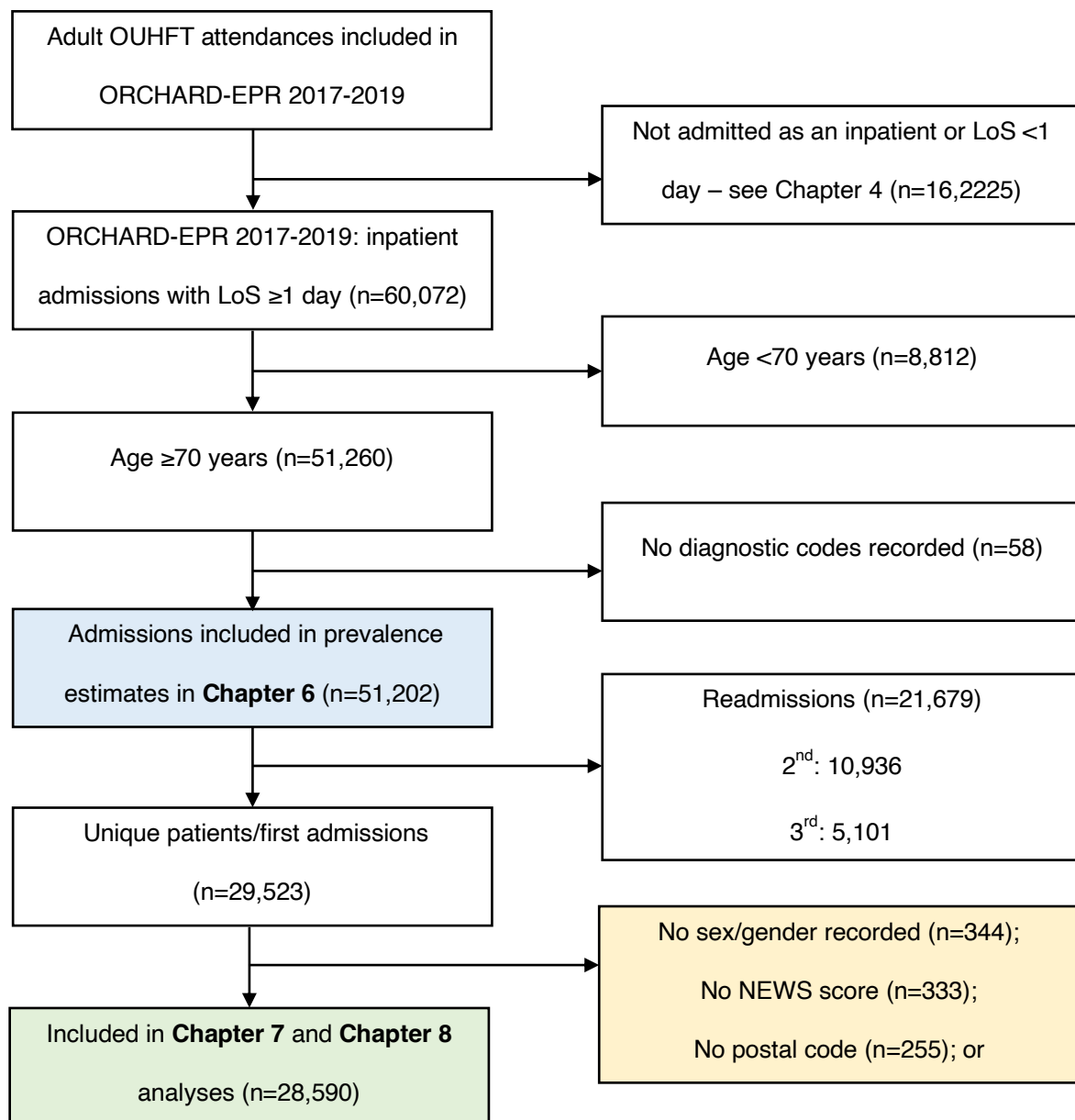
I did four additional sensitivity analyses. First, I calculated relative risks as described above; second, outcomes for delirium defined as certain cases only; third, outcomes using the original CCI including coded dementia and fourth, outcomes stratified by specialty group (i.e., General Medicine, Trauma and Orthopaedics, General Surgery, Specialty Medicine and Specialty Surgery).

7.3 RESULTS

7.3.1 Population characteristics

A total of $n=28,590$ first admissions of people ≥ 70 years (mean/SD=81.8/7.4 years; 52% female) (**Figure 7.1**), of whom 71% had cognitive data recorded (screen or codes). Within the cohort, 3,845 (13.4%) people had delirium alone, 2,352 (8.2%) had delirium on dementia, 2,156 (7.5%) had dementia alone and 784 (2.7%) had a low cognitive test score (AMTS<8) without a delirium or dementia diagnosis. Patients with any cognitive frailty (9,137/28,590) were older (mean/SD any cognitive frailty: 84.8/7.0 years vs no cognitive frailty: 80.4/7.1 years; $p<0.001$), more likely to be female (56% vs 50%; $p<0.001$), have greater comorbidity burden (mean/SD original CCI for any cognitive frailty: 13.4/10.3 vs no cognitive frailty: 6.8/7.8; $p<0.001$ and mCCI excluding dementia for any cognitive frailty: 7.3/8.3 vs no cognitive frailty: 6.8/7.8; 0.002), live in a care home (24% vs 7.1%) and be in a higher NEWS category (i.e., high 8.5% vs 5.6%; $p<0.001$ for all categories). Characteristics stratified by type of cognitive frailty (i.e., dementia alone, delirium alone, delirium on dementia and low cognitive test score) are shown in

Figure 7.1 CONSORT diagram (see Chapter 4 for more detail)



Other: N=1 individual removed because date deceased preceded the individual's admission date.

Table 7.1 Cohort characteristics at first admission by type of cognitive frailty

Characteristic	Overall, N = 28,590	No cognitive frailty, N = 19,453	Delirium only, N = 3,845	Delirium on dementia, N = 2,352	Dementia only, N = 2,156	Low cognitive test score, N = 784	p-value ¹
Age, Mean (SD)	81.8 (7.4)	80.4 (7.1)	84.0 (7.4)	85.8 (6.6)	85.1 (6.6)	85.0 (7.1)	<0.001
Female, n (%)	14,689 (52%)	9,676 (50%)	2,101 (55%)	1,359 (58%)	1,234 (57%)	443 (57%)	<0.001
NEWS category, n (%)							<0.001
Low	21,396(75%)	15,046 (77%)	2,563 (67%)	1,585 (67%)	1,585 (74%)	609 (78%)	
Low-Medium	2,548 (8.4%)	1,559 (8.0%)	454 (12%)	260 (11%)	197 (9.1%)	78 (9.7%)	
Medium	2,789 (9.6%)	1,767 (9.1%)	480 (12%)	275 (12%)	201 (9.3%)	66 (8.4%)	
High	1,857 (6.4%)	1,081 (5.6%)	348 (9.1%)	224 (9.5%)	173 (8.0%)	31 (4.0%)	
CCI, Mean (SD) ²	8.9 (9.2)	6.8 (7.8)	8.2 (8.7)	19.3 (8.9)	18.3 (9.1)	7.8 (8.7)	<0.001
Care home resident, n (%)	3,594 (13%)	1,378 (7.1%)	601 (16%)	855 (36%)	628 (29%)	132 (17%)	<0.001

¹Kruskal-Wallis rank sum test (continuous variables with two or more groups), Wilcoxon rank sum test (continuous variables with two groups [shown in the text only]); Pearson Chi Squared (categorical variables)

²Mean (SD) for the modified CCI excluding dementia was 6.6 (7.8) in the group with delirium on dementia and 6.2 (7.7) in the group with dementia alone but was unchanged for all other groups.

7.3.2 In hospital death

All cognitive frailty except for low cognitive test score ($p=0.48$) was associated with increased death in hospital including after adjustment for age, sex, mCCI and NEWS ($p<0.001$). Adjusted ORs for in hospital death were 2.23 (95% CI 1.98 to 2.50; 558/3,845 [15%]) for delirium alone, 1.45 (1.22 to 1.71; 191/2,156 [8.9%]) for dementia only, 2.14 (1.86 to 2.47; 319/2,352 [14%]) for delirium on dementia and 1.11 (95% CI 0.82 to 1.48; 55/784 [7.0%]) for low cognitive test score compared to no cognitive frailty (1,074/19,453 [5.5%]; see Table 7.2, Table S7.1 for descriptive statistics for outcomes and Appendix Table 7.2 for full model). Stratification by NEWS modified the association between delirium and in hospital death, but not dementia. The age, sex and mCCI-adjusted OR for delirium alone was 2.60 (2.25 to 3.00; 340/3,005 [11%]) in the group with NEWS <5 compared to 1.80 (1.48 to 2.18; 217/828 [26%]) for NEWS ≥ 5 (both $p<0.001$), with similar results for delirium on dementia (NEWS <5 : 2.44 [2.04 to 2.91]; 191/1,863 [10%] vs NEWS ≥ 5 : 1.81 [1.43 to 2.28]; 125/499 [25%]; both $p<0.001$).

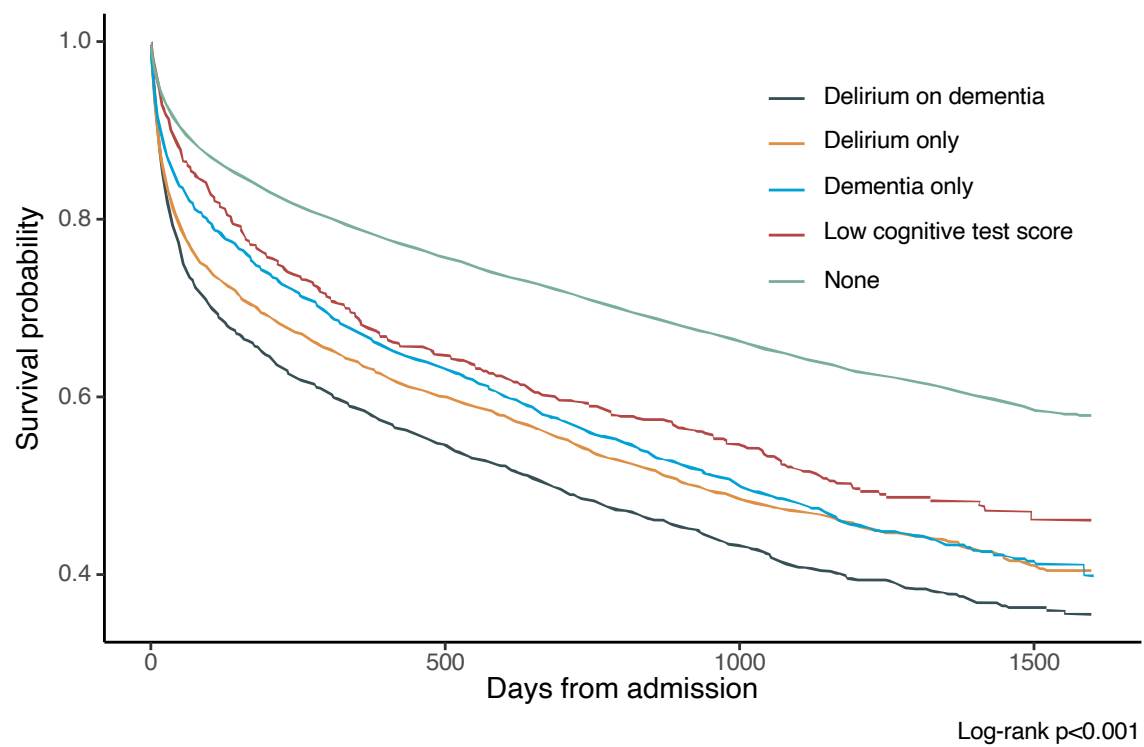
7.3.3 Mid and long-term survival

All cognitive frailty was associated with death in the year after discharge independent of age, sex, mCCI and NEWS ($n=26,393$ survivors; ORs provided in Table 7.3 and full models in Appendix Table 7.3). Survival over the entire study period is shown on a Kaplan-Meier plot (Figure 7.2). As visible on the plot, mortality risk varied over the follow-up period for delirium (Schoenfeld test $p<0.001$ for delirium alone and delirium on dementia in adjusted and unadjusted Cox proportional hazard models) but not for dementia alone ($p>0.2$) or low cognitive test score ($p>0.1$). Hazards for the covariates mCCI and NEWS (medium and high categories) were also non-

proportional (Schoenfeld test $p < 0.001$). In the time-varying model adjusted for age, sex, mCCI and NEWS, the adjusted HR at time=0 (i.e., day of admission) was 1.56 (95% CI 1.46 to 1.67; 865/3,287) for delirium alone, 1.43 (1.34 to 1.52; 535/1,965) for dementia alone, 1.89 (1.75 to 2.04; 682/2,033) for delirium on dementia and 1.21 (1.09 to 1.35; 202/729) for low cognitive test score compared to no cognitive frailty (6,753/19,340), with negative coefficients for the interactions between time and delirium alone, delirium on dementia, mCCI and NEWS indicating front-loading of mortality risk ($p < 0.001$ all).

A time-stratified analysis was also done as to understand the time-dependent effects of covariates using 90 days as an empirically determined cut-point. Only data >90 days are reported for the fully adjusted model because the proportional hazards assumption was violated by NEWS at earlier time points ($p < 0.001$ for medium and high NEWS categories). Nevertheless, after 90 days all forms of cognitive frailty remained associated with mortality. HRs for the fully adjusted model were 1.25 (95% CI 1.17 to 1.34; 1,026/2,849 admitted patients surviving >90 days) for delirium alone, 1.42 (1.31 to 1.54; 705/1,729) for dementia alone, 1.43 (1.32 to 1.55; 698/1,675) for delirium on dementia and 1.29 (1.13 to 1.47; 240/655) for low cognitive test score compared to no cognitive frailty (3,120/18,379). See Appendix Table 7.4 for full models for time-varying HRs and Appendix Table 7.5 for landmark analyses.

Figure 7.2 Kaplan-Meier plot for survival by cognitive frailty subtype over the follow-up period



Note: Median follow-up was 21.4 (IQR=3.4-36.8) months for any cognitive frailty vs 27.9 (16.9-40.0) for none.

Table 7.2 ORs for in hospital death for each type of cognitive frailty stratified by NEWS score <5 (low and low-medium) and ≥5 (medium and high groups) and adjusted for age, sex, mCCI and NEWS as appropriate

Cognitive frailty	Full cohort					NEWS <5			NEWS ≥5		
	N (%)	Unadjusted OR (95% CI) ¹	p	Adjusted OR (95% CI) ^{1,2}	p	N (%)	Adjusted OR (95% CI) ^{1,3}	p	N (%)	Adjusted OR (95% CI) ^{1,3}	p
Delirium only	558 / 3,845 (15%)	2.91 (2.60 to 3.24)	<0.001	2.23 (1.98 to 2.50)	<0.001	341 / 3,017 (11%)	2.60 (2.25 to 3.00)	<0.001	217 / 828 (26%)	1.80 (1.48 to 2.18)	<0.001
Dementia only	191 / 2,156 (8.9%)	1.66 (1.41 to 1.95)	<0.001	1.45 (1.22 to 1.71)	<0.001	103 / 1,782 (5.8%)	1.36 (1.08 to 1.69)	0.006	85 / 374 (23%)	1.66 (1.26 to 2.15)	<0.001
Delirium on dementia	319 / 2,352 (14%)	2.69 (2.35 to 3.06)	<0.001	2.14 (1.86 to 2.47)	<0.001	191 / 1,863 (10%)	2.44 (2.04 to 2.91)	<0.001	125 / 499 (25%)	1.81 (1.43 to 2.28)	<0.001
Low cognitive test score	55 / 784 (7.0%)	1.29 (0.96 to 1.69)	0.075	1.11 (0.82 to 1.48)	0.48	37 / 687 (5.4%)	1.15 (0.80 to 1.60)	0.42	17 / 97 (18%)	1.04 (0.58 to 1.74)	0.90
None	1,074 / 19,453 (5.5%)	1.00	NA	1.00	NA	658 / 16,605 (4.0%)	1.00	NA	418 / 2,848 (15%)	1.00	NA

¹ OR = Odds Ratio, CI = Confidence Interval

² Adjusted for age, sex, mCCI and NEWS category (Low, Low-Medium, Medium, High)

³ Adjusted for age, sex and mCCI (with stratification by NEWS)

Table 7.3 ORs and HRs for death for each type of cognitive frailty adjusted for age, sex, mCCI and NEWS (all *p*-values <0.001 unless stated)

Cognitive frailty	n/N (%)	ORs for 1-year mortality ¹		HRs for mortality over the follow-up period ²					
				Time-varying model		Stratified ≤90 days		Stratified >90 days	
		OR (95% CI)	aOR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI) ³	HR (95% CI)	aHR (95% CI)
Delirium alone	865 / 3,287 (26%)	1.75 (1.60-1.90)	1.44 (1.32-1.58)	1.42 (1.35-1.49)	1.56 (1.46-1.67)	2.19 (2.03-2.36)	NA	1.52 (1.42-1.63)	1.25 (1.17-1.34)
Dementia alone	535 / 1,965 (27%)	1.83 (1.64-2.03)	1.64 (1.46-1.83)	1.43 (1.34-1.52)	1.43 (1.34-1.52)	1.67 (1.50-1.85)	NA	1.68 (1.55-1.82)	1.42 (1.31-1.54)
Delirium on dementia	682 / 2,033 (34%)	2.47 (2.23-2.73)	2.12 (1.90-2.35)	1.65 (1.56-1.75)	1.89 (1.75-2.04)	2.54 (2.33-2.76)	NA	1.78 (1.64-1.92)	1.43 (1.32-1.55)
Low AMTS	202 / 729 (28%)	1.87 (1.58-2.21)	1.57 (1.32-1.87)	1.21 (1.09-1.34)	1.21 (1.09-1.35)	1.28 (1.07-1.54)*	NA	1.61 (1.42-1.83)	1.29 (1.13-1.47)
None	3,120 / 18,379 (17%)	1	1	1	1	1	NA	1	1

¹ OR = Odds Ratio, aOR = Odds Ratio adjusted for age, sex, mCCI and NEWS, CI = Confidence Interval,

² HR = Hazard Ratio, aHR = Hazard Ratio adjusted for age, sex, mCCI and NEWS, CI = Confidence Interval

³ aHR for ≤90 day landmark analysis are not shown because the fully adjusted model violated the proportional hazards assumption

**p*=0.007

7.3.4 Length of hospital stay

The median (IQR) was 8.0 (13.0) days for delirium only, 8.0 (14.0) for delirium on dementia, 4.0 (9.0) for dementia only and 6.0 (12.0) for those with a low cognitive test score but no diagnosis of delirium or dementia compared to 4.0 (6.0) for no cognitive frailty ($p < 0.001$; $n = 28,590$). After adjusting for age, sex, mCCI and NEWS, all types of cognitive frailty were associated with longer stays, i.e., adjusted OR (95% CIs) of 2.62 (2.43 to 2.82; 1,546/3,845) for delirium only, 2.64 (2.40 to 2.89; 941/2,352) for delirium on dementia, 1.34 (1.20 to 1.49; 542/2,156) for dementia only and 1.80 (1.54 to 2.10; 252/784) for those with a low cognitive test score (**Table 7.4**; Appendix Table 7.6 for full models and Appendix Table 7.7 for length of stay modelled as a count instead of a binary variable).

Table 7.4 ORs for length of stay >10 days by type of cognitive frailty

Cognitive frailty	N (%)	Unadjusted OR (95% CI) ¹	p	Adjusted OR (95% CI) ¹	p
Delirium only	1,546 / 3,845 (40%)	2.82 (2.62 to 3.03)	<0.001	2.62 (2.43 to 2.82)	<0.001
Dementia only	542 / 2,156 (25%)	1.41 (1.27 to 1.56)	<0.001	1.34 (1.20 to 1.49)	<0.001
Delirium on dementia	941 / 2,352 (40%)	2.80 (2.56 to 3.06)	<0.001	2.64 (2.40 to 2.89)	<0.001
Low cognitive test score	252 / 784 (32%)	1.99 (1.70 to 2.31)	<0.001	1.80 (1.54 to 2.10)	<0.001
None	3,746 / 19,453 (19%)	1.00	NA	1.00	NA

¹ OR = Odds Ratio, CI = Confidence Interval

7.3.5 Delayed Discharge

After being declared medically fit for discharge, $n = 3,319$ patients remained in hospital for ≥ 2 days because of delayed transfers of care (DTC). The most

common reasons given for a DTOC were waiting for further non-acute NHS care in a community hospital (n=735), awaiting homecare reassessment and reablement (n=446) or a care package with therapy support (n=330). All forms of cognitive frailty were associated with DTOC ≥ 2 days, with the strongest associations after adjusting for age, sex, mCCI and NEWS seen for delirium: adjusted ORs were 3.06 (2.77 to 3.38; 819/3,287) for delirium only, 3.27 (2.91 to 3.7; 566/2,033) for delirium on dementia, 1.72 (1.50 to 1.97; 307/1,965) for dementia only and 2.35 (1.93 to 2.84; 151/729) for those with a low cognitive test score compared to no cognitive frailty (1,476/18,379; **Table 7.5** and Appendix Table 7.8 for full models). When data were stratified by care home residence prior to admission, DTOC ≥ 2 days remained associated in all groups except for the group with dementia already resident in a care home at the time of admission (OR=1.09, 95% CIs 0.84 to 1.40; $p=0.52$); Appendix Table 7.9 for care home residents and Appendix Table 7.10 for non-residents).

Table 7.5 ORs for DTOC >2 days by type of cognitive frailty

Cognitive frailty	N (%)	Unadjusted OR (95% CI) ¹	p	Adjusted OR (95% CI) ¹	p
Delirium only	819 / 3,287 (25%)	3.67 (3.33 to 4.05)	<0.001	3.06 (2.77 to 3.38)	<0.001
Dementia only	307 / 1,965 (16%)	2.12 (1.85 to 2.42)	<0.001	1.72 (1.50 to 1.97)	<0.001
Delirium on dementia	566 / 2,033 (28%)	4.13 (3.69 to 4.62)	<0.001	3.27 (2.91 to 3.67)	<0.001
Low cognitive test score	151 / 729 (21%)	2.96 (2.44 to 3.56)	<0.001	2.35 (1.93 to 2.84)	<0.001
None	1,476 / 18,379 (8.0%)	1.00	NA	1.00	NA

¹OR = Odds Ratio, CI = Confidence Interval

7.3.6 Discharge destination

Discharge destination data were available for 25,745 patients who survived until discharge (missing n=650 [2.5%]). All cognitive frailty was associated with discharge to a destination other than home: ORs adjusted for age, sex, mCCI and NEWS were 2.74 (95% CI 2.50 to 2.99; 1,015 / 3,158) for delirium alone, 3.15 (2.84 to 3.50; 728/1,977) for delirium on dementia, 1.99 (1.77 to 2.22; 505/1,911) for dementia alone and 1.88 (1.57 to 2.24; 180/710) for those with a low cognitive test score going to a new care home or other facility compared to (2,291/17,989) of survivors with no cognitive frailty (**Table 7.6** and Appendix Table 7.11 for full models). The most common discharge destinations other than to “usual place of residence” was to another hospital including community hospitals and rehabilitation units but not psychiatric hospitals (2,615/4,722 [55%]) or care home (1,339/4,722 [28%]).

Table 7.6 ORs for discharge destination other than home by type of cognitive frailty

Cognitive frailty	N (%)	Unadjusted OR (95% CI) ¹	p	Adjusted OR (95% CI) ¹	p
Delirium only	1,015 / 3,158 (32%)	3.25 (2.98 to 3.54)	<0.001	2.74 (2.50 to 2.99)	<0.001
Dementia only	505 / 1,911 (26%)	2.46 (2.20 to 2.75)	<0.001	1.99 (1.77 to 2.22)	<0.001
Delirium on dementia	728 / 1,977 (37%)	3.99 (3.61 to 4.42)	<0.001	3.15 (2.84 to 3.50)	<0.001
Low cognitive test score	183 / 710 (26%)	2.38 (2.00 to 2.83)	<0.001	1.88 (1.57 to 2.24)	<0.001
None	2,291 / 17,989 (13%)	1.00	NA	1.00	NA

¹OR = Odds Ratio, CI = Confidence Interval

7.3.7 Readmission

About 14% of discharged patients (3,523/25,815 for whom full follow-up data were available and 3,569/26,596 including those censored due to <30 days of follow-up) were readmitted to hospital within 30 days of discharge. Among readmitted patients, delirium was prevalent (first readmission – delirium only: 219/505 [43%] vs delirium on dementia: 176/301 [58%] vs dementia only: 128/279 [58%] vs low AMTS: 37/109 [34%] vs none: 312/2,329 [14%]). The adjusted (i.e., age, sex, mCCI and NEWS) cause-specific HRs for readmission within 30 days of discharge were 1.18 (95% CI 1.07 to 1.30; 505/3,192 [16%]) for delirium only, 1.17 (1.03 to 1.32; 301/1,993 [15%]) for delirium on dementia, 1.10 (0.97 to 1.25; 279/1,930 [14%]) for dementia only and 1.13 (0.93 to 1.38; 109/706 [15%]) for those with a low cognitive test score compared to no cognitive frailty (2,329/17,994 [13%]; **Table 7.7** and full models for adjusted ORs in Appendix Table 7.12 and HRs in Appendix Table 7.13), with similar results for the subdistribution hazard, i.e., competing risk model (see cumulative incidence in Appendix Figure 7.1). However, residence in a care home prior to admission modified associations between delirium alone (aHR care home: 1.01 [0.80 to 1.28]; $p=0.94$ vs not living in care home: 1.18 [1.06 to 1.32]; $p=0.002$) and superimposed on dementia (aHR care home: 0.83 [0.66 to 1.04]; $p=0.10$ vs not living in care home: 1.25 [1.08 to 1.45]; $p=0.004$) and readmissions compared to no delirium (reference group; see Appendix Table 7.14 for adjusted and unadjusted models). No cognitive frailty subtypes predicted readmission in those living in care homes prior to admission.

Table 7.7 Cause-specific HRs for in readmission <30 days of discharge in survivors for each type of cognitive frailty stratified by care home residence prior to admission. Adjusted for age, sex, mCCI and NEWS as appropriate.

Cognitive frailty	Full cohort					Care home residents			Non-care home residents		
	N (%)	Unadjusted HR (95% CI) ¹	p	Adjusted HR (95% CI) ^{1,2}	p	N (%)	Adjusted HR (95% CI) ²	p	N (%)	Adjusted HR (95% CI) ²	p
Delirium only	505 / 3,192 (16%)	1.26 (1.14 to 1.38)	<0.001	1.18 (1.07 to 1.30)	<0.001	94 / 552 (17%)	1.01 (0.80 to 1.28)	0.94	411 / 2,640 (16%)	1.18 (1.06 to 1.32)	0.002
Dementia only	279 / 1,930 (14%)	1.14 (1.01 to 1.29)	0.037	1.10 (0.97 to 1.25)	0.13	87 / 577 (15%)	0.86 (0.67 to 1.11)	0.25	192 / 1,353 (14%)	1.11 (0.95 to 1.28)	0.19
Delirium on dementia	301 / 1,993 (15%)	1.22 (1.08 to 1.38)	<0.001	1.17 (1.03 to 1.32)	0.20	107 / 782 (14%)	0.83 (0.66 to 1.04)	0.10	194 / 1,211 (16%)	1.25 (1.08 to 1.45)	0.004
Low cognitive test score	109 / 706 (15%)	1.19 (0.98 to 1.44)	0.077	1.13 (0.93 to 1.38)	0.20	20 / 127 (16%)	0.91 (0.58 to 1.44)	0.70	89 / 579 (15%)	1.15 (0.93 to 1.42)	0.20
None	2,329 / 17,994 (13%)	1.00	NA	1.00	NA	227 / 1,330 (17%)	1.00	NA	2,102 / 16,664 (13%)	1.00	NA

¹ OR = Odds Ratio, CI = Confidence Interval

² Adjusted for age, sex, mCCI and NEWS category (Low, Low-Medium, Medium, High)

³ N represent those used to calculate ORs

7.3.8 Sensitivity analyses

I performed four different sensitivity analyses. First, RRs were calculated in addition to ORs to evaluate “inflation” of effect sizes due to the high frequency of events in the cohort, but findings were similar with all associations reported in main analyses remaining significant (Appendix Table 7.15). Second, the definition of delirium was restricted to certain cases only (delirium only: n=2,290 vs delirium on dementia: n=1,439 vs dementia only: n=3,069 vs low cognitive test score: n=1,309) whereas in the main analyses delirium was defined as certain or uncertain cases. Results for sensitivity analyses were similar, although adjusted ORs with in hospital death for delirium alone and on dementia and delayed transfers of care for delirium on dementia were attenuated slightly (Appendix Table 7.16 & 7.17). Third, main analyses were repeated using the original CCI in place of the modified version excluding coded dementia (Appendix Table 7.18), which increased multicollinearity (although the variance inflation factor remained close to 1, i.e., 1.02, [1.01 to 1.03] for the modified CCI versus 1.25, [1.24 to 1.27] for the original in the full model for in hospital death). Fourth, in hospital outcomes for specialty groups were calculated to explore variation within the hospital setting (see Appendix Table 7.19-7.23).

7.4 DISCUSSION

I found that delirium, dementia and other cognitive frailty identified through routine screening predicted death, days in hospital, discharge delays and destination independent of age, sex, comorbidity and illness severity in older people with unplanned hospital admissions. Delirium, either alone or superimposed on dementia, was most strongly associated with in hospital death but conveyed an increased risk of mortality which persisted over the entire follow-up period of up to four years. Only delirium in non-care home residents predicted 30-day readmission.

In-hospital death was increased in the group with delirium independent of age, sex and comorbidity with the strongest associations seen in the group with low or low-medium NEWS scores, who comprised the majority of admissions. It was previously shown that delirium was most strongly associated with death in fit versus frail medical patients, but our data do not support the author's hypothesis that this difference is likely explained by greater illness severity in the fit group (although this hypothesis will be explored formally in **Chapter 8**).⁴¹ Notably, delirium was associated with worse survival up to four years after the index admission. This association between delirium and long-term survival may be confounded by risk factors such as frailty but is probably partly causal with recent evidence identifying delirium as a risk factor for incident cognitive decline.⁴²⁻⁴⁴ Delirium was also associated with more time spent in hospital in addition to delays in discharge. Hospital admission may increase the risk of falls and other iatrogenic events which could contribute to mortality.^{45,46} A "post-hospital syndrome" has also been proposed in which people are at an increased risk of *new* acute illness for a period after discharge.⁴⁷ Delirium was not associated with readmissions in the group resident in

care homes prior to admission, possibly because of readmission avoidance strategies or a comparatively greater ability of care homes (versus home care packages) to adapt to meet increased patient needs post-discharge.

Previous data on dementia outcomes hospital-wide were also limited, despite policy emphasis on improving care for this population.^{22,48} In ORCHARD-EPR, dementia in the absence of delirium was associated with increased in-hospital death independent of age, sex, comorbidity and illness severity compared to patients with no cognitive frailty with relative risks remaining constant over the entire follow-up period in contrast to delirium. Dementia alone was also associated with increased length of stay in hospital but notably the median length of stay was approximately half of that for the delirium group, including after adjustment for comorbidity and illness severity. Dementia alone was also independently associated with delayed discharge and discharge to a destination other than home but was not associated with readmission. Associations were comparatively weaker for dementia versus delirium (evaluated based on overlapping 95% CIs). Possible explanations might include residual confounding by illness severity, differences in hospital care or discharge planning (LoS was more variable for delirium, i.e., IQR of 13-14 days versus 8 for dementia),⁴⁹ and the independent effects of delirium (i.e., on cognition).⁴²⁻⁴⁴ Outcomes for delirium on dementia were mostly similar to those for delirium alone, which suggests that delirium has a smaller contribution to outcomes in dementia patients and that interventions for preventing and treating delirium may have a quantitatively larger impact on outcomes in patients without diagnosed dementia.

Comparison to other studies

Results for dementia and delirium in ORCHARD-EPR were mostly similar to overall findings from previous hospital-wide and general medicine cohorts (see **Appendix**). However, only two cohorts controlled for demographics, comorbidity and illness severity of which one reported outcomes for delirium alone as well as delirium on dementia. Delirium was associated with mortality in hospital (RR 3.90 and HR 3.5) in the two studies adjusting for illness severity (n=278 and n=542), remaining associated with death over at least two years of follow-up where reported (HR 2.0), similar to ORCHARD-EPR.^{7,8} Length of stay varied more widely from a mean difference of -0.2 to +13 days for delirium compared to no delirium and no studies reported on delayed transfers of care, despite its frequent emphasis by policymakers.^{6,7,10,16,17} Delirium was associated with 1.26 to 2.86-fold (n=278-626) increased risk of discharge to an institution after adjustment for demographics, comorbidity, illness severity and other factors but the quality of the evidence in a mix of hospital-based cohorts was rated very low due to selection, reporting bias and imprecision in a systematic review.^{7,9,16,50} A lower risk of readmission in people with delirium was reported in two out of three studies but data were not stratified by care home residence or other factors.^{9,12,13,51}

Multiple reviews on dementia in hospital patients in a mix of hospital-based cohorts have reported associations with mortality (pooled RR 1.74, 1.50-2.05 for n=3 studies), length of stay and discharge destination (pooled OR 2.14, 1.24–3.70 for n=5 studies), but adjustment for confounding was limited and few data are from hospital-wide or general medicine cohorts.^{2,3,5} Hospital-wide, “known dementia without a current cognitive concern” (n=8,202) was associated with reduced inpatient

death (OR 0.69, 0.50-0.95) and greater length of stay (LoS >10 days: 2.16, 1.79-2.61), risk of delayed discharge (2.17, 1.80-2.62), discharge to a care home (2.51, 2.00-3.14), but had no impact on readmission (1.10, 0.96-1.25) after adjustment for age, sex, comorbidity and illness severity in addition to other variables.^{14,52} In the general medicine setting, dementia was associated with death in hospital (unadjusted RR 2.1; n=617) and increased length of stay (mean difference of 8 and 32 days), but there were a lack of data on readmission and the impact of care home residence unlike in ORCHARD-EPR.¹⁹ In the one study reporting delirium, delirium on dementia and dementia separately, outcomes of delirium and delirium on dementia were mostly similar. The study also reported data for low AMTS, which were consistent with ORCHARD-EPR findings.^{13,51}

7.4.1 Strengths and limitations

The main strength of this study is that it provides more granular and robust data on a hospital-wide cohort of consecutive, unselected patients whereas most previous studies were smaller, limited to general medicine patients and/or were selective, for instance requiring consent or excluding patients with terminal illness.^{6-12,18} It also adjusts for and explores important confounders and effect modifiers, reports data on several outcomes relevant to practice and policy and includes up to four years of follow-up. The collection of these data was made feasible through the extraction of routinely collected data from the hospital electronic patient record, including the exploitation of routine cognitive screening practices in OUHFT to obtain clinical assessments of cognitive status rather than rely on administrative coding data.

This study also has several limitations. First, ORCHARD-EPR data are real-world rather than collected according to a standard protocol and misclassification is possible, particularly for cognitive frailty status. Sensitivity analyses of certain versus uncertain delirium did not show any meaningful differences in results, however, as also shown in **Chapter 5**. Additionally, some patients were missing cognitive screens but this group tended to have fewer risk factors for cognitive frailty as discussed in **Chapter 6**. Second, there may be residual confounding. In particular, comorbidity and illness severity are complex concepts which are not fully captured by CCI or NEWS scores. The CCI includes dementia so to avoid over adjustment a modified CCI excluding coded dementia was used in main analyses, with the original CCI used in sensitivity analyses, but models produced conflicting results for dementia (and delirium on dementia). Third, first admissions were analysed as opposed to all admissions to avoid violating the assumption of independent observations which involved a trade-off with data loss but given the size of the dataset probably had a minimal impact on results. Fourth, long-term data on disposition were not available. About 55% of patients discharged to a destination other than their usual residence were discharged to a community hospital or rehabilitation unit, but it was not possible to determine what proportion of these patients returned home or what their care needs were. Lastly, all data are from four hospitals in one region of England so results may not be fully applicable to other centers. For example, different service models, practices and resources could impact outcomes, particularly length of stay, discharge destination and delayed transfers of care.

7.4.2 Implications

My research has several implications for clinicians, policymakers and researchers.

First, the consistent associations seen between cognitive frailty and adverse outcomes independent of age, sex, comorbidity, and illness severity in the ORCHARD-EPR cohort supports current guidance recommending routine screening for delirium and dementia in older people with unplanned hospital admissions, regardless of specialty.^{1,53-55} The finding that associations between cognitive frailty and adverse outcomes were strongest for delirium underscores the need for improved delirium recognition and management hospital-wide in particular. Across the NHS (and likely other health systems), as little as 40% of delirium in older people with emergency admissions is recognised.¹ In clinical practice, poor delirium recognition has been associated with increased mortality and functional decline although no randomised trials for screening as an intervention have been done.⁵⁶⁻⁵⁸

Second, short-term outcomes and the finding that cognitive frailty is associated with delayed discharges and discharges to places other than patients' homes including intermediate care settings provide large-scale evidence to support research and policy change related to these outcomes, for example more integration between acute hospital, intermediate care and community services for this population. Third, although several current policies emphasise reducing readmissions in people with dementia, dementia was not associated with readmissions in ORCHARD-EPR.²² Readmissions were only increased for delirium in people living at home prior to admission and the proportion of all 'first' readmissions attributable to delirium in the ORCHARD-EPR cohort was about 3% (55 per year) based on adjusted HRs. Fourth, the finding that patients with delirium have worse long-term prognoses than patients

without delirium supports a role for follow-up with GPs to optimise care, discuss goals of care and power of attorney or memory clinics.²⁰

7.4.3 Conclusion

In conclusion, all types of cognitive frailty are associated with increased short and long-term mortality, length of stay, delayed discharge and discharge to a place other than home, but readmission was only associated with delirium in patients living at home prior to hospital admission. These data, together with the prevalence data that presented in **Chapter 6**, support guidance on routine screening for cognitive frailty in the hospital setting, including delirium and dementia. In addition, data support the targeting of resources to patients with delirium, particularly those living in the community prior to admission, who may have the most to gain through multidisciplinary interventions. Additionally, findings encourage future research on interventions to improve short- and long-term delirium outcomes in patients with unplanned hospital admissions. In the next chapter, I will look at physical frailty as an effect-modifier to understand its contribution to cognitive frailty outcomes in the acute hospital population and obtain a more granular understanding of outcome with the goal of informing routine screening and the targeting of interventions.

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Chapter 8

Prevalence and outcomes of physical frailty in older people who have unplanned hospital admissions by cognitive frailty and delirium status in ORCHARD-EPR

ABSTRACT

Background: Cognitive and physical frailty are prevalent in older hospital patients with unplanned admissions as shown in Chapters 2 & 6 and might differentially impact survival and care needs. Most existing studies focus on cognitive or physical frailty alone; therefore, in this chapter, I aimed to determine the prevalence of concurrent cognitive and physical frailty and impact on outcomes in this population.

Methods: ORCHARD-EPR (2017-2019) includes routine data from older patients with unplanned hospital admissions in Oxfordshire, UK including a mandatory cognitive screen (Abbreviated Mental Test Score-AMT, dementia and delirium) for those ≥ 70 years. I determined associations between moderate/ severe physical frailty (modified Hospital Frailty Risk Score-mHFRS ≥ 5) and survival, length of stay in hospital (LoS), delayed discharge, discharge home and readmissions for groups

with no cognitive frailty, any cognitive frailty and delirium only using regression models adjusted for age, sex, comorbidity and illness severity.

Results: Most patients with cognitive frailty had moderate/severe physical frailty (73%; 6,677/9,137), but fewer than half with moderate/severe physical frailty were cognitively frail (46%; 6,677/14,544). Despite being independently associated with survival, moderate (adjusted HR 1.11 [95% CI 1.04 to 1.19], $p<0.001$ vs cognitive frailty/mHFRS <5) and severe (1.01 [95% CI 0.92 to 1.11], $p=0.82$) physical frailty added little to mortality risk in those with cognitive frailty. In contrast, long LoS, delayed discharge and discharge to a place other than home were markedly increased by physical frailty in all groups including patients with cognitive frailty (e.g., adjusted ORs for LoS >10 days, moderate: 2.77 [95% CI 2.46 to 3.11] & severe physical frailty: 6.98 [5.99 to 8.15]; $p<0.001$ both vs cognitive frailty/mHFRS <5). Physical frailty was not associated with readmission in any group ($p>0.1$).

Discussion: Moderate/severe physical frailty was common in inpatients with cognitive frailty, but not ubiquitous. Cognitive and physical frailty were both independently predictive of outcomes, with physical frailty adding to risks of long LoS, delayed discharge and discharge to a place other than home in patients with cognitive frailty. Findings support separate cognitive *and* physical frailty screening in hospitals and delivery of holistic interventions to high-risk groups. Future work could develop and evaluate tailored frailty pathways based on cognitive and physical frailty status using routine screening data from hospital EPRs.

8.1 INTRODUCTION

Several guidance documents aiming to improve hospital care for people living with cognitive and physical frailty recommend that older people identified as having either condition receive comprehensive geriatric assessment (CGA) or similar care but, as discussed earlier, efforts to expand CGA across specialty acute services are limited by resources including geriatrician availability.¹⁻³ Improved risk stratification could help individualise care and target interventions to those most likely to benefit from specialist geriatric input but data on which patients are most likely to benefit are limited outside of specialist settings.⁴ I reported on outcomes in patients with physical frailty in **Chapter 3** and cognitive frailty in **Chapter 7**, but many patients will have both conditions concurrently which might differentially affect survival and care needs.^{5,6} “Broad-brush” approaches to care may result in less efficient use of resources, especially in settings where specialist geriatric input is too limited to provide to all frail patients.¹ Other examples of how better prognostic data on the combined burden of cognitive and physical frailty could be useful include informing decision-making, for example regarding living arrangements, rehabilitation goals and advance care planning; service-planning, for example streamlining of frailty and delirium care pathways and trial design.

I identified few studies in general medicine or hospital-wide populations that reported prevalence and outcomes of both cognitive and physical frailty although there is strong evidence that both conditions are related (see Introduction chapter and Appendix Table 1.5). Frailty is an established risk factor for delirium, and both are associated with mortality as shown in earlier chapters.⁷ The association between

delirium and mortality was found to weaken at lower levels of frailty (measured using a frailty index which included comorbidity, observations, lab values and functional status measures) although there are few data on other outcomes (e.g., length of stay, discharge outcomes and readmission).⁸ The reasons for this finding are unclear but illness severity was suggested to confound the association.⁹ Additional studies on cognitive frailty outcomes have adjusted for physical frailty in regression models such that risk ratios represent outcomes for people with no frailty (i.e., when dichotomised) or the average level of frailty in the cohort (i.e., when continuous) and did not account for potential interactions.¹⁰⁻¹² Some frailty measures in published studies include both cognitive and physical frailty but most do not ascertain cognitive frailty accurately, for example, using ICD codes in non-validated datasets and delirium/confusion was only evaluated in two measures (see **Chapter 2**).¹³⁻²⁶

Thus, my objectives in this chapter were to determine (i) the prevalence of concurrent physical and cognitive frailty; and (ii) the predictive value of physical frailty for poor outcomes related to unplanned admissions (i.e., death, length of stay, delayed discharge, discharge destination and readmission) by cognitive frailty and delirium status.

8.2 METHODS

8.2.1 Study design

In this study, I used pseudo-anonymized data for consecutive, unselected adult hospital and ambulatory admissions to four Oxfordshire hospitals captured in ORCHARD-EPR 2017-2019 (hereafter 'ORCHARD-EPR') as described previously.

Individual consent was not required but individuals could opt-out (REC reference: 18/SC/0184).

8.2.2 Eligibility

I included consecutive unplanned admissions ≥ 70 years to all specialties if they had a length of stay ≥ 1 day and age, sex, National Early Warning Score (NEWS) version 1 and one or more ICD-10 codes were recorded.

8.2.3 Cognitive screen and procedures

Oxfordshire University Hospitals NHS Foundation Trust (OUHFT) policy requires all patients with unplanned admissions ≥ 70 years of age (and younger patients at high-risk) to be screened for cognitive frailty via an EPR-embedded form that includes:

- The 10-point Abbreviated Mental Test Score (AMT; score out of 10)
- “Does the patient have a known diagnosis of dementia?” (‘Yes,’ ‘Uncertain,’ ‘No’; confirmed with the patient, relatives and/or medical records)
- “Does the patient have delirium?” (‘Yes,’ ‘Uncertain,’ ‘No’; informed by the Confusion Assessment Method-CAM)

I defined dementia as present if ‘yes’ was given for the dementia question on the cognitive screen or dementia ICD-10 codes were present. I defined delirium as present if a response of ‘yes’ or ‘uncertain’ was given for the delirium question on the screen and/or at least one ICD-10 code for main analyses (see Chapter 5). I defined low cognitive test score as an AMTS <8 in the absence of diagnosed dementia or delirium.²⁷ I defined cognitive frailty as delirium, dementia or a low AMTS score in the absence of delirium or dementia as per previous chapters.

8.2.4 Modified hospital frailty risk score

I measured physical frailty using a modified version of the Hospital Frailty Risk Score (mHFRS). The original HFRS is a 109-item score derived from ICD-10 codes that was developed to measure frailty from administrative data in the hospital setting and validated in NHS Digital's Hospital Episode Statistics database.¹⁵ In this study, I calculated the HFRS using data from the index admission: previously it was shown that associations between the HFRS and outcomes were broadly similar when the score was calculated from the index admission versus the index admission and all other admissions from the previous two years, although frailty prevalence was higher when more admissions were included.²⁸ To create the mHFRS, I excluded ICD-10 codes specific for cognitive frailty diagnoses (i.e., dementia and delirium) from the HFRS. This approach allowed me to obtain a measure of "physical frailty" (with the secondary benefit of avoiding bias related to differences in dementia and delirium coding accuracy between the dataset used to derive the HFRS and ORCHARD-EPR which is likely more accurate).^{29,30} Of note, conditions in the HFRS were selected based on their prevalence in patients identified as frail using a proxy measure based on clustering of ICD-10 codes, bed days and cost data. Therefore, it was not possible to fully differentiate between the cognitive and physical impacts of conditions scored in the HFRS. The inclusion of conditions associated with both cognitive and physical frailty in the HFRS such as epilepsy, cerebrovascular and Parkinson's highlights this issue. These conditions were retained in the mHFRS because they were assumed to contribute significantly to physical frailty and according to NHS England Clinical Coding Standards, associated cognitive deficits are required to be coded separately (e.g., F01X for "vascular dementia").³¹

I categorised the mHFRS as <5, 5-15 and >15 (corresponding to low, moderate and severe frailty) or dichotomised it as <5 vs ≥ 5 (i.e., no to mild frailty vs moderate to severe frailty) in main analyses as per the original HFRS paper and visually inspected outcomes across the full range of both scores.¹⁵ See Supplemental Methods 1-4 for comparisons of the mHFRS and HFRS, as well as the distribution of clinical frailty markers (i.e., incontinence, bedfast/chairfast and high pressure sore risk; see Chapter 8 appendix, pg. 485 and Appendix Figure 8.0 for a comparison of the predictive value of the mHFRS vs HFRS for outcomes). I performed sensitivity analyses including (i) re-analysis of select outcomes using the HFRS instead of the mHFRS and (ii) using more sensitive cut points as suggested by one study in COPD patients comparing HFRS and Clinical Frailty Scale (i.e., <1.5, 1.5-5 & >5) to evaluate the robustness of my findings.³²

8.2.5 Outcomes and group at risk

I assessed death (censored May 21, 2021), length of stay (LoS), delayed transfer of care (DTOC), discharge to different place of residence and readmissions as described in Chapter 7. Analyses for 1-year mortality, DTOC > 2 days, discharge destination and 30-day readmissions were limited to those who survived to discharge to avoid bias from the competing risk of death, with binary analyses of 30-day readmissions limited to those with 30-days of follow-up.

8.2.6 Covariate measurement and choice

Full detail on routine variables reported by clinical and administrative staff are provided in Chapter 4. I adjusted for age, sex, illness severity and comorbidity in all

models unless otherwise specified.³³⁻³⁵ I used NEWS version 1 as a proxy for illness severity (categorised as low, low-medium, medium or high in regression models or low/low-medium and medium/high for stratification (i.e., scores of < or ≥ 5).³⁶ I used a modified Charlson co-morbidity Index (mCCI) based NHS Digital Summary Hospital-level Mortality Indicator (SHMI) weightings but excluding dementia to avoid bias due to coding variation (see sensitivity analysis in the Chapter 7 supplement).³⁷

8.2.7 Statistical analysis

In main analyses, I grouped patients (first admissions only) based on the presence of cognitive frailty only, physical frailty only, cognitive+physical frailty or neither.

Regression was also done to estimate the relative risk of moderate to severe physical frailty (HFRS 5-15 and >15 vs <5) in groups with any cognitive frailty, delirium only and no cognitive frailty. I analysed data for delirium only separately because delirium was the most common form of cognitive frailty and most strongly associated with poor outcomes in Chapter 7. General analytical considerations are discussed in Chapter 4; however, additional detail is included below:

Descriptive statistics

I calculated descriptive statistics for characteristics on admission, including by HFRS and mHFRS frailty group using mean/standard deviation or n/% as appropriate with statistical tests (see figure legends).

Outcomes

I modelled relative risks using regression with unadjusted and fully adjusted (i.e., age, sex, mCCI and NEWS category) results reported. As described in Chapter 7, I

modelled binary outcomes with logistic regression and reported results as odds ratios with 95% Wald confidence intervals. I plotted time-to-event outcomes on Kaplan-Meier curves and did analysis with Cox proportional hazards regression. I evaluated model fit by plotting binned residuals versus fitted values and for survival analysis, the proportional hazards assumption was checked with Schoenfeld tests and plots. Where the proportional hazards assumption was violated, I included time-by-covariate interactions in models (but I only reported non-time-varying models where there was no difference between models). I evaluated for multicollinearity and the linearity of continuous covariates versus outcomes as previously described.

Effect modification

Effect modification describes when the association between the exposure and outcome is modified by another variable. In addition to the stratification approach described above, I formally quantified effect modification on multiplicative and additive scales. I reported additive effect modification as the relative excess risk of interaction (RERI) which describes departures from an additive scale (i.e., the sum of the effects of the two factors differs from their effects individually). I also reported multiplicative effect modification which describes departures from a multiplicative scale (i.e., the product of the effects of the two factors differs from their effects individually).^{38,39} For these analyses, I used binary categories for the mHFRS (i.e., <5 and ≥ 5) to aid in interpretability. Results are shown in the appendix.

Software

I performed all statistical analyses in R version 4.2.1 using the packages *stats*, *interactionR*, *performance*, *survival*, *survminer*, *tidycmprsk* and the *tidyverse*.⁴⁰⁻⁴⁵

8.3 RESULTS

8.3.1 Overlap between cognitive and physical frailty

Of 28,590 first admissions of people ≥ 70 years, cognitive frailty was present in 32% ($n=9,137$; mean/SD= 84.8/7.0 years and 56% female) and moderate to severe physical frailty in 51% (i.e., $n=14,544$ with mHFRS ≥ 5 ; mean/SD= 83.5/7.3 years and 55% female), with 59% of admissions having cognitive or physical frailty. Moderate to severe physical frailty (hereafter “physical frailty”) was present in 73% of patients with cognitive frailty (6,677/9,137 with mHFRS ≥ 5 and cognitive frailty); whereas cognitive frailty was present in 46% of patients with physical frailty (6,667/14,544; **Figure 8.1**).

Patients with cognitive frailty only were older ($n=2,460$; mean/SD cognitive frailty only: 83.8/7.0 years vs physical only: 82.1/7.3 years; $p<0.001$), more likely to live in a care home (21% vs 11%; $p<0.001$) and be in a higher NEWS category (i.e., high 9.3 vs 6.2; $p<0.001$), but less likely to have a primary diagnosis of infection (2.7% vs 13%; $p<0.001$) than those with physical frailty alone ($n=7,867$; see **Table 8.1**). The burden of comorbidity was greater in the group with cognitive frailty only (mean/SD CCI: 12.0/9.5 vs 8.3/8.7; $p<0.001$), but lower after dementia was excluded from the CCI (mCCI: 5.7/7.0 vs 8.3/8.7; $p<0.001$). Patients with both cognitive and physical frailty were the oldest ($n=6,627$; 85.2/7.0 years; $p<0.001$), most likely to live in a care home (25%; $p<0.001$) and had the greatest overall comorbidity burden (CCI: 13.9/10.6; $p<0.001$) of all groups. All groups differed from those without cognitive or physical frailty, i.e., $p<0.001$ for all characteristics examined except for mCCI ($p=0.69$) and infection in the cognitive frailty only group ($p=0.38$).

The most common type of cognitive frailty was delirium alone in both cognitive only and cognitive+physical frailty groups (cognitive only: 891/2,460 [36%] vs both: 2,954/6,667 [44%]), followed by dementia alone in the cognitive only group (cognitive only: 841 [34%] vs both: 1,315 [20%]) and delirium on dementia in the cognitive+physical group (457 [19%] vs 1,895 [28%]). Low cognitive test score was the least common (271 [11%] vs 513 [7.7%]). Physical frailty was the most prevalent in the groups with delirium compared to those with dementia (Figure 8.2 and Appendix Figure 8.1).

Figure 8.1 Venn Diagram showing overlap between cognitive and moderate to severe physical frailty, i.e., mHFRS ≥ 5 .

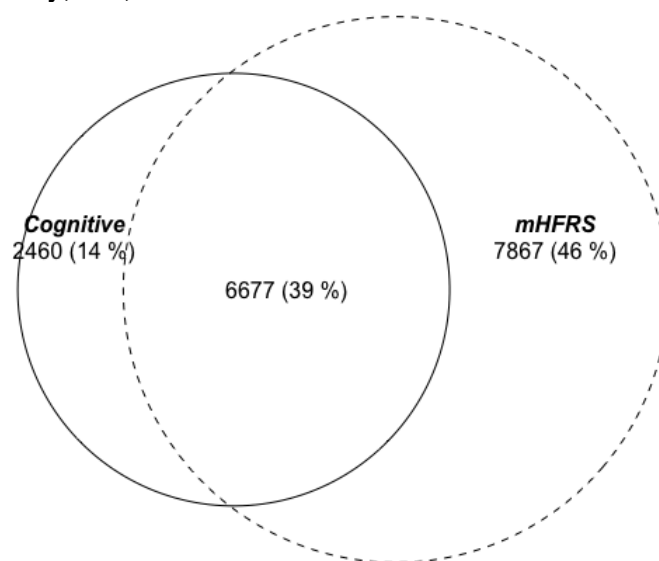


Figure 8.2 Physical frailty severity (mHFRS) by cognitive diagnosis

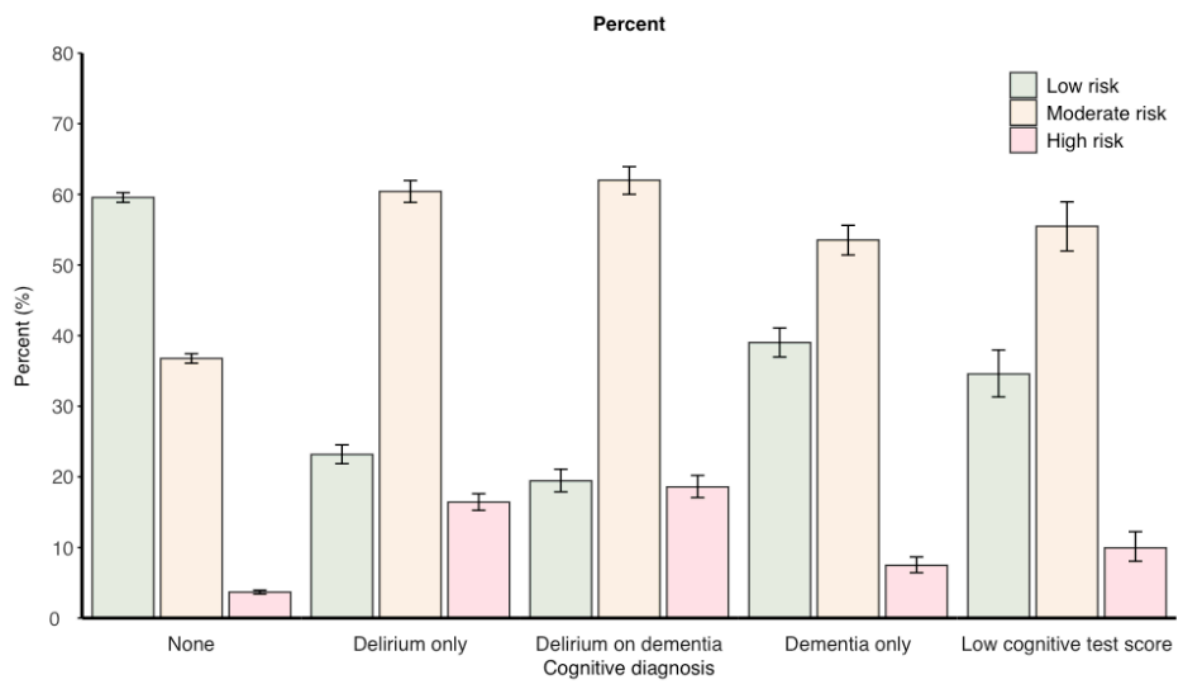


Figure 8.2 Physical frailty severity (mHFRS) by cognitive diagnosis

Table 8.1 Characteristics of groups with cognitive or physical frailty only, neither or both

Characteristic	Overall, N = 28,590	Neither, N = 11,586	Cognitive only, N = 2,460	Physical only, N = 7,867	Both, N = 6,677	p-value, all ^{1,3}
Age, Mean (SD)	81.8 (7.4)	79.2 (6.7)	83.8 (7.0)	82.1 (7.3)	85.2 (7.0)	<0.001
Female, n (%)	14,813 (52%)	5,523 (48%)	1,292 (53%)	4,153 (53%)	3,845 (58%)	<0.001
Care home resident, n (%)	3,594 (13%)	531 (4.6%)	526 (21%)	847 (11%)	1,690 (25%)	<0.001
CCI, Mean (SD)	8.9 (9.2)	5.7 (7.0)	12.0 (9.5)	8.3 (8.7)	13.9 (10.6)	<0.001
mCCI, Mean (SD) ²	7.0 (8.0)	5.7 (7.0)	5.7 (7.0) [#]	8.3 (8.7)	7.9 (8.7)	<0.001
Primary diagnosis of infection, n (%)	2,231 (7.8%)	354 (3.1%)	67 (2.7%) [#]	1,021 (13%)	789 (12%) [‡]	<0.001
NEWS category, n (%)						<0.001
- Low	21,396 (75%)	9,092 (78%)	1,697 (69%)	5,954 (76%)	4,653 (70%) [†]	
- Low-Medium	2,548 (8.9%)	881 (7.6%)	244 (9.9%)	678 (8.6%)	745 (11%)	
- Medium	2,789 (9.8%)	1,016 (8.8%)	291 (12%)	751 (9.5%)	731 (11%)	
- High	1,857 (6.5%)	597 (5.2%)	228 (9.3%)	484 (6.2%)	548 (8.2%)	
Treating specialty, n (%)						<0.001
- General Medicine	17,478 (61%)	5,765 (50%)	1,749 (71%)	4,836 (61%)	5,128 (77%)	
- General Surgery	2,304 (8.1%)	1,511 (13%)	276 (11%)	352 (4.5%)	165 (2.5%)	
- Specialty Medicine	3,065 (11%)	1,743 (15%)	165 (6.7%)	833 (11%)	324 (4.9%)	
- Specialty Surgery	3,129 (11%)	1,875 (16%)	179 (7.3%)	801 (10%)	274 (4.1%)	
- Trauma and Orthopaedics	2,614 (9.1%)	692 (6.0%)	91 (3.7%)	1,045 (13%)	786 (12%)	

¹Kruskal-Wallis rank sum test; Pearson's Chi-squared test

²The mCCI is the CCI excluding coded dementia

³All comparisons were significant at the <0.001 level, except those indicated by symbols: [#]p=0.69 and p=0.38 vs neither, respectively, [†]p=0.1 vs cognitive only, [‡]p=0.034 vs physical only.

8.3.2 In hospital death

Cognitive and physical frailty (mHFRS $\geq$ 5) were both independently associated with hospital death including after adjustment for age, sex, comorbidity and illness severity, but concurrent moderate to severe physical frailty contributed little additional risk above that of cognitive frailty with similar findings for delirium alone (see interaction effects in Appendix Table 8.1). In the group with no cognitive frailty, adjusted odd ratios (aORs) for in hospital death were 1.83 (95% CIs 1.59 to 2.10; 573/7,151 [8.0%]) for an mHFRS of 5-10 and 2.10 (1.59 to 2.73; 84/716 [12%]) for an mHFRS of >15 compared to an mHFRS of <5 (417/11,586 [3.6%]; p for both comparisons <0.001; **Table 8.2**). In the group with any cognitive frailty, aORs for in hospital death were 1.25 (1.07 to 1.47; p =0.006; 689/5,370 [13%]) for an mHFRS of 5-10 and 1.24 (1.00 to 1.54; p =0.05; 186/1,307 [14%]) for an mHFRS of >15 vs mHFRS<5 (248/2,460 [10%]) and in the group with delirium only, aORs for in hospital death were not significant (mHFRS 5-10: 1.01, [0.80 to 1.28]; p =0.94; mHFRS >15: 1.04, [0.77 to 1.41]; p =0.78 vs mHFRS<5; 119/891 [13%]). Stratification by illness severity (NEWS <5 vs $\geq$ 5) did not impact findings for any group (Appendix Table 8.2).

8.3.3 Mid and long-term survival

Survival for all cognitive and physical frailty groups over the entire study period is shown on a Kaplan-Meier plot (**Figure 8.3**). Again, cognitive and moderate to severe physical frailty were independently associated with death in the year following discharge (OR) and also over the entire study period (HR) including after adjustment for age, sex, comorbidity and illness severity, but physical frailty added little

additional risk above that of cognitive frailty or delirium when concurrent (see interactions in Appendix Table 8.1). In the group with no cognitive frailty, mHFRS predicted death: the aHR for mHFRS 5-15 was 1.22 (95% CI 1.16 to 1.29; $p<0.001$) and for mHFRS >15 was 1.30 (1.16 to 1.45; $p<0.001$) compared to mHFRS <5. However, in the group with any cognitive frailty aHRs were 1.11 (1.04 to 1.19; $p<0.001$) for mHFRS 5-15 and 1.01 (0.92 to 1.11; $p=0.82$) for mHFRS >15. In the subset of patients with delirium only, mHFRS 5-15 ($p=0.28$) or >15 ($p=0.50$) did not predict death.

Table 8.2 ORs for outcomes by cognitive and physical frailty status adjusted for age, sex, comorbidity and illness severity

Outcome and strata	mHFRS <5		mHFRS 5-15			mHFRS >15		
	n/N	OR	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value
In hospital death								
No cognitive frailty	417/11,586 (3.6%)	1	573/7,151 (8.0%)	1.83 (1.59 to 2.10)	<0.001	84/716 (12%)	2.10 (1.59 to 2.73)	<0.001
Any cognitive frailty	248/2,460 (10%)	1	689/5,370 (13%)	1.25 (1.07 to 1.47)	0.006	186/1,307 (14%)	1.24 (1.00 to 1.54)	0.05
Delirium only	119/891 (13%)	1	336/2,323 (14%)	1.01 (0.80 to 1.28)	0.94	103/631 (16%)	1.04 (0.77 to 1.41)	0.78
Death up to 1 year								
No cognitive frailty	1,662/11,169 (15%)	1	1,302/6,578 (20%)	1.11 (1.02 to 1.21)	0.016	156/632 (25%)	1.12 (0.92 to 1.37)	0.26
Any cognitive frailty	565/2,213 (26%)	1	1,376/4,655 (30%)	1.15 (1.02 to 1.29)	0.019	388/1,107 (31%)	1.10 (0.94 to 1.30)	0.24
Delirium only	174/772 (23%)	1	549/1,987 (28%)	1.16 (0.95 to 1.42)	0.16	142/528 (27%)	0.98 (0.75 to 1.29)	0.91
LoS >10 days		1						
No cognitive frailty	1,311/11,586 (11%)	1	2,039/7,151 (29%)	2.91 (2.69 to 3.15)	<0.001	396/716 (55%)	8.31 (7.07 to 9.77)	<0.001
Any cognitive frailty	445/2,460 (18%)	1	2,037/5,370 (38%)	2.77 (2.46 to 3.11)	<0.001	799/1,307 (61%)	6.98 (5.99 to 8.15)	<0.001
Delirium only	205/891 (23%)	1	950/2,323 (41%)	2.30 (1.93 to 2.75)	<0.001	391/631 (62%)	5.28 (4.21 to 6.65)	<0.001
DOOC >2 days								
No cognitive frailty	282/11,169 (2.5%)	1	951/6,578 (14%)	5.63 (4.90 to 6.48)	<0.001	202/632 (32%)	14.7 (11.9 to 18.1)	<0.001
Any cognitive frailty	176/2,212 (8.0%)	1	1,107/4,681 (24%)	3.49 (2.95 to 4.14)	<0.001	469/1,121 (42%)	7.99 (6.57 to 9.75)	<0.001
Delirium only	65/772 (8.4%)	1	489/1,987 (25%)	3.39 (2.59 to 4.50)	<0.001	226/528 (43%)	7.64 (5.63 to 10.5)	<0.001
Discharge destination								
No cognitive frailty	758/11,040 (6.9%)	1	1,284/6,325 (20%)	3.05 (2.76 to 3.36)	<0.001	224/581 (39%)	7.02 (5.81 to 8.48)	<0.001
Any cognitive frailty	389/2,180 (18%)	1	1,511/4,519 (33%)	2.26 (1.99 to 2.57)	<0.001	531/1,057 (50%)	4.61 (3.91 to 5.45)	<0.001
Delirium only	138/760 (18%)	1	620/1,903 (33%)	2.06 (1.67 to 2.55)	<0.001	257/495 (52%)	4.59 (3.55 to 5.97)	<0.001
Readmitted <30 days								
No cognitive frailty	1,355/11,103 (12%)	1	880/6,537 (13%)	1.03 (0.94 to 1.14)	0.49	76/606 (13%)	0.82 (0.63 to 1.05)	0.12
Any cognitive frailty	317/2,214 (14%)	1	714/4,657 (15%)	1.09 (0.94 to 1.26)	0.25	155/1,111 (14%)	0.95 (0.76 to 1.17)	0.61
Delirium only	122/762 (16%)	1	313/1,934 (16%)	1.00 (0.80 to 1.27)	0.99	70/496 (14%)	0.82 (0.59 to 1.14)	0.24

[†] OR = Odds Ratio, CI = Confidence Interval

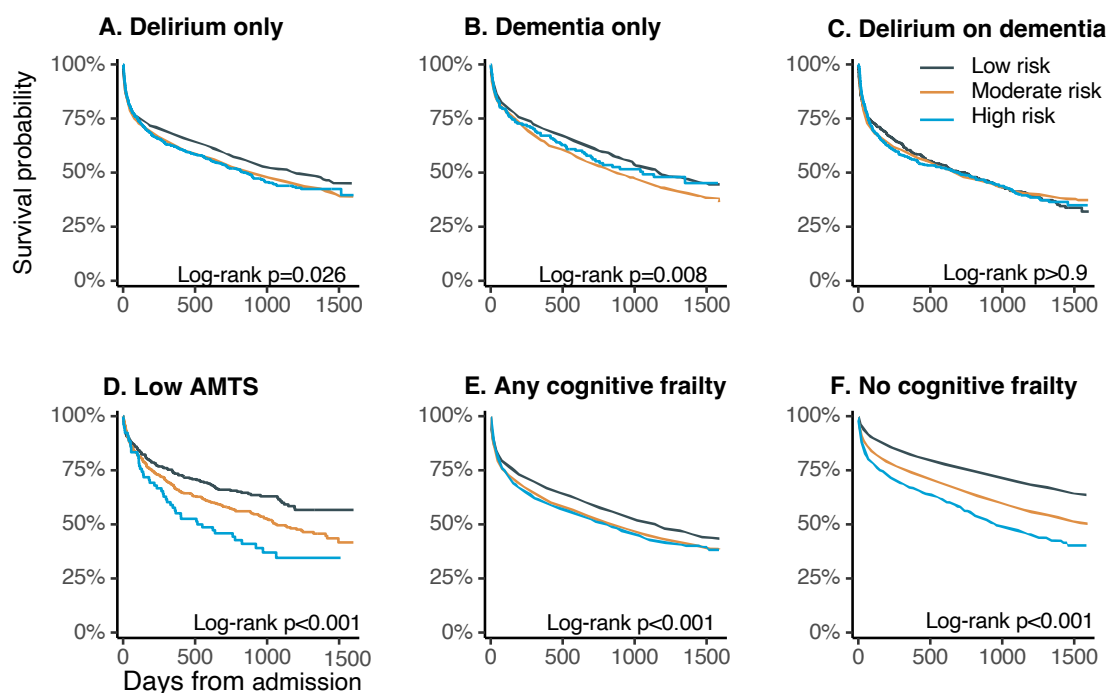
Table 8.3 Hazard ratios for death over the study period by cognitive and physical frailty status adjusted for age, sex, comorbidity and illness severity

Strata	mHFRS <5	mHFRS 5-15		mHFRS >15	
	HR ¹	HR (95% CI) ¹	p-value	HR (95% CI) ¹	p-value
No cognitive frailty	1	1.22 (1.16 to 1.29)	<0.001	1.30 (1.16 to 1.45)	<0.001
Any cognitive frailty	1	1.11 (1.04 to 1.19)	<0.001	1.01 (0.92 to 1.11)	0.82
Delirium only	1	1.06 (0.95 to 1.19)	0.28	0.95 (0.82 to 1.10)	0.50

¹ HR = Hazard Ratio, CI = Confidence Interval

Note: although Schoenfeld's test was <0.05 for high NEWS scores, results for non-time varying models are presented because estimates for both models were not different.

Figure 8.3 Kaplan-Meier plot for survival by cognitive frailty subtype and physical frailty (mHFRS<5, 5-15 and >15) over the follow-up period



8.3.4 Length of hospital stay

The median (IQR) for LoS was 3 (1 – 8) days for cognitive frailty only, 6 (2 – 13) for physical frailty only, 8 (3 – 18) for cognitive and physical frailty compared to 3 (1 – 6) for neither ($p<0.001$). Moderate to severe physical frailty added to the risk of a long length of stay in hospital (>10 days) in groups with concurrent cognitive frailty and delirium alone including after adjustment for age, sex, mCCI and NEWS (see interactions in Appendix Table 8.1). More severe physical frailty was associated with worse outcomes. In the group with no cognitive frailty, aORs for length of stay greater than 10 days were 2.91 (95% CIs 2.69 to 3.15; 2,039/7,151 [29%]) for an mHFRS of 5-10 and 8.31 (7.07 to 9.77; 396/716 [55%]) for an mHFRS of >15 compared to an mHFRS of <5 (both $p<0.001$; mHFRS <5 : 1,311/11,586 [11%]; **Table 8.2**). In the group with any cognitive frailty, aORs were 2.77 (2.46 to 3.11; 2,037/5,370 [38%]) for an mHFRS of 5-10 and 6.98 (5.99 to 8.15; 799/1,307 [61%]) for an mHFRS of >15 vs <5 (445/2,460 [18%]), with similar or weaker associations seen for the delirium only group (mHFRS 5-10: 2.30 [1.93 to 2.75]; 950/2,323 [41%]; and mHFRS >15 : 5.28 [4.21 to 6.65]; 391/631 (62%); $p<0.001$ for both vs mHFRS <5 : 205/891 [23%]).

8.3.5 Delayed Discharge

Moderate to severe physical frailty contributed to the likelihood of having discharge delayed >2 days independently and in groups with cognitive frailty including after adjustment to age, sex, mCCI and NEWS (see interactions in Appendix Table 8.1), with more severe frailty associated with worse outcomes (see **Table 8.2**). In the

group with no cognitive frailty, aORs for delayed discharge >2 days were 5.63 (95% CIs 4.90 to 6.48; 951/6,578 [14%]) for an mHFRS of 5-10 and 14.7 (11.9 to 18.1; 202/632 [32%]) for an mHFRS of >15 compared to an mHFRS of <5 (both $p<0.001$; 282/11,169 [2.5%]). In the group with any cognitive frailty, aORs were 3.49 (2.95 to 4.1; 1,107/4,681 [24%]) for an mHFRS of 5-10 and 7.99 (6.57 to 9.75; 469/1,121 [42%]) for an mHFRS of >15 vs <5 (both $p<0.001$; 176/2,212 [8%]), with similar or weaker associations seen for the delirium only group (mHFRS 5-10: 3.39 [2.59 to 4.50]; 489/1,987 [25%]; and mHFRS>15: 7.64 [5.63 to 10.5]; 226/528 [43%]; $p<0.001$ for both vs mHFRS<5: 65/772 [8.4%]). When data were stratified by care home residence prior to admission, DTOC ≥ 2 days remained associated in all groups (Appendix Table 8.3 & 8.4).

8.3.6 Discharge destination

Moderate to severe physical frailty remained associated with discharge destination independently and over and above cognitive frailty including after adjustment for age, sex, mCCI and NEWS (see interactions in Appendix Table 8.1), with the greatest risk seen for more severe frailty both in groups with and without cognitive frailty (**Table 8.2**). In the group with no cognitive frailty, aORs were 3.05 (95% CIs 2.76 to 3.36; 1,284/6,325 [20%]) for an mHFRS of 5-10 and 7.02 (5.81 to 8.48; 224/581 [39%]) for an mHFRS of >15 compared to an mHFRS of <5 (both $p<0.001$; 758/11,040 [6.9%]). In the group with any cognitive frailty, aORs were 2.26 (1.99 to 2.57; 1,511/4,519 [33%]) for an mHFRS of 5-10 and 4.61 (3.91 to 5.45; 531/1,057 [50%]) for an mHFRS of >15 vs <5 (both $p<0.001$; 389/2,180 [18%]), with similar or weaker

associations seen for the delirium only group after adjustment (mHFRS 5-10: 2.06 [1.67 to 2.55]; 620/1,903 [33%]; and mHFRS>15: 4.59 [3.55 to 5.97]; 249/484 [52%]; $p<0.001$ for both vs mHFRS<5: 138/760 [18%]). Other than usual residence, the most common discharge destination was to another NHS hospital, regardless of cognitive and physical frailty status (e.g., for rehabilitation; cognitive: 207/2,180 [9.5%]; physical: 918/6,949 [13%]; both: 976/5,576 [18%] vs neither: 512/11,040 [4.6%]) or a care home (cognitive: 118/2,180 [5.4%]; physical: 362/6,949 [5.2%]; both: 741/5,576 [13%] vs neither: 118/11,040 [1.1%]).

8.3.7 Readmission

Readmissions within 30 days of discharge were associated with cognitive frailty but not physical frailty regardless of severity after adjustment for age, sex, mCCI and NEWS. Physical frailty also did not add to readmission risk in groups with cognitive frailty or delirium ($p>0.1$ for moderate or severe physical frailty vs no physical frailty in all strata; see Appendix Table 8.1 and **Table 8.2**). Results were similar in the time-to-event analysis and after stratification by care home residence prior to admission (Appendix Table 8.3 & 8.4).

8.3.8 Sensitivity analyses

Main analyses were repeated using the original HFRS instead of the mHFRS (Appendix Table 8.5-8.6 & Appendix Figure 8.2) and mHFRS with more sensitive risk groups (i.e., <1.5, 1.5-5 and >5; Appendix Table 8.7-8.8 & Appendix Figure 8.3), with broadly similar results.

8.4 DISCUSSION

I found that over half of inpatients aged 70 years or over in the ORCHARD-EPR cohort had cognitive frailty or moderate to severe physical frailty. Cognitive frailty was identified in about 46% of patients with physical frailty whereas physical frailty was present in about 73% of those with cognitive frailty. Cognitive and physical frailty both independently predicted survival although physical frailty contributed little additional risk beyond that associated with cognitive frailty with findings robust to adjustment for age, sex, comorbidity, and illness severity. Although cognitive and physical frailty both independently predicted long stays in hospital, delayed discharge and discharge destination, the cognitive+physical frailty group was at the greatest risk of these poor outcomes with more severe physical frailty associated with greater risk. Cognitive but not physical frailty was associated with readmission.

Cognitive and physical frailty were often concurrent with the greatest overlap seen for delirium: 80% of the delirium only group had an mHFRS ≥ 5 . Frailty is a known risk factor for delirium although most evidence is from specialist surgical settings.³³ A meta-analysis showed that the strength of association between frailty and delirium depended on the method of frailty ascertainment but did not report data for the HFRS from which the mHFRS is derived. Based on pooled results, the strongest associations were seen for the frailty index, which includes comorbidities and lab values (OR=6.15, 95% CI 3.75 to 10.07, n=3) and Clinical Frailty Scale, which accounts for functional impairment related to physical and cognitive frailty (4.07, 3.71 to 6.11, n=3) with the weakest associations seen for phenotypic frailty, which

includes physical characteristics (i.e. weight loss, energy, physical activity, grip strength and walking speed; 2.3, 1.36 to 3.88; n=7).^{7,46} It is uncertain if there is a causal relationship between frailty and delirium, but shared risk factors or pathology may account for some of the observed overlap.

Physical frailty measured with the mHFRS did not add to mortality risk in the group with cognitive frailty. One explanation for this apparent ceiling effect is that delirium conveys less risk (on average) in those who are already physically frail. However, the HFRS does not capture all aspects physical frailty which could bias the association towards the null.⁴⁷ Codes for weakness and weight in the absence of a specific diagnosis are not included in the HFRS despite being included in other frailty measures such as the Fried phenotype and the tool might underestimate frailty in patients with a lower comorbidity burden.^{15,46} A study in COPD patients reported that the original HFRS had a sensitivity of 27% and specificity of 93% compared to the CFS for identifying global frailty in inpatients with COPD, although poor coding of cognitive frailty in the study could have also contributed to this discrepancy.^{32,47} Notwithstanding, groups with physical frailty had the highest burden of frailty markers in ORCHARD-EPR including incontinence, immobility and pressure sore risk, followed by cognitive frailty alone and no frailty.

For the outcomes of length of stay, delayed discharge or discharge destination other than home, more severe physical frailty added to the 'baseline' risk associated with cognitive frailty. For example, the median length of stay was 3 days in the group with

cognitive frailty alone versus 8 days in the group with cognitive+physical frailty (and 6 days in the group with physical frailty alone). Cognitive+physical frailty could increase length of stay and other adverse outcomes through several mechanisms including increased complexity of care needs and a longer process of recovery. For example, delirium may increase length of stay which might contribute to loss of muscle mass and longer recovery times.⁴⁸ The additional complexity and uncertainty may also lead to disagreement within the patient's family and care team about the discharge goals for the patient, potentially contributing to delays.⁴⁹ Importantly, physical frailty predicted discharge to a destination other than home, again over and above the risk associated with cognitive frailty indicating that physical frailty underscores the increased care needs of this group. No association between physical frailty and readmission was found even after stratification by care home residence prior to admission, although it is possible that the lack of readmissions in the ORCHARD-EPR cohort indicate that effective discharge planning is taking place for this group.⁵⁰

Despite the increasing number of older people with cognitive and physical frailty, there is little evidence on outcomes for this population in the hospital setting. The finding that the impact of frailty on survival was greatest in the group without cognitive frailty was similar to findings from two studies of delirium and frailty. Dani et al (2018) found that delirium was most strongly associated with mortality in medical patients with the lowest tertile of the frailty index, which included comorbidities, observations, lab findings and functional status (age, sex-adjusted, (least frail HR

3.4, [95% CI 2.1-5.6] versus most frail HR 1.9, [1.2-3.0]).⁹ Similarly, Eeles et al (2012) found that increased frailty had the greatest impact on mortality in acute medical patients who did not have delirium, although delirium was associated with higher frailty scores.⁵¹ It had been hypothesised that associations between delirium and death were strongest in fit versus frail medical patients because of greater illness severity in the fit group. However, the finding that physically frail patients in ORCHARD-EPR were more likely to have high NEWS scores does not support this hypothesis. Another hypothesis was that delirium was more severe in the fit group, but delirium severity was binarised in both studies and physical frailty was not associated with delirium severity in a separate study.^{9,51,52} Additionally, neither Dani or Eeles et al. assessed the impact of physical and cognitive frailty on length of stay, delayed discharge or discharge destination for which physical frailty added to the risks associated with cognitive frailty alone in ORCHARD-EPR. Findings for cognitive and physical readmission were mixed in previous studies as discussed in earlier chapters, so the finding that physical frailty did not predict readmission regardless of cognitive status was not inconsistent with prior data.^{12,47,53-56}

8.4.1 Strengths and limitations

The main strength of this study is that it differentiates between cognitive and physical frailty, thus providing more granular risk-stratification in a large and heterogenous cohort of consecutive, unselected hospital admissions which was accomplished by exploiting routine EPR data. As mentioned in **Chapter 2**, cognitive frailty was rarely measured using validated tools in existing frailty studies and is poorly captured in

administrative datasets so its impact on outcomes could not be determined previously despite the implications for patient care.^{29,30} Nevertheless, this study using ORCHARD-EPR has several limitations including those discussed previously: (i) generalisability could be impacted by the study's single-centre design; (ii) misclassification of cognitive frailty due to the use of real-world clinical data rather than prospectively collected data; (iii) residual confounding due to incomplete adjustment for the constructs of comorbidity and illness severity with CCI and NEWS scores; and (iv) the use of retrospective coding data to measure frailty.⁴⁷ Different frailty measures identify distinct but overlapping groups, so it is possible that results will not be fully replicated if clinically administered tools such as the Clinical Frailty Scale are applied.³² In **Chapter 3**, I showed that clinically ascertained frailty was generally the most predictive of poor outcomes but routine screening using the CFS was not implemented at the time of ORCHARD-EPR data collection so only the HFRS was available. In addition, it was necessary to create a modified HFRS measuring predominantly physical frailty which was not externally validated, although as per the data and figures in the supplement, differences in predictive value of the HFRS and mHFRS appeared small.¹⁵ As noted in the Methods, some conditions are associated with both cognitive and physical frailty and as such cognitive frailty could not be fully removed from the mHFRS.

8.4.2 Implications

My findings have implications for frailty risk-stratification in clinical practice and policy. Differential associations between cognitive and physical frailty and outcomes

may help focus clinical interventions, research outcomes and policy objectives instead of broad-brush approaches. For example, the NHS “Delivery Plan for Recovering Urgent and Emergency Care Services” aims to reduce delays in discharging ‘complex’ patients. The data in this study suggest that those with concurrent cognitive and physical frailty (i.e., highest-risk group) could be a focus for intervention.⁵⁷ Physical frailty had a particularly strong impact on delayed discharge as well as length of stay and could be investigated further to understand the underlying issues and deficits in resources/services but also raises questions about the relevance of policy such as the UK Government’s “criteria to reside,” which aims to shorten time in hospital but includes limited mention of frailty despite over 75% of days in hospital and 90% of delayed discharges occurring in cognitively and/or physically frail patients in ORCHARD-EPR.⁵⁸ Additionally, my findings show that with current OUHFT practices, most older people with cognitive or physical frailty, with the exception of those with delirium who live in the community are not at an increased risk of readmission. Lastly, there is an important role for future research in elucidating the relationship between physical and cognitive frailty and developing tailored strategies for preventing further functional decline, for example increased emphasis on delirium prevention in physically frail patients.

8.4.3 Conclusion

In conclusion, I found that most older inpatients with cognitive frailty have moderate to severe physical frailty, whereas only about half of those with moderate to severe physical frailty are cognitively frail. While cognitive and moderate to severe physical

frailty both predicted mortality risk, there was a ceiling effect such that physical frailty had limited predictive value in patients with cognitive frailty and in particular delirium; however, for length of stay, delayed transfers of care and discharge destination, physical frailty added to the risk conveyed by cognitive frailty indicating that policy and service-planning should target resources to this high-risk group. Lastly, neither physical frailty nor cognitive frailty (except delirium in people living at home as mentioned in the last chapter) were associated with readmission. Future research should develop and evaluate interventions tailored to frailty status to improve short and long-term outcomes of cognitively and physically frail patients admitted to hospital.

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Chapter 9

Conclusions

9.1 Overview

In this thesis, I aimed to evaluate the value of hospital electronic patient records (EPRs) for determining the prevalence and prognosis of cognitive and physical frailty. Data on the burden of these conditions hospital-wide and by specialty are needed to enable the provision of good quality acute hospital care to an ageing population through informing clinical guidance, service-planning and policy, including routine cognitive and physical frailty screening as recommended by NHS England (Getting It Right First Time-GIRFT) and other organisations.¹⁻³ However, older people admitted to hospital with acute illness are a challenging population to conduct large-scale prospective research studies in for ethical and practical reasons, and widely-used secondary data sources (e.g., ICD codes) poorly capture the complexity of this population.⁴⁻⁶ Routinely acquired clinical data in hospital EPRs was anticipated to have advantages for measuring cognitive and physical frailty at-scale over both existing study designs by combining large, unselected samples with accurate ascertainment, but the value of these data had not previously been studied.

To identify gaps in the evidence and understand the limitations of existing study designs, I reviewed evidence on cognitive and physical frailty prevalence and outcomes in unplanned hospital and general medicine admissions. Previous

systematic reviews of cognitive frailty prevalence and outcomes mostly included small, selected prospective cohorts, underscoring the challenges of studying older people with unplanned hospital admissions.⁷⁻¹⁴ A handful of administrative coding and routine clinical data studies were also included although only one was hospital-wide and none had been validated.¹⁵⁻²² For comparison, only one systematic review on physical or global frailty in this population had been published and it did not include routine frailty screening data or the widely-used ICD code-derived Hospital Frailty Risk Score (HFRS).¹⁵

Therefore, in the first section of my thesis (Chapters 2 & 3) I undertook a systematic review/meta-analysis of physical and global frailty prevalence and outcomes in the acute hospital population including all observational study designs (i.e., prospective, routine clinical and administrative coding data studies). In the second section of my thesis (Chapter 5-7), I validated and analysed routine cognitive screening data from ORCHARD-EPR 2017-2019 with the aim of evaluating its potential for overcoming the limitations of previous prospective and administrative coding study designs. ORCHARD-EPR is a unique and potentially powerful research resource which captures EPR data from >100,000 acute care admissions including a routine cognitive screen for known dementia, delirium and low cognitive test score in those ≥70 years. In the final chapter (Chapter 8), I evaluated the overlap between cognitive and physical frailty in ORCHARD-EPR and impact on outcomes.

Key findings, implications and future research are discussed below:

9.2 Key findings

Physical frailty, prevalence and outcomes (Chapters 2 & 3)

To address the lack of evidence synthesis on physical or global frailty in hospital-wide and general medicine populations (which Hoogendijk et al. described as “emerging” in a 2018 Lancet review article),²³ I undertook a systematic review and meta-analysis of 45 hospital-wide and general medicine cohorts. In Chapter 2, I identified 22 tools used to measure frailty. Despite varying in length and complexity, these tools predominantly measured physical domains, justifying separate analysis of cognitive frailty domains in the remainder of the thesis. I also found that moderate/severe frailty was common in older patients with unplanned hospital admissions, with prevalence exceeding 25% in 37/40 cohorts despite heterogeneity (range 14-80%) not explained by setting or tool.

In Chapter 3, I showed that despite this heterogeneity in prevalence, moderate/severe frailty was associated with increased mortality with the strongest, most consistent associations seen in studies using clinically administered tools ($n = 11$; pooled $RR = 2.53$, 95% $CI = 2.15$ to 2.97 , $p_{het} = 0.08$) compared to tools using administrative coding data, with associations remaining significant after adjustment for age, sex, comorbidity and illness severity. Moderate/severe frailty was also associated with increased length of stay (LoS) and discharge to a destination other than home, but associations with readmission were conflicting. Taken together, the prevalence of frailty and adverse impact on outcomes over and above other risk factors provide evidence to support more widespread frailty screening in older hospital patients using pragmatic clinical tools such as the Clinical Frailty Scale

(CFS) to identify patients for comprehensive geriatric assessment (CGA) and frailty pathways in line with current guidance.

Cognitive frailty data in ORCHARD-EPR vs a prospective audit (Chapter 5)

Routinely acquired cognitive screening data had not been validated for research use previously, so I compared cognitive frailty prevalence (i.e., dementia, delirium, low cognitive test score) for general medicine admissions in ORCHARD-EPR to prospectively collected audit data in Chapter 5. Cognitive frailty prevalence was 35% in ORCHARD-EPR (n=18,614 of whom 78% had completed cognitive screens) when limited to certain cases compared to 50% in the audit data (n=731), mostly owing to differences in delirium diagnosis. In ORCHARD-EPR, in which clinicians could record delirium as 'yes,' 'no,' or 'uncertain,' the prevalence of certain delirium was 17% and uncertain was 11% compared to delirium prevalence of 38% in the audit cohort, where delirium was dichotomised as 'yes' or 'no.' Importantly, I showed that patients with uncertain delirium were a high-risk group with similar mortality risk to those with certain delirium. Risks of long LoS in hospital, delayed discharge and discharge to a destination other than home were higher for uncertain delirium versus no delirium but were attenuated compared to certain delirium possibly as a result of lower physical frailty scores in the uncertain delirium group (revisited in Chapter 8). Overall, I concluded that the accuracy of cognitive frailty data in ORCHARD-EPR improved on other large-scale research methods including labour intensive chart review (0.1-64% of cases documented) and analysis of administrative coding data (1.5-49% of cases coded) and was suitable for future research.⁶

Cognitive frailty prevalence and outcomes in ORCHARD-EPR (Chapters 6 & 7)

As described in the Introduction chapter, previous prospective studies of cognitive frailty prevalence and outcomes were mostly small, selected and limited to a single specialty whereas administrative data studies were large ($n > 4,957$) but were likely to underreport delirium. Using ORCHARD-EPR data to overcome these limitations, I found that cognitive frailty prevalence was 35% among 51,202 admissions hospital-wide, of whom 73% had cognitive screens, with a mean age of 82 years. Delirium in the absence of established dementia was the most common cognitive diagnosis (15%; $n = 7,411/51,202$) even though dementia has received comparatively more attention from policymakers and funders; followed by delirium on dementia (9%; $n = 4,757$), dementia alone (7%; $n = 3,784$) and low Abbreviated Mental Test Score (AMTS) score with no delirium or dementia (3%; $n = 1,514$).

Additionally, cognitive frailty was prevalent in all 29 specialties I examined. Although most cognitively frail patients were admitted to three large services (general medicine - 41% [$n = 13,879/33,512$] prevalence, trauma/orthopaedics - 35% [$n = 1,304/3,673$] and general surgery - 21% [$n = 801/3,819$]), cognitive frailty was frequent in patients admitted to other specialty services, including some not traditionally associated with caring for older people, for example infectious disease (27%; $n = 41/152$), neurosurgery (22%; $n = 154/702$), gastroenterology/hepatology (18%; $n = 44/250$) and radiotherapy (16%; $n = 50/234$). Findings indicate that specialised geriatric services should be scaled hospital-wide to increase access to recommended care for rising numbers of older people with unplanned admissions to generalist and specialist hospital services.

ORCHARD-EPR also provided a rich and granular data source from which outcomes could be evaluated: using data from 28,432 first admissions hospital-wide, I showed that all cognitive frailty was predictive of death, long stays in hospital, delayed discharge, and discharge to a destination other than home, including after adjustment for age, sex, comorbidity and illness severity. Mortality risk was front-loaded for delirium (adjusted ORs for in hospital death for delirium alone 2.56, [95% CI 2.29-2.86], delirium on dementia 2.27 [1.97 to 2.60] and dementia alone 1.41 [1.19 to 1.66] vs no cognitive frailty; all $p<0.001$) but remained elevated over up to four years of follow-up ($p<0.001$). Additionally, delirium was most strongly associated with death in those with lower illness severity scores (National Early Warning Score-NEWS <5) and no known dementia. Regarding readmissions, only delirium in non-care home residents was predictive (aORs for 30-day readmission for delirium alone 1.18 [1.06 to 1.31] and delirium on dementia 1.22 [1.05 to 1.42] vs no cognitive frailty; both $p<0.01$).

Overlap of cognitive and physical frailty and impact on outcomes (Chapter 8)

Most patients with cognitive frailty had moderate/severe physical frailty (73%; 6,627/9,092), but only half with physical frailty were cognitively frail (54%; 7,820/14,447). Despite being independently associated with survival, moderate (adjusted HR 1.11 [95% CI 1.04 to 1.18], $p=0.003$) and severe (aHR 1.00 [95% CI 0.91 to 1.10], $p>0.99$) physical frailty added little to mortality risk in those with cognitive frailty. This finding was consistent with two previous studies, one of which hypothesised that the weaker association between delirium and mortality in individuals with more severe frailty might be explained by lower illness severity in these patients.^{24,25} However, this hypothesis was not supported in ORCHARD-EPR

because illness severity was relatively unaffected by frailty status and delirium more strongly predicted mortality in the group with lower illness severity. In contrast to mortality (but consistent with Chapter 5), long LoS in hospital, delayed discharge and discharge to a destination other than home were markedly increased by physical frailty regardless of cognitive frailty status. For example, among individuals *with* cognitive frailty, aORs for LoS >10 days were 2.73 (95% CI 2.43 to 3.07) for moderate and 7.00 (6.00 to 8.18) for severe versus no/mild physical frailty ($p<0.001$ for both comparisons). Physical frailty was not associated with readmission in any group ($p>0.1$).

9.3 Implications and future research

The value of EPRs for measuring frailty hospital-wide

In the Introduction chapter, I argued that to provide advantages over existing study designs, routine clinical data studies must provide valid, population-representative estimates of the burden of frailty at large-scale, i.e., hospital-wide and enable more granular understanding of frailty prevalence and outcomes. In this thesis, I showed that routine clinical data captured in ORCHARD-EPR combined accurate ascertainment of cognitive frailty (41% vs 50% in prospective audit data) with large sample size ($n=51,202$ admissions), hospital-wide coverage (29 specialty services) and independent associations (i.e., over age, sex, comorbidity and illness severity) with death, LoS in hospital, delayed discharge and discharge destination. For comparison, sample sizes of prospective studies of delirium and dementia ranged from $n=200$ -1,507 ($n=14$ studies) and most had eligibility criteria that could introduce bias, for example requirements for consent, which was also a concern in studies

included in my systematic review of physical/global frailty prevalence and outcomes.^{4,26-34}

Delirium and dementia prevalence was also higher in ORCHARD-EPR than in most retrospective coding data studies indicating that they likely underestimated prevalence (i.e., 25% for delirium in ORCHARD-EPR vs 1.7% and 10% in coding studies; 20% for dementia in ORCHARD-EPR vs 7%, 8% and 25% in coding studies). Additionally, ORCHARD-EPR improves on earlier studies of routine cognitive frailty screening data, two of which were limited to general medicine admissions and did not adjust outcomes for illness severity and one which only screened for delirium in patients without dementia. These studies had not been validated, whereas I showed that cognitive frailty prevalence in ORCHARD-EPR compared favourably to prospective audit data, although delirium was probably underestimated in ORCHARD-EPR.^{20,21,35}

Additionally, the richness of data fields in ORCHARD-EPR enabled adjustment for confounding and investigation of effect heterogeneity in order to improve understanding and prediction of cognitive frailty outcomes. For example, using ORCHARD-EPR data I was able to show that cognitive frailty, and particularly delirium, predicted in hospital mortality over and above illness severity on admission measured with NEWS and that the only form of frailty associated with readmission was delirium in individuals not living in care homes prior to admission. After finding that cognitive frailty was poorly captured by global frailty measures in my systematic review, I investigated the overlap between cognitive and physical frailty and found that physical frailty measured using a modified version of the HFRS markedly

increased the risk of with long LoS, delayed discharge and discharge destination, but not mortality in individuals with cognitive frailty.

Implications for guidance, services and policy

As outlined above, real-world, routine cognitive screening data in ORCHARD-EPR provides important data on the burden of frailty to inform guidance, service-design, research and policy priorities. First and foremost, findings support more widespread implementation of routine screening for cognitive and physical frailty in people of 70 years and over with unplanned admissions to any specialty using clinically administered tools. I showed that cognitive frailty was present in 35% of individuals 70 years and over hospital-wide and moderate/severe frailty in 51% (compared to a range of 14-80% across n=40 cohorts in my systematic review).³⁴ Both cognitive and physical frailty independently predicted death, LoS, delayed discharge and discharge to a destination other than home over and above other prognostic factors including age, sex, comorbidity and illness severity. Crucially, ORCHARD-EPR demonstrates that routine cognitive screening at scale is both feasible and sustainable over the long-term with screening ongoing since 2013- on paper and 2015- via the EPR.

Findings also support separate screening for both cognitive and physical frailty in line with GIRFT and other guidance.¹ Cognitive frailty domains were poorly captured by global measures of frailty, with all tools identified in my systematic review predominantly or exclusively measuring physical frailty. Also, cognitive and physical frailty were not ubiquitous in ORCHARD-EPR: most (but not all) cognitively frail patients were physically frail whereas only about half of physically frail patients had cognitive frailty. Future guidance, services and policy may aim to address cognitive

and physical frailty more holistically, for example, through coordinated delirium and frailty pathways instead of in siloed approaches.^{36,37}

Additionally, the finding that cognitive frailty was prevalent in all acute hospital specialties is important. Routine cognitive screening could lead to improved quality of care for frail patients treated by specialist services, for example by improving the identification of patients who might lack capacity and the ability to consent to procedures.³⁸ This finding additionally provides evidence to support expansion of acute frailty services hospital-wide despite initial challenges with scaling services.³⁹ As mentioned in Chapter 6, a mix of mobile frailty teams in 'low prevalence' specialties and ward-based teams, which have a stronger evidence-base and may be more cost effective in 'high prevalence' specialties could be considered.³⁹ It is important to acknowledge that cognitive frailty prevalence was likely underestimated in specialties with low screening rates, but addressing barriers to screening such as insufficient resources might improve compliance.^{40,41}

ORCHARD-EPR data could also be used to risk-stratify groups and target resources. Delirium was the most common form of cognitive frailty identified in ORCHARD-EPR and most strongly associated with poor short-term outcomes including in hospital death which provides evidence to prioritise the establishment of delirium pathways which are recommended by GIRFT.¹ In another example, physical frailty markedly increased length of stay in hospital, delayed discharge and discharges to a destination other than home with patients with concurrent cognitive frailty at the greatest risk which could help focus discharge planning. Coordination between

hospital and community services likely improves outcomes for this population and is an ongoing area of research.⁴²

Suggestions for future research

Strengths of ORCHARD-EPR were discussed above, however, data have some shortcomings which could be addressed by future work. First, although 73% of patients had cognitive screening data and patients missing data were younger, with fewer frailty markers and shorter LoS, screening varied across specialties (i.e., 38-90%). Multiple imputation could be used to in future work to better understand the impact of missing data. Second, ORCHARD-EPR data were only available from one acute trust from 2017-2019 which might impact the generalisability of some findings. From 2024 onwards, ORCHARD-EPR aims to include data from the Royal Berkshire NHS Foundation Trust which will increase representativeness of the study population, bringing it more in line with England overall. Future research might seek to continue to improve implementation nationally with the dual goals of increasing uptake of cognitive and physical frailty screening in line with current guidance and increasing the number of sites with EPR data available for research.^{5,43}

Third, there were limitations in the availability of data in ORCHARD-EPR 2017-2019 which are relevant to informing clinical guidance, particularly data on screening patients at younger ages (e.g., <70 years) and clinically administered frailty measures (only the ICD code-derived HFRS was available for my thesis). However, from 2020 onwards, OUHFT began introducing the CFS to measure global frailty and from 2024 onwards, routine cognitive screening is mandated for patients ≥ 65 years

and will be able for future analysis, thus future evidence could support routine screening in patients 65-70 years as well.

Future research could also build on the findings presented in my thesis by providing a more granular understanding of frailty outcomes. In this thesis I explored the impacts of dementia, frailty, care home residence and illness severity on delirium outcomes but did not, for example, consider delirium burden. While delirium burden is unlikely to be assessed for in ORCHARD-EPR in the future, it may be possible to develop proxy measures to capture severity and duration using existing data such as the AMTS and length of stay. Trials could also use data on cognitive frailty including severity to automatically flag patients for recruitment into prospective studies and trials. As demonstrated in Chapters 6 & 7, delirium has a large burden in the acute hospital setting and is an important target for future research in light of recent work showing that it increases the risk of future dementia by 2-3 fold, with individuals with high baseline cognition at the greatest risk.⁴⁴⁻⁴⁶ Additionally, a tool for real-time risk-stratification from routine frailty screening data could also be developed to flag patients for review by an acute frailty service and help target services in hospital and the community, for example automated frailty data sharing with primary care.

9.4 Conclusions

This thesis demonstrates that routinely collected cognitive screening data embedded in hospital EPRs can be a powerful tool for acute frailty research by combining accurate cognitive frailty ascertainment and a large, inclusive sample size, as demonstrated in ORCHARD-EPR. These real-world data are important for filling

gaps in research where prospective cohorts are not feasible or ethical and administrative data fails to capture the complexity of the older hospitalised population. Overall findings from ORCHARD-EPR support more widespread implementation of cognitive screening and frailty pathways. Notably, delirium in the absence of diagnosed dementia was the most common form of cognitive frailty in hospitals and should be a focus of future research, service-planning and policy given its outsized impact on short- and long-term outcomes.

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Appendices

Appendix 1 Supplemental material for Chapter 1

Appendix Table 1.1 Examples of national-level guidance on screening for cognitive and physical frailty in general medical admissions and hospital-wide

Author (Year)	Screening recommended?		Screening methods	Population
	Physical or global frailty	Cognitive frailty		
Australia				
Australia Quality Commission (2021)A,1	NR	Delirium	No	Age ≥ 65 years (≥ 45 years for Aboriginal and Torres Strait Islander), known cognitive impairment or dementia, previous delirium, severe medical illness or hip fracture (pg. 11)
Canada				
Canadian Coalition for Seniors' Mental Health (2006)B,2	NR	Delirium	No	Older people in acute care hospitals
Netherlands				
Veiligheids-management-systeem (VMS; 2012)C,3,4	Yes	Memory problems, delirium	VMS	Age ≥ 70 years admitted to hospital
UK				
Department of Health (CQUIN; 2012)D,5	NR	Dementia, Delirium	Known dementia, clinical diagnosis of delirium, AMT-10	Age ≥ 75 years with emergency hospital admission
Scottish Intercollegiate Guidelines Network (SIGN; 2019)E,6	NR	Delirium	4AT	Patients at risk of delirium

Royal College of Physicians (RCP; 2021)F,7	Yes	Dementia, Delirium	CFS, history, 4AT	Age ≥75 years admitted to acute medical units
Getting it Right First Time (GIRFT; 2021)G,8	Yes	Delirium	CFS, 4AT	Older people (≥ 65 years) in the emergency pathway
National Institute of Health and Care Excellence (NICE; 2010, updated 2023)H,9	No	Delirium	4AT	Age ≥18 years in hospital or residential care with indicators of delirium
Department of Health (CQUIN; 2023)I,10	Yes	No	CFS	Age ≥65 years in emergency department or same day emergency care

AComprehensive Care Standard, Minimising patient harm, Action 5.29

BNational Guidelines for Seniors' Mental Health: The Assessment and Treatment of Delirium

CNEN 8009:2018 nl; Safety management system for hospitals and organisations which deliver hospital care

DUsing the Commissioning for Quality and Innovation (CQUIN) payment framework: Guidance on new national goals for 2012-13.

ESIGN 157: Risk reduction and management of delirium: A national clinical guideline

FAcute Care Toolkit 3

GGIRFT Geriatric Medicine: GIRFT Programme National Specialty Report

HDelirium: prevention, diagnosis and management in hospital and long-term care. Clinical guideline [CG103]

IAbbreviations: NR – no recommendation; CFS – Clinical Frailty Scale

Literature Review

I reviewed observational reporting delirium and dementia prevalence in adults >18 years with unplanned admissions hospital-wide or to general medicine services.

Search: I searched MEDLINE and EMBASE from inception to 28/02/2024 using MeSH and Emtree terms and text keywords related to [Delirium], [Dementia], [Cognitive Impairment], [Cognitive Defect/Decline], [Cognitive Spectrum Disorder] and [Hospitalisation]. I also searched reference lists of relevant reviews.

Eligibility: Studies were included if they (i) reported delirium or dementia ascertained using validated screening tools or diagnosed clinically in hospital (within the first three days of admission, unless assessed retrospectively); (ii) included mostly unplanned admissions (>70% as stated by the study author or inferred from the study description); and (iii) reported data for hospital-wide or general medicine admissions. Studies were excluded if they were (i) conducted in outpatient, emergency department, short-stay, geriatric, rehabilitation, mixed or specialty-specific settings; (ii) conducted in non-representative populations (diagnosis, clinical trial, risk profile, excluded patients with dependency, etc.); (iii) $n < 100$; (iv) did not report cohort age and/or (v) the full text was not available in English.

Screening and data extraction: I performed title-abstract ($n=2,148$) and full-text screening. I extracted data including study and participant characteristics, recruitment method, delirium/dementia ascertainment method and prevalence, including by specialty where available. See tables below.

Appendix Table 1.2 Studies reporting delirium prevalence in general medicine and hospital-wide cohorts

Study (n=17)	Country	N	Sampling (% enrolled)	Age in years	Female (%)	Exclusion criteria	Delirium ascertainment	Details of ascertainment	Prev (%)	Prev dementia group (%)
Hospital-wide										
GMRC (2019) ^{*11}	UK	1,507	Convenience (63%)	80	54%	Age <65 years, ICU, palliative, logistics	DSM-V if 4AT ≥4/12	Assessed day of study by research team (P)	15% (20% possible delirium)	32%
GMRC (2021) ¹²	UK	626	Retrospective (NA)	80	54%	Age <65 years, LoS <2 days, elective	Chart review	Done by research team (O)	21%	44%
General medicine										
Anand (2022; Lothian) ¹³	UK	43,946	Consecutive (100%)	79	56%	Age <65 years, elective	4AT ≥4/12	On admission by clinician (C)	14%	NA
Bonjour (2021) ¹⁴	Switzerl and	22,323	Retrospective (100%)	80	52%	Age <65 years	ICD-10 codes	Administrative coding data (A)	10%	NA
Collins (2010) ¹⁵	UK	710	Consecutive (88%)	83	59%	Age <70 years, elective, logistics, refused, non- English speaking	CAM	Assessed by psychiatrist or registrar <72 h of admission (P)	16%	50%

Dani (2017) ¹⁶	UK	710	Consecutive (NA)	83	59%	Age <70 years, LoS <48 hours, non-English speaking	Clinical assessment including CAM	Assessed on admission by psychiatrist (P)	10%	NA
Eeles (2010) ¹⁷	UK	278	Unclear, presumed consecutive (71%)	83	58%	Age <75 years, no patient/proxy consent	DSM-IV	Assessed on admission and every 48 h by geriatrician (P)	37%	57%
Erkinjuntti (1986) ¹⁸	Finland	2000	Consecutive (100%)	79	57%	Age <55 years	Clinical criteria	Assessed by internists (O)	15%	41%
Fortini (2014) ¹⁹	Italy	560	Consecutive (94%)	80	50%	Age <65 years, no patient/proxy consent	CAM	Assessed daily by doctor (P)	11%	NA
Gallerini (2013) ²⁰	Italy	74,379 (38,607 >75 years)	Retrospective (100%)	71	53%	NA	ICD-9-CM	Administrative coding data (A)	1.7% (1.8% >75 years)	NA
Gonzalez (2007) ²¹	Chile	542	Consecutive (NA)	78	62%	Age <65 years, no patient/proxy consent, unable to do assessments (incl. coma, severe aphasia)	CAM	Assessed every 48 h by research team (P)	35%	NA
Gottlieb (1991) ²²	USA	235	Consecutive (33%)	77	61%	Age <70 years, admitted for short stay or terminal care, ICU, coronary	DSM-III	Assessed within ~24 of admission by research team; diagnoses	20%	NA

						care, stepdown care, dialysis or chemotherapy admissions, repeat admissions, no consent		confirmed by psychiatrist (P)		
Lakhan (2011) ²³	Australia	413	Random (72%)	82	55%	Age <70 years, LoS <48 hours, coronary or intensive care unit, palliative, transferred	DSM-IV	Assessed daily by nurses; diagnosis confirmed by geriatrician if available (P)	18%	NA
Muresan (2016) ²⁴	Ireland	200	Consecutive (93%)	81	50%	Age <70 years, palliative, severe aphasia, intubation, sensory problems, non-English speaking, no patient/proxy consent or consultant assent	CAM and DRS-R-98	Assessed day of enrolment and days 3, 7 and 10 by research team (P)	23%	NA
Pendlebury (2015) ²⁵	UK	503 (308 >65 years)	Consecutive (100%)	72 (81 >65 years)	52% (54% >65 years)	Age <65 years (unless received CAM or cognitive test)	DSM-IV, informed by CAM	Assessed by clinician on admission, reviewed daily with consultant geriatrician (P)	20% (31% >65 years)	51% (NA >65 years)

Praditsuwan (2013) ²⁶	Thailand	225	Consecutive (50%)	78	49%	Age <70 years, intubated, unable to communicate, uncooperative, transferred or too unwell	DSM-IV	Assessed on admission and every 48 h by geriatrician (P)	49%	72%
Reynish (2018) ²⁷	UK	10,014	Consecutive (79%)	79	57%	Age <65 years, <1 year follow-up, no OPRAA assessment (incl. LoS <24 h, imminent death and ICU)	CAM or clinical diagnosis	Assessed on admission by specialist nurses (C)	25%	46%

Legend: Prev = Prevalence. NA = not available. See details of ascertainment: (P) = Prospective ascertainment. (C) = Routine clinical data. (A) = Routine administrative data. (O) = Other or unclear. Ascertainment tools: DSM = Diagnostic and Statistical Manual of Mental Disorders. ICD-10 = International Classification of Diseases, Tenth Revision. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification. Note: Studies with n<100 were excluded.

Appendix Table 1.3 Studies reporting dementia prevalence in general medicine and hospital-wide cohorts

Study (n=10)	Country	N	Sampling (% enrolled)	Age in years	Female (%)	Exclusion criteria	Delirium ascertainment	Details of ascertainment	Prev (%)	Prev dementia group (%)
Hospital-wide										
Bickel (2018) ²⁸	Germany	1,439	Entire wards on single day (58%)	79	54%	Age <65 years, rehabilitation, geriatrics, neurology, psychiatry, ICU or isolation ward; moribund; non-German speaking; patient/proxy consent	DSM-IV	Assessed by research team (inferred) (P)	18% (DSM-IV); 6.8% (medical records)	18% (CAM)
Eckart (2019) ²⁹	Switzerland	4,957	Retrospective (100%)	82	51%	Age <75 years, elective	ICD-10 codes	Administrative coding data (A)	7%	NA
Gilbert (2018; national validation cohort) ³⁰	UK	1,013,590	Retrospective (100%)	84	57%	Age <75 years, elective	ICD-10 codes	Administrative coding data (A)	26%	NA
Romero-Ortuno (2017) ³¹	UK	8,202	Consecutive (NA)	84	56	<75 years, non-elective admission	"Known dementia without a current cognitive concern"	Assessed by admitting clinician (C)	10%	NA

Timmons (2015) ^{*32}	Ireland	598	Consecutive (88%)	80	51%	<70 years, day-cases, moribund, refused	DSM-IV or known dementia	Screening by nurse or psychologist, if SMMSE<27/30 or unavailable and no previous diagnosis recorded, then the patient was diagnosed by study author or expert panel (P)	25%	57%
General medicine										
Erkinjuntti (1986) ¹⁸	Finland	2,000	Consecutive (100%)	79	57%	Age <55 years	Cognitive decline impacting function	Assessed by internist if untestable or ≥2 mistakes on SPMSQ (O)	9%	41% (clinical criteria)
Muresan (2016) ²⁴	Ireland	200	Consecutive (93%)	81	50%	Age <70 years, palliative, severe aphasia, intubation, sensory problems, non-English speaking, no patient/proxy consent or consultant assent	Pre-existing dementia	Identified by study team from medical/GP records, collateral history and neuroimaging (O)	62%	NA
Reynish (2018) ²⁷	UK	10,014	Consecutive (79%)	79	57%	<65 years, no cognitive assessment done	Known dementia	Identified by specialist nurses from patient/ caregiver,	17%	46% (CAM or clinical diagnosis)

										hospital or primary care records (C)
Sampson (2009) ³³	UK	617	Consecutive (77%)	83	59%	<70 years, LoS <48 hours, unresolved delirium, non- English speaking	DSM-IV	Diagnosed in- hospital by psychiatrist (P)	42%	NA
Zuliani (2022) ³⁴	Italy	3,695,2 78	Retrospective (100%)	78	48%	Age <65 years	ICD-9-CM codes	Administrative coding data (A)	8%	NA

Legend: Prev = Prevalence. NA = not available. See details of ascertainment: (P) = Prospective ascertainment. (C) = Routine clinical data. (A) = Routine administrative data. (O) = Other or unclear. Ascertainment tools: DSM = Diagnostic and Statistical Manual of Mental Disorders. ICD-10 = International Classification of Diseases, Tenth Revision. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Note: Studies with n<100 were excluded.

Appendix Table 1.4 Hospital-wide studies reporting cognitive frailty prevalence by specialty

Study and disorder	Medicine	Surgery	Trauma and orthopaedics	Other specialties
GMRC (2019); Delirium (DSM-V if 4AT ≥4/12) ¹²	Acute (general) medicine 16% (106/648)	General surgery and other 5.5% (7/128)	Orthopaedic surgery 16% (15/95)	Geriatrics 22% (59/265) Other medicine 9.8% (31/315) Stroke 7% (4/56)
Bickel (2018); Dementia (DSM-IV) ²⁸	Internal medicine 21% (157/736)	General surgery 13% (32/250)	Trauma surgery 22% (58/265)	Other including orthopaedics, urology, gynaecology, ear, nose and throat, etc. 12% (23/187)
Timmons (2015); dementia (DSM-IV or known dementia) ³²	Medicine 26% (104/397)	Surgery 12% (14/117)	Geriatrics and orthopaedics combined 42% (31/73)	NA

Legend: Prev = Prevalence.

Appendix Table 1.5 Summary of studies reporting outcomes for delirium in hospital-wide and general medicine cohorts

Study (n=9)	N	Age in years	Female (%)	Summary of exclusion criteria	Delirium ascertainment	Prev (%)	Outcomes (delirium vs no delirium)	Adjusted for
Hospital-wide								
GMRC (2019) ¹¹	1,507	80	54%	Age <65 years, ICU, palliative, logistics	DSM-V if 4AT $\geq 4/12$ (P)	15%	LoS: MD 3.5 days; 1-month mortality: aOR 2.43 (CI 1.44-4.09); HR 1.62 (CI 1.00-2.61)	Age, gender, frailty, specialty and dementia
GMRC (2021) ¹²	626	80	54%	Age <65 years, LoS <2 days, elective	Chart review (O)	21%	LoS: MD 0.07 days; 1-month mortality: aOR 3.27 (1.65-6.48) ; HR 2.65 (1.40-5.01) Discharge to new care home: aOR 1.26 (CI 0.48-3.36)	Age, gender, dementia status, frailty and specialty
General medicine								
Anand (2022; Lothian) ¹³	43,946	79	56%	Age <65 years, elective	4AT $\geq 4/12$ (C)	14%	Inpatient mortality: aOR for 4AT 1-3 vs 0: 1.84 (CI 1.62-2.08) aOR for 4AT >4 vs 0: 5.53 (CI 4.99-6.13) 1-year mortality:	Age, sex

								aOR for 4AT 1-3 vs 0: 1.82 (CI 1.67-1.99) aOR 4AT for >4 vs 0: 3.49 (CI 3.20-3.80) 30-day readmission: aOR for 4AT 1-3 vs 0: 1.04 (CI 0.93-1.16) aOR for 4AT >4 vs 0: 0.59 (CI 0.51-0.67)	
Eeles (2010) ¹⁷	278	83	58%	Age <75 years, no patient/proxy consent	DSM-IV (P)	37%	LoS: MD 13 days In-hospital death: aHR 3.5 (CI 2.3-5.6) 1-year mortality: aHR 3.2 (CI 2.1-4.8) 2-5 year mortality: aHR 2.0 (CI 1.3-.3.2) Discharge: Discharged home: 36% delirium vs 81% no delirium Institutionalisation up to 5 years: 12% vs 13%; Time in hospital in year after admission: MD 13 days	Age, dementia, placement, Greenfield index (illness severity), CCI and Barthel Index (dependency)	
Gallerini (2013) ²⁰	74379 (38,607	71	53%	NA	ICD-9-CM (A)	1.7%	LoS: MD 0.2 days	NA	

>75 years)							
Gonzalez (2007) ²¹	542	78	62%	Age <65 years, no patient/proxy consent, unable to do assessments (incl. coma, severe aphasia)	CAM (P)	35%	LoS: MD 1.7 days In-hospital mortality: RR 4.90 (CI 1.95-7.88) 3-month mortality: RR 4.50 (CI 2.76-7.33); aHR 4.04 (CI 2.19-7.46) Age, sex, APACHE II (illness severity), Charlson Index, Pfeffer Functional Activities Questionnaire and Barthel (dependency) indices
Pendlebury (2015) ²⁵	503 (308 >65 years)	72 (81 >65 years)	52% (54% >65 years)	Age <65 years (unless received CAM or cognitive test)	DSM-IV (P)	20% (31% >65 years)	LoS >7 days: aOR 2.82 (CI 1.68-4.75) Discharge: New care home placement aOR 2.86 (CI 1.24-6.63) Increased care needs: aOR 2.45 (CI 1.28-4.70) in-hospital mortality: aOR 3.15 (CI 1.11-8.90) 30-day readmission: OR 0.31 (CI 0.09-1.1) Age, SIRS, dementia, pre-admission dependency (note: LoS was only adjusted for age and readmission data were unadjusted)
Praditsuwana (2013) ²⁶	225	78	49%	Age <70 years, intubated, unable to communicate, uncooperative, transferred or too unwell	DSM-IV (P)	49%	LoS: MD (-)2 days In-hospital mortality: aHR 7.34 (1.51-35.69) 3-month mortality: aHR 3.33 (1.45-7.62) Mortality: Severe illness (9-point ordinal scale reported by geriatricians), infection, malignancy, pre-renal azotaemia (BUN:Cr >20)

Reynish (2017, 2021) ^{27,35}	10,014 (6,724 incident admission s included in outcome analysis)	79	57%	Age <65 years, <1 year follow-up, no OPRAA assessment (incl. LoS <24 h, imminent death and ICU)	CAM or clinical diagnosis (C)	23.4% (15.8% delirium alone, 7.6% DSD)	LoS: RR delirium alone 1.91 (CI 1.76- 2.08); vs RR DSD 3.09 (CI 2.74-3.46) <30 day mortality: HR delirium alone 1.46 (CI 1.29-1.66); vs DSD 1.19 (CI 0.97-1.46); 1-2 year mortality, HR delirium alone 1.45 (1.18- 1.78); DSD not reported 30-day readmission, HR Delirium alone 1.18 (1.08- 1.30); DSD 1.07 (0.86-1.3	Demographics, comorbidity (ADL- adjusted models also reported)

Legend: Prev = prevalence. MD = mean or median difference. DSD = Delirium on Dementia. RR = risk ratio. OR = odds ratio. HR = hazard ratio. DSD = delirium on dementia. An 'a' before RR, OR or HR indicates that the estimate is adjusted as described in the table. CI = 95% confidence interval unless otherwise indicated. See delirium ascertainment: (P) = Prospective ascertainment. (C) = Routine clinical data. (A) = Routine administrative data. (O) = Other or unclear. Ascertainment method: DSM = Diagnostic and Statistical Manual of Mental Disorders. ICD-10 = International Classification of Diseases, Tenth Revision. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification. CAM = Confusion Assessment Method. DRS-98 = Delirium Rating Scale-Revised 98.

Notes: Muresan (2016) was not included because they did not report quantitative data, although they did show a Kaplan-Meier curve and mortality data for Gallerini (2013) was not reported because the follow-up time was unclear.

Appendix Table 1.6 Summary of studies reporting outcomes for dementia in hospital-wide and general medicine cohorts

Study (n=4)	N	Age in years	Female (%)	Summary of exclusion criteria	Delirium ascertainment	Prev (%)	Outcomes (delirium vs no delirium)	Adjusted for
Hospital-wide								
Romero-Ortuno (2017) ³¹	8,202	84	56%	<75 years, elective	"Known dementia without a current cognitive concern" (C)	10%	LoS >10 days: aOR 2.16 (CI 1.79-2.61) Inpatient mortality: aOR 0.69 (CI 0.50-0.95) Delayed discharge: aOR 2.17 (CI 1.80-2.62) Discharge to care home: aOR 2.51, (CI 2.00-3.14) 30-day readmission: aOR 1.10 (0.96-1.25)	Age, sex, acute confusional state, CFS>6 (frailty), CCI, ED-MEWS (illness severity), discharge specialty
General medicine								
Erkinjuntti (1986) ¹⁸	2000	79	57%	Age <55 years	Cognitive decline impacting function (O)	15%	LoS: MD 32 days	NA
Reynish (2017, 2021) ^{27,35}	10,014 (6,724 incident admissions)	79	57%	Age <65 years, <1 year follow-up, no OPRAA assessment (incl. LoS <24 h,	Identified by specialist nurses from patient/ caregiver, hospital or	15.4% (7.8% dementia alone;	LoS: MD 8 days for dementia alone (vs 22 days DSD) RR dementia alone 1.73 (CI 1.54-1.94); vs	Demographics, comorbidity (ADL-adjusted models also reported)

				included in outcome analysis)	imminent death and ICU)	primary care records (C)	7.6% DSD)	RR DSD 3.09 (CI 2.74-3.46) <30 day mortality: HR dementia alone 1.04 (CI 1.04-1.29); vs DSD 1.19 (CI 0.97-1.46); 1-2 year mortality, Not reported 30-day readmission, HR dementia alone 1.40 (1.23-1.59); DSD 1.07 (0.86-1.32);	
Sampson (2009) ³³	617	83	59%		<70 years, LoS <48 hours, unresolved delirium, non- English speaking	DSM-IV (P)	42%	In-hospital death: aHR 2.1 (95% CI 1.1-4.0)	Age, APACHE (illness severity)

Legend: Prev = prevalence. MD = mean or median difference. RR = risk ratio. OR = odds ratio. HR = hazard ratio. An 'a' before RR, OR or HR indicates that the estimate is adjusted as described in the table. CI = 95% confidence interval unless otherwise indicated. ADL = activities of daily living. See delirium ascertainment: (P) = Prospective ascertainment. (C) = Routine clinical data. (A) = Routine administrative data. (O) = Other or unclear. Ascertainment tools: DSM = Diagnostic and Statistical Manual of Mental Disorders. ICD-10 = International Classification of Diseases, Tenth Revision. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

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Appendix 2 Supplementary methods for Chapters 2 & 3

Appendix Table 2.1 Search strategy

#	MEDLINE 1946 to present	EMBASE 1974 to present	CINAHL
1	Frailty/	Frailty.tw,kw.	(MH "Frailty Syndrome") OR "frail" OR debilit* OR (TX (frail* W3 (assessment or index or scale or phenotype or indicator or risk or score or framework or tool or screen* or syndrome))) OR (MH "Geriatric Assessment") OR (MH "Geriatric Functional Assessment") OR (MH "Patient Assessment") OR (MH "Clinical Assessment Tools/CL/SN/MO") OR (MH "Functional Assessment")
2	Frail elderly/	Frail elderly/	("physical frailty phenotype" OR "deficit accumulation" OR "clinical frailty scale" OR "Fried frailty" OR "brief frailty index" OR "frail scale" OR frail-scale OR "modified frailty index" OR interRAI OR (vulnerable W1 (elders* W1 survey*) or VES-13) OR "Edmonton Frail Scale" OR "frailty staging system" OR "Conselice Study of Brain Aging Score" OR "geriatric screening tool" OR G-8 OR "multidimensional prognostic index" OR "kimon checklist" OR ((("Cardiovascular Health Study" or CHS) N2 criteria) OR "hospital frailty risk score" OR HFRS OR "electronic frailty index" OR eFI OR "geriatric assessment"))
3	Geriatric Assessment/	Geriatric Assessment/	1 OR 2
4	(frail* adj3 (assessment or index or scale or phenotype or indicator or risk or score or framework or tool or screen* or syndrome)).mp.	(frail* adj3 (assessment or index or scale or phenotype or indicator or risk or score or framework or tool or screen* or syndrome)).mp.	((MH "Hospitalization") OR "hospitalization" OR (MH "Inpatients") OR (MH "Aged, Hospitalized")) OR ((in#patient or in#hospital or hospital*)) OR ((admitted or admission*))
5	debilit*.tw,kf.	debilit*.tw,kw.	(MH "Prevalence") OR "Prevalence"
6	frail*.tw,kf.	frail*.tw,kw.	(MH "Treatment Outcomes") OR "Outcomes"
7	"physical frailty phenotype".tw,kf.	"physical frailty phenotype".tw,kw.	(MH "Hospital Mortality") OR (MH "Fatal Outcome") OR mortality OR death OR (MH "Survival Analysis") OR surviv\$
8	"deficit accumulation".tw,kf.	"deficit accumulation".tw,kw.	(MH "Readmission") OR (readmission* or re-admission* or readmitted or re-admitted) OR (re-hospital* or rehospital*) OR (return or re-attend* or

			reattend or re-visit* or revisit* or recidivism)
9	"clinical frailty scale".tw,kf.	"clinical frailty scale".tw,kw.	(MH "Length of Stay") OR (length or duration) adj3 (stay or hospital or admission*)
10	"Fried frailty".tw,kf.	"Fried frailty".tw,kw.	5 OR 6 OR 7 OR 8 OR 9
11	"brief frailty index".tw,kf.	"brief frailty index".tw,kw.	(MH "Prospective Studies+")
12	("frail scale" or frail-scale).tw,kf.	("frail scale" or frail-scale).tw,kw.	(MH "Epidemiological Research") OR (MH "Prospective Studies+") OR (MH "Case Control Studies+")
13	"modified frailty index".tw,kf.	"modified frailty index".tw,kw.	TX (Cohort OR prospective OR retrospective OR Longitudinal) OR TX (Case-control OR case control) OR TX (Follow-up or "follow up" W2 (study or studies)) OR TX (observational W2 (study or studies))
14	interRAI*.tw,kf.	interRAI*.tw,kw.	11 OR 12 OR 13
15	((vulnerable adj (elders* adj survey*)) or VES-13).tw,kf.	((vulnerable adj (elders* adj survey*)) or VES-13).tw,kw.	3 AND 4 AND 10 AND 14 [*Exclude Medline results filter applied]
16	"Edmonton Frail Scale".tw,kf.	"Edmonton Frail Scale".tw,kw.	
17	"frailty staging system".tw,kf.	"frailty staging system".tw,kw.	
18	"Conselice Study of Brain Aging Score".tw,kf.	"Conselice Study of Brain Aging Score".tw,kw.	
19	("geriatric screening tool" or G-8).tw,kf.	("geriatric screening tool" or G-8).tw,kw.	
20	"multidimensional prognostic index".tw,kf.	"multidimensional prognostic index".tw,kw.	
21	"kihon checklist".tw,kf.	"kihon checklist".tw,kw.	
22	((("Cardiovascular Health Study" or CHS) adj2 criteria).tw,kf.	((("Cardiovascular Health Study" or CHS) adj2 criteria).tw,kw.	
23	("hospital frailty risk score" or HFRS).tw,kf.	("hospital frailty risk score" or HFRS).tw,kw.	
24	("electronic frailty index" or eFI).tw,kf.	("electronic frailty index" or eFI).tw,kw.	
25	"geriatric assessment".tw,kf.	"geriatric assessment".tw,kw.	
26	or/1-25	or/1-25	
27	Hospitalization/	Hospitalization/	
28	Patient Admission/	Hospital patient/	
29	Inpatients/	(in#patient or in#hospital or hospital*).tw,kw.	
30	(in#patient or in#hospital or hospital*).tw,kf.	(admitted or admission*).tw,kw.	

31	(admitted or admission*).tw,kf.	or/27-30	
32	or/27-31	Prevalence/ or prevalence.tw,kw.	
33	Prevalence/ or prevalence.tw,kf.	outcome*.tw,kw.	
34	outcome*.tw,kf.	Hospital mortality/	
35	Hospital mortality/	mortality.tw,kw.	
36	mortality.tw,kf.	death*.tw,kw.	
37	death*.tw,kf.	Survival analysis/ or Proportional hazards/	
38	Survival analysis/ or Proportional hazards/	surviv\$.tw,kw.	
39	surviv\$.tw,kf.	Patient Readmission/	
40	Patient Readmission/	(readmission* or re-admission* or readmitted or re-admitted).tw,kw.	
41	(readmission* or re-admission* or readmitted or re-admitted).tw,kf.	(re-hospital* or rehospital*).tw,kw.	
42	(re-hospital* or rehospital*).tw,kf.	return.tw,kw.	
43	return.tw,kf.	(re-attend* or reattend*).tw,kw.	
44	recidivism.tw,kf.	(re-visit* or revisit*).tw,kw.	
45	(re-attend* or reattend*).tw,kf.	recidivism.tw,kw.	
46	(re-visit* or revisit*).tw,kf.	exp Length of Stay/	
47	exp Length of Stay/	((length or duration) adj3 (stay or hospital or admission*)).tw,kw.	
48	((length or duration) adj3 (stay or hospital or admission*)).tw,kf.	or/32-47	
49	or/33-47	(epidemiolog* adj (study or studies)).mp.	
50	Epidemiologic studies/	exp cohort analysis/	
51	exp Cohort studies/	exp Case control studies/	
52	exp Case control studies/	cohort.mp.	
53	cohort.mp.	"case control".mp.	
54	"case control".mp.	(observational adj (study or studies)).mp.	
55	(observational adj (study or studies)).mp.	((Follow-up or "follow up") adj (study or studies)).mp.	
56	((Follow-up or "follow up") adj (study or studies)).mp.	(prospective or retrospective).mp.	

57	(prospective or retrospective).mp.	or/49-56	
58	or/50-57	26 and 31 and 48 and 57	
59	26 and 32 and 49 and 58		

Modified Joanna Briggs Institute Tools for Risk of Bias

A list of items included in Joanna Briggs Institute (JBI) Checklists for prevalence studies and cohort studies are provided,^{1,2} along with specific considerations for this review.

Guidance for scoring is provided in the table below. Each item was answered as “yes,” “no,” “not applicable” or “unclear,” however, the overall assessment was made holistically. A study providing an estimate for the prevalence of frailty or its association with outcomes that is very likely, likely, or unlikely to be correct for the author’s stated target population would be assigned a low, moderate or high risk of bias, respectively. In general, a study at a low risk of bias would meet or nearly meet all criteria, whereas a study could be assigned a high risk of bias based on one or more serious flaws in the study design. A study at a moderate risk of bias would be in between—not meeting all criteria, but not having serious methodological concerns either. Additionally, an assessor could describe an entire study as uncertain if there is insufficient information.

Appendix Table 2.1 Modified Joanna Briggs Institute Checklist for Prevalence Studies

Item	Scoring Guidance
1 Was the sample frame appropriate to address the target population and was sufficient coverage of the sample frame achieved? (Original items #1 & 5)	Yes: The prevalence of frailty is likely to be similar between the sample frame and target population identified by the authors. This may be inferred from participant characteristics, and eligibility criteria AND there should also be no important differences in age, sex, or other factors between participants and eligible non-participants. No: The prevalence of frailty is unlikely to be similar between the target population and the sample frame OR the characteristics of participants and eligible non-participants are different such that the prevalence of frailty is unlikely to be similar between groups. Also see: NIHR (2020) Improving inclusion of under-served groups in clinical research: Guidance from the NIHR-INCLUDE project. UK: NIHR. Available at: www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435 (date link accessed)
2 Were study participants recruited appropriately?	Yes: The study uses random sampling, consecutive enrolment or near complete (≥90%) ascertainment of the target population. No: Convenience sampling is used.
3 Was the sample size adequate?	Yes: The sample size was ≥384 or a smaller sample size with at least 80% power was calculated and justified by the authors. The minimum sample size was estimated using the method described in the JBI manual and published statistical guidance:^{2,3} $Sample\ size = \frac{Z^2 P(1 - P)}{d^2}$ Where: Z = Z statistic for a level of confidence (95% level) P = Expected prevalence (50%) d = Desired precision (5%) An expected prevalence of 50% was selected based on the median frailty reported in a scoping review of frailty prevalence in acute care and general medicine settings.⁴ No: The sample size was <384.

4	Were the study subjects and setting described in detail?	Yes: The distribution of age, sex, co-morbidities and other characteristics was reported, such that it is clear who the study results apply to. No: Age, sex or co-morbidities were not reported.
5	Were valid methods used for the identification of the condition?	Yes: The authors reference an appropriate validation study or evaluated the performance of the frailty measure used against the frailty evaluated as part of Comprehensive Geriatric Assessment. The method of frailty measurement appears to have reasonable internal, external, construct and conclusion validity and reliability. No: No validation study is referenced, or the performance of the frailty measure was not evaluated. The method of frailty measurement does not appear to have reasonable internal, external, construct and conclusion validity and reliability.
6	Was the condition measured in a standard, reliable way for all participants?	Yes: If different frailty assessment methods, settings, or assessors were used, the Kappa value was at least 0.80 or stratified data was reported. No: The prevalence of frailty is unlikely to be similar for all participants, because of the differences listed above.
7	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes: The number of participants analysed was not substantially reduced (<20%) by attrition or missing data. Reasons for withdrawal are reported, and characteristics of participants who completed the study are similar to those who did not. For data that is not missing at random, multiple imputation or other appropriate methods were used. No: The number of participants analysed was substantially reduced (>20%) by attrition or missing data. There were important differences between those who withdrew and those who completed the study. Data that is missing not at random was managed with listwise deletion or complete cases analysis.

Appendix Table 2.2 Modified Joanna Briggs Institute Checklist for Cohort Studies

Item		Scoring Guidance
1	Were the two groups similar and recruited from the same population?	Yes: The two groups had similar characteristics, except for the exposure and were recruited from the same population. This may be inferred from participant characteristics, and eligibility criteria. No: The two groups had substantially different characteristics, except for the exposure, and/or were recruited from different populations.
2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes: Frailty was measured similarly between groups and described in detail. No: Frailty was not measured similarly between groups.
3	Was the exposure measured in a valid and reliable way?	Yes: The study clearly described the method for measuring frailty, which appeared reliable (e.g. measure used, timing of assessment and training of assessor or a measure of reliability was reported). The method for assessing frailty was valid (see item #6-7 in the modified Checklist for Prevalence Studies). No: The method for measuring frailty did not appear to be reliable or valid.
4	Were confounding factors identified and handled appropriately?	Yes: There does not appear to be important confounding, OR confounding factors were identified and controlled for (e.g. multivariable regression, standardization, or stratification). A minimum of age, sex, co-morbidity and illness acuity were adjusted for. No: Confounding factors (including a minimum of age, sex, and co-morbidity) were not identified or controlled for. Ideally, illness severity will be controlled for as well.
5	For the outcome, “discharge to a location other than home” ONLY: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes: The participants were free of the outcome (i.e. living in a care home or residential facility) at the start of the study/moment of exposure OR the study only counted discharge to a <i>new</i> care home or residential facility as an event. No: No, some participants were living in a care home or residential facility at the start of the study and this was not taken into account in evaluating the outcome.
6	Were the outcomes measured in a valid and reliable way?	Yes: Outcomes were assessed in the same way for all participants and the method was valid. In general, this criterion should be satisfied, for example, if the outcome is mortality and it was assessed using a national registry.

		No: Outcomes were not assessed in the same way for all participants, or the method used was not valid.
7	Was the follow up time reported and sufficient to be long enough for outcomes to occur? If the length of follow-up differed between groups, were appropriate strategies used to address it? (Original items #8 & 10)	Yes: Follow-up time was sufficient for the outcomes reported OR if substantially different between groups, the difference in follow-up time was accounted for in the analysis, for example by using person-time at risk. No: Follow-up time was not sufficient AND not accounted for in the analysis. For example, if a study reported in-patient mortality only, then deaths related to the reason for hospitalization that occurred after discharge would not be counted and could introduce bias.
8	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes: The number of participants analysed was not substantially reduced (<20%) by loss to follow up. Reasons for loss to follow up were described, and characteristics of participants who were lost to follow up were reported and were similar to those who were not. No: The number of participants analysed was substantially reduced (>20%) by loss to follow up. There were important differences between those who were lost to follow up and those who were not.

Statistical reporting was also considered for as part of both checklists

1	Was there appropriate statistical analysis for all relevant outcomes?	Yes: Sufficient information are provided to reproduce the analysis, including methods used to adjust for confounding variables. Confidence intervals or a comparable measure of uncertainty are reported or can be calculated. No: Insufficient information were reported to reproduce the analysis and confidence intervals were not reported/could not be calculated.

Appendix Table 2.3 Cut points selected for methods of frailty ascertainment with more than one frailty category

A) Ordinal cut points

Assessment tool	Mild or no frailty	Moderate frailty	Severe frailty	Reference
9-point CFS	0-5	6	7-9	5
BISEP	0-1	2	≥3	6
eFI/eFI-AH	0-0.24	>0.24-0.36	>0.36	7
FCS-1	Risk strata 1	Risk strata 2	Risk strata 3	8
FI-CGA	<0.45	0.45-0.55	>0.55	9
FRAIL	0	1-2 (Pre-frail)	3-5	10
HFRS	<5	5-15	>15	11
ISAR-HP	0-1	2-3	4-5	12
MAPLe-AC	Low or mild	Moderate	High or very high	13
MPI	<33 (Group 1)	33-66 (Group 2)	>66 (Group 3)	14
REFS/EFS	0-9	10-11	11-18	15

B) Dichotomous cut points

Assessment tool	Fit or mildly frail	Moderate-to-severely frail	Reference
7-point CFS	1-5	6-7	5
9-point CFS	1-5	6-9	5
FI (Eeles et al., 2015)	<0.25	≥0.25	16
FRAIL	0-2	3-5	10
Fried	0-2, or 0-3	3-5, or 4-5	17
HFRS	<5	≥5	11
ISAR-HP	<2	≥2	12
REFS/EFS	Not frail	Vulnerable-Severe	15
SOF-I	0-1	≥2	18
	Mild or no frailty ordinal category	Sum of moderate and severe ordinal categories	

Note: Values represent acceptable ranges. Tools with uncertain cut-offs included the Frail-PPS, FAM and method used by Soong et al., 2015.

Potential bias related to the definition of the denominator

For the outcome of long length of stay (LoS), I included people who died in hospital in the main analysis. Consequently, Forti et al. (2014) was excluded from the main analysis because the study excluded people who died in hospital.¹⁹

For the outcomes of discharge destination and readmission, I presented data using people who survived until discharge as the denominator in the main analyses. For discharge destination, I subtracted in-hospital deaths from the denominator in Bonjour et al. (2021) and Eckart et al. (2019).^{20,21} Warnier et al. (2017) and Ramdass et al. (2018) excluded people who died in hospital.^{22,23}

For readmissions, Warnier et al. (2017), Fitriana et al. (2021) and Laura et al. (2022) excluded people who died in hospital.^{22,24,25} Anani et al. (2020) and Wallis et al. (2015) were assumed to exclude people who died in hospital.^{26,27} For Bonjour et al. (2021) it was not possible to exclude inpatient deaths from the denominator used for readmissions, so I excluded the study from main analyses.²⁰ For Subramanian et al. (2020), Eckart et al. (2019), Street et al. (2021), Lujic et al. (2022) and Gilbert et al. (2022) I subtracted inpatient deaths from the denominators reported by the authors.^{21,28-31} For McAlister et al. (2019), I calculated the denominator from the number of readmissions and % of participants alive/discharged who were readmitted.³² For Gilbert et al. (2018), I calculated the denominator by multiplying deaths 30 day after admission (including in-hospital deaths) for each frailty category by the % of overall deaths that occurred in hospital.¹¹

In supplemental & subgroup analyses, I used the denominators reported in studies.

Appendix 3 Supplementary results for Chapters 2 & 3

Appendix Table 3.1 Summary of characteristics of included studies and prevalence estimates

Characteristic, n, % or range n cohorts	Setting		
	All (n=45)	Hospital-wide (n=17)	General medicine (n=28)
Participant characteristics			
Median age years (range), n=42	64-87	74-85	64-86
55-65	1	0	1
65-75	3	1	2
75-85	29	11	18
>85	4	2	2
Female, % (range), n=41	38-72	50-60	38-65
Cognitive impairment, % (range), n=24	1-68	7-51	1-68
Median CCI (range), n=14	2-8	2-3	2-8
Social context, n=8			
Living alone, % (range)	12-61	29-39	12-61
Living with others, % (range)	48-62	57-62	48-52
Living situation, n=13*			
At home, with assistance or independently, % (range)	68-97	72-96	58-97
Residential facility, % (range)	4-34	4-11	5-34
n estimates (n=54)			
Frailty ascertainment			
Included non-physical domains			
Cognitive (not including delirium)	29	14	15
Social supports	18	12	6
Type of frailty tool used			
Brief screening tool	5	3	2
Clinical frailty scale	10	2	8
Deficit accumulation	18	10	8
Fried phenotype	9	2	7
Multiple domains based on the CGA ('multi-domain')	7	2	5
Other	5	1	2

Legend: CCI = Charlson Comorbidity Index. *4 additional studies excluded participants from care homes. **Some studies had multiple estimates available (e.g., measured frailty with multiple tools).

Appendix Table 3.2 Descriptions of included hospital-wide cohorts (n=17 with prevalence estimates)

Author & Year (Study aims)	Location, enrollment dates, sample size	Age, % female	Comorbidity, cognitive impairment	Exclusion criteria	Frailty assessment	Outcomes
Asmus-Szepesi et al., 2013 ³³ (P)	Netherlands (regional, 450 bed hospital) 2010 n=460	76 (7.2) years 56% F	73% (>1 comorbidity) 51% (4% severe) (MMSE, cut-off value not reported)	Age <65 years, refused participation, terminally ill, unable to follow instructions, included in previous admission, LOS <48 hours, not contacted before discharge	ISAR-HP	Mortality, ADLs/IADLs, MMSE, Loneliness Scale, Short Form-20 (1 year)
Fujita et al., 2022 (C) ³⁴	Australia (single hospital) 2019-2020 n=6771	83.5 (N/A) years 52% F	(9% (CCI>3), N/A)	Age <75 years, no valid eFI-AH, first admission only, <30 eFI-AH items evaluated	eFI-AH, HFRS	Mortality, >10-day LOS, unplanned and fall-related readmission and fall-related readmission (28 days)
Geriatric Medicine Research Collaborative 2019 ³⁵ (O)	England (45 acute hospitals) 2018 n=1507	80.0 (8.3) years 53% F	N/A N/A	Age <65 years, critical care, imminently approaching the end of life, logistical, missing 4AT score and delirium status	9-point CFS	N/A

Gilbert et al., 2018 (local validation cohort) ¹¹ (D,V)	England (single hospital, unclear) 2013-2015 n=569	79.9 (6.4) years 56% F	1.9 (2.1) (CCI) N/A	Age <75 years	HFRS	N/A
Gilbert et al., 2018 (national validation cohort) ¹¹ (D,V)	England (NHS Hospital Episode Statistics) 2014-2015 n=1013590	84.1 (5.9) years 57% F	2.9 (2.6) (CCI) 26% (ICD-10 dementia/ Alzheimer's)	Age <75 years, not admitted as an emergency	HFRS	Mortality, emergency readmission (30 days), >10-day LOS
Gilbert et al., 2022 ³¹ (V)	France (743 hospitals, PMSI database) 2017 n=1,042,234	84.9 (5.8) years 80% F	1.5 (1.4) (CCI)	Age <75 years, not hospitalised as an emergency, first admission only, missing socioeconomic data	HFRS	Mortality, LOS > 10 days and 30-day emergency readmissions (30 days)
Hollinghurst et al., 2021 ³⁶ (C, P)	Wales (multiple hospitals, SAIL Databank) 2013-2017 N=126600	79.3 (8.4) years 53% F	N/A N/A	Age <65 years, emergency admission, registered with a GP contributing to SAIL, residential history in Wales	HFRS, eFI	Mortality (inpatient, 90 days), >10day LOS, readmission (30, 90 days), care home admission (1 year)
Lim et al., 2023 ³⁷ (C, V)	Singapore (tertiary hospital) n=366	74 years 56% F	2.9 (chronic health conditions)	Age <65 years, admitted to ICU, transferred from another hospital, diagnosed with a terminal illness, cognitive impairment/dementia,	Frail-PPS, FAM, ISAR-HP	N/A

				admitted for a stroke or had LOS<48h		
Lujic et al., 2022 ³⁰ (O)	Australia (New South Wales Admitted Patient Data) 2008-2013 n=257,535	83 years 57% F	48% (2+ conditions)	Age <75 years	HFRS	Mortality, LOS >10 days, unplanned readmission (30 days)
McAlister et al., 2018 ³² (C, P)	Ontario, Canada (CIHI Discharge Abstract Database**) 2004-2010 n=452785	83 (5.6) years 60% F	2 (2.2) (CCI) N/A	Age <75 years, psychiatric admissions, not urgent admission	HFRS	Mortality, urgent readmission, >10 day LOS, post-discharge ED visits (30 days)
Romero-Ortuno et al., 2016a, ³⁸ Romero-Ortuno et al., 2016b ³⁹ (P)	England (large tertiary university hospital with 1000 acute beds) 2014- 2015 n=5899	84.1 (5.9) years 56% F	N/A 14% (hx dementia)	Age <75 years, elective admission	9-point CFS	Mortality (inpatient), readmission (30 days), >10 day LOS, discharge to care home, delayed discharge
Soong et al., 2015 ⁴⁰ (Prev)	England (NHS Hospital Episode Statistics) 2005- 2013 n=50540141 (prevalence for approximately n=34044050)	N/A 50% F	7% (ICD-10, dementia)	Age <65 years	Author- designed	N/A

Soong et al., 2019* (development cohort) ⁴¹ (Prev, P, V)	Global Comparators Database (34 hospitals in Australia, Belgium, Denmark, Finland, Italy, Netherlands, Norway, United Kingdom, USA) 2010-2014 n=1366187	N/A 72% F	N/A 16% (ICD-9/10 dementia/delirium)	Age <75 years, missing age/sex/LOS, LOS <2 days	Dr Foster GFS	Mortality (inpatient), non-elective readmission (30 days), LOS in upper quartile for country
Street et al., 2021 ²⁹ (O)	Yorkshire and Humber regions, England (13 acute NHS hospitals/49 urban, suburban and rural sites, CUREd database) 2013-2017 n=282091 patients, 675155 admissions	N/A N/A	2.0 (1.9) (CCI) N/A	Age <75 years, emergency admission.	HFRS	Mortality (inpatient), readmission (30 days), >10 day LOS
Timmons et al., 2015 ⁴² (O)	Cork County, Ireland (three urban public hospitals, two rural public hospitals, and one private hospital) 2012-2013 n=598	79.7 (6.6) years 51% F	N/A 25% (SMMSE<27/30, IQCODE, health records, DSM-IV, expert review)	Age <70 years, day-cases, moribund on admission, refused participation	SHARE-FI	N/A

Wallis et al., 2015 ²⁷ (P)	England (tertiary/university hospital) 2013-2014 n=5764	84.6 (5.9) years 56% F	N/A 24% (hx dementia)	Age <75 years, not admitted as an emergency	9-point CFS	Mortality (inpatient), readmission (30 days), >10 day LOS, mean LOS, transfer to geriatric ward
Warnier et al., 2017, ²² Warnier et al., 2019 ⁴³ (P)	Maastricht University Medical Center+, Maastricht, Netherlands (university hospital with 715 beds) 2013 n=2691	78.9 (6.4) years 51% F	N/A N/A	Age <70 years, not community-dwelling, not admitted to a regular/general ward, or LOS <48 hours	MFST-HP	Mortality, readmission (30 days, 120 days), mean LOS, discharge to care facility,

Legend: C=compare existing tools, D=develop a new tool, P=investigate prognosis, Prev=describe frailty prevalence, V=validate a tool, O=other.

SAIL=Secure Anonymised Information Linkage Databank; CUREd=The Connected Health Cities Urgent and Emergency Care Research database. A sMMSE<27 is suggestive of dementia or mild cognitive impairment, but additional criteria must be met to formally diagnose dementia based on the DSM-V (i.e. cognitive deficits interfere with daily activities and are not explained by delirium or another mental condition). *Prevalence estimate only available for development cohort, so the validation cohort was not included in the summary descriptive measures; ** Linked to Registered Person's Database, National Ambulatory Care Reporting System, Continuing Care Reporting System.

Appendix Table 3.3 Description of included general medicine cohorts (n=28 with prevalence estimates)

Author & Year (Study aims)	Location, enrollment dates, sample size	Age, % female	Comorbidity, cognitive impairment	Admission diagnoses, 3 most common (%)	Exclusion criteria	Frailty assessment	Outcomes (follow- up)
Anani et al., 2020 ²⁶ (P)	Israel (Internal medicine department at a tertiary care hospital) (dates not reported) n=980	72 (65-79) years 43% F	N/A 1% (dementia, unspecified)	N/A N/A N/A	Age <55 or >85 years, no consent, advanced malignancy, cirrhosis, dementia, COPD or CHF, hx major stroke, admitted for diabetic foot or severe PVD, bedridden, mechanical ventilation on admission, or hospitalized <30 days ago, not admitted from emergency department	FRAIL	Readmission (30 days)
Belga et al., 2016 ⁴⁴ , Kahlon et al., 2015, ⁴⁵ McAlister et al., 2019 ⁴⁶ (C, P)	University of Alberta and Royal Alexandra hospitals, Edmonton, Canada (General internal medicine wards at teaching hospitals (n=2)) (2013-2014) n=495	64 years 51% F	2.4 (CCI) N/A	1. Circulatory (10%), 2. Respiratory (8%), 3. Infection (5%)	Age <18 years, life expectancy <3 months, admitted from or discharged back to long- term care facilities or other hospitals, out-of-province, poor English, moderate- severe cognitive impairment	9-point CFS, Fried, HFRS	Comparison with other risk measures, LOS, readmission, mortality, composite of readmission & mortality, emergency department visit (30 days)

Bonjour et al., 2021 ²⁰ (Pr, P)	CHUV, Lausanne, Switzerland (Internal medicine unit at university hospital) (2009-2017) n=22,323	80.2 (8.2) years 52% F	2 (0-4) (CCI) 10% (delirium, ICD-9 codes)	1. Other (65.4%), 2. Circulatory (12.4%), 3. Infection (>10.8%)	Age <65 years	HFRS	LOS, ICU stay, discharge destination, mortality (30, 90 days, 1 year), readmission rate, costs, DRG category
Buurman et al., 2012 ⁴⁷ (DEFENCE cohort) (P, O)	Academic Medical Center, Amsterdam; University Medical Centre Utrecht, Utrecht; and Spaarne Hospital, Hoofddorp, Netherlands (General medical wards at tertiary and regional hospitals with >1000 beds (n=2), and 455 beds (n=1), respectively) (2006-2008) n=639	78.2 (7.8) years 54% F	3.5 (2.3) (CCI) 40% (MMSE≤15 and CGA during admission)	1. Infection (41%), 2. Circulatory (4%) N/A	Age <65 years, patient/relative did not consent, too ill to participate, transferred from other ward, >48 hours after admission, transferred to ICU, CCU or other ward within 48 hours of admission, or poor Dutch	ISAR-HP	Clinical characteristics, mortality, functional decline (3 months and 1 year)
Dani et al., 2017 ⁴⁸ (O)	London, England (Acute medical unit at an urban general hospital) (2007-2007) n=710	83.1 (7.4) years 59% F	N/A 42% (dementia, DSM-IV)	N/A N/A N/A	Age <70 years, LOS <48 hours, poor English	FI	Mortality in the absence or presence of delirium (3 years)

Eckart et al., 2019 ²¹ (TRIAGE cohort) (P, V)	Kantonsspital, Aarau, Switzerland (Medical admissions to a tertiary care hospital) (2015-2018) n=4957	82 (75-85) years 51% F	N/A 7% (dementia, ICD-10)	N/A N/A N/A	Age <75 years, non-urgent admission	HFRS	Discharged home (with or without help) or assisted living, all-cause mortality, readmission (30 days)
Eeles et al., 2012 ¹⁶ (P, O)	South Wales, UK (General medical service at a district general hospital) n=273	82.3 (7.5) years N/A	N/A N/A	N/A N/A N/A	Age <75 years, patient/proxy did not consent, readmission	FI	Mortality (5 years)
El-Sharkaway et al., 2005 ⁴⁹ (O)	Queens Medical Centre Nottingham, England (Medical wards) (2012-2014) n=187	81.6 (7.4) years 47% F	4 (3-5) (CCI)* 24.5 (6.2) (mean/SD MMSE, cut-point unclear)	N/A N/A N/A	Age <65 years, terminal illness and life expectancy <3 months	CFS	Hydration status in-hospital
Evans et al., 2014 ⁹ (P, V)	Mercy Hospital, Buffalo, New York, USA (General medicine) (2010-2011) n=751	84 (5.5) years 64% F	7.5 (2.3) (CCI) 29% (hx dementia)	N/A N/A N/A	Age <75 years, over 24 hours passed since admission	FI-CGA	Mortality, discharge to nursing home, rehab or assisted living (120 days), time-to-complete assessment

Fitriana ²⁴ et al., 2021 (P)	Cipto Mangunkusumo Hospital, Jakarta, Indonesia (Acute care ward) (2019)	N/A N/A	N/A 26% (AMT<8)	N/A N/A N/A	Age<60 years, died in hospital, transferred to other hospital	FRAIL	Readmission (30 days)
	N=266						
Forti et al., 2014 ¹⁹ (P)	S.Orsola-Malpighi University Hospital, Bologna, Italy (General internal medicine unit at a university hospital) (2012)	80.8 (7.5) years 53% F	66% (CCI>=2) 52% (hx cognitive impairment)	1. Stroke (17%), 2. Respiratory (15%), 3. Digestive (8%)	Age <65 years, died, terminal illness or coma, discharged/transferred within 48 hours of admission, refused participation or incomplete data	SOF-I	Composite of mortality and discharge location other than previous residence, ward LOS greater than median (i.e. >8 days)
	n=470						
Gregoravic et al., 2016 ⁵⁰ (P)	St Vincent's Hospital, Melbourne, Australia (General medical unit at an inner-city tertiary care university-associated hospital) (2013)	82 years 49% F	6.6 (CCI) N/A	N/A N/A N/A	Age < 65 years, transferred to a specialty unit	9-point CFS	Mortality, functional decline (3 months)
	n=170						

Hernandez-Luis et al., 2018 ⁵¹ (O)	Canary Islands University Hospital, Tenerife, Spain (Internal medicine department at a teaching hospital) (2013-2015) n=298	76.6 (61-98) years 53% F	36% (CCI >3) 11.7% (dementia, unspecified)	1. Sepsis (37%), 2. Pneumonia (24%), 3. UTI (18%)	Age <61 years, life expectancy <6 months, acute delirium or impaired consciousness persisting on second day of admission, not admitted from emergency department	7-point CFS, Fried	Mortality, rapid cognitive decline (100 days)
Hoogerduijn et al., 2012 ¹² (P)	The Netherlands (Internal medicine wards at a teaching hospital) (2002-2006) n=492	78 years 56% F	N/A. 34% (MMSE <24)	1. Infection (9%), 2. Circulatory (1%) N/A	Age <65 years, too ill to participate	ISAR-HP	Functional decline (3 months)
Inouye et al., 2003 ⁶ (D, V)	Yale New Haven Hospital, New Haven, USA (Medicine service at a teaching hospital with 800 beds) n=535	78.7 (6.1) years 56% F	71% (CCI ≥2) 27% (dementia, unspecified)	1. Infection (13%), 2. Circulatory (12%), 3. Malignancy (2%)	Age < 70 years, terminal condition, severe dementia, aphasia, coma, intubation, discharge within 48 hours, prior enrollment, refused participation	BISEP	Comparison with other illness measures, mortality (1 year)
Irina et al., 2018 ⁵² (O)	Chaim Sheba Medical Center, Ramat Gan, Israel (Internal medicine department at a large	72 (65-79) years 46% F	N/A N/A	N/A N/A N/A	Age <18 years, dementia/cognitive decline, admission ALT >40 IU/L, no follow-up data, unable to complete frailty assessment	FRAIL	Mortality, correlation with serum ALT (maximum 456 days)

	tertiary care hospital)						
	n=179						
Juma et al., 2016 ⁵³ (P)	Victoria Hospital, London, Canada (Clinical teaching unit) n=75	81.4 (8.8) years 64% F	6.2 (2.1) (Mean comorbidities) N/A	N/A N/A N/A	Age <65 years, palliative designation or life expectancy <7 days, no chronic health conditions, independent ambulation at baseline	9-point CFS	Readmission (90 days)
Khandelwel et al., 2012 ⁵⁴ (Prev, P, O)	India (Medical wards at a public teaching hospital) n=250	66.4 (6.3) years 38% F	N/A 25.79 (4.04) (mean/SD MMSE)	1. Infection (31%), 2. Circulatory (20%), 3. Respiratory (15%)	Age <60 years, requiring mechanical ventilation/life support, comatose, obvious neurologic deficits	Fried	Mortality (45 days)
Laura et al., 2012 ²⁵ (O)	Singapore (General medicine department at hospital) (2018-2020) n=1619*	76.4 (7.9) years 51% F	60% (CCI≥3) 27% (dementia or AMTS<8), 10% delirium-CAM	N/A N/A N/A	Age <65 years, admitted from shelters or nursing homes, via HDU/ICU or non-medical units; died in hospital, transferred, or discharged against medical advice, did not consent.	9-point CFS	Readmission (30 days)
McCrow et al., 2016 ⁵⁵ (O)	Queensland, Australia (Internal medicine unit at a large tertiary care	81 (8.5) years 55% F	1.93 (1) (CCI) 61% (RUDAS ≥23)	N/A N/A N/A	Age <60 years, unstable CHF, severe CKD, nil by mouth on admission, expected LOS <24 hours, baseline assessment not	7-point CFS	Association with dehydration and cognitive impairment

	hospital) (2012-2013)					completed within 24 hours of admission, poor English		
	n=44							
Nardi et al., 2019 ⁵⁶ (P, V)	Italy (Internal medicine departments (n=29)) (2014)	79.9 (12) years 51% F	N/A N/A	N/A N/A N/A	Age <40 years, fewer than two chronic diseases	MPI	Mortality (1 year), time-to-complete assessment	
	n=541							
Noro et al., 2011 ⁵⁷ (D, P)	Nordic countries (Acute medical care in hospitals with a catchment of >90 000 persons (multiple))	N/A 65% F	N/A N/A	N/A N/A N/A	Age <75 years, in critical condition/admitted to critical care	FCS-1	Mortality, institutionalization, composite measure (at discharge and 1 year)	
	n=763							
Polidoro et al., 2013 ⁵⁸ (O)	Santa Maria Goretti Hospital, Latina, Italy (Internal medicine unit at a university hospital)	79.3 (7.4) years 60% F	N/A 62% (MMSE<24)	N/A N/A N/A	Not reported	MAPLe-AC	Association with atrial fibrillation	
	n=140							

Ramdass et al., 2018 ⁵⁹ (P)	Baystate Medical Center, Springfield, USA (Medical service) (2014-2016) n=503	80 (75-86) years 54% F	1 (0-4) (GCI)* 52 % (Mini-Cog<3)	1. Infection (22%), 2. Respiratory (20%), 3. Circulatory (19%)	Age <65 years, refused participation, died during hospitalization, advanced dementia, transferred from other facility, admitted under observation, not living in community	REFS	Discharge to skilled nursing or inpatient rehab facility
Rizza et al., 2021 ⁶⁰ (V)	Italy (internal medicine department) n=80	82.3 (4.4) years 46%			Age <75 years, unable to complete CGA, no consent, end-stage cancer or CKD, connective tissue or inflammatory bowel diseases, sepsis	MPI	N/A
Rose et al., 2014 ⁶¹ (Prev, P)	Melbourne, Australia (General medical unit at a private hospital) (2012) n=133	86.5 (6.1) years 61% F	N/A 68% (Clock drawing errors)	N/A N/A N/A	Age <70 years, unable to complete REFS, refused participation	REFS	Discharge disposition (return to previous residence, rehabilitation, geriatric evaluation and management, palliative care and death), time-to-complete assessment
Sharma et al., 2022 ⁶² (O)	Flinders Medical Centre, Adelaide, Australia (medical admissions at a tertiary care hospital) N=263	84.1 (6.6) years 52%	5.6 (3.5) (CCI) N/A	N/A N/A N/A	Age <65 years, no consent, terminally ill	REFS	N/A

Subramanian et al., 2020 ²⁸ (P, O)	Frankston Hospital, Melbourne, Australia (Acute medical unit at a metropolitan hospital) (2015) n=1118	N/A	5 (range: 4-6) (CCI) 9% (dementia, delirium, senility, ICD-10)	1. Injury or orthopaedic (19%), 2. Infection (14%), 3. Circulatory (10%)	Age <80 years, admitted for <24 hours	HFRS	Mortality (in-hospital), GOC/ACP, LOS (stratified by GOC), rapid response call during admission, discharge location (rehab, previous residence), readmission (28 days)

Legend: C=compare existing tools, D=develop a new tool, P=investigate prognosis, Prev=describe frailty prevalence, V=validate a tool, O=other. An MMSE<24 is suggestive of dementia, whereas a MMSE≤15 is suggestive of moderate-severe dementia. An AMT<8 is suggestive of any cognitive impairment (e.g. dementia, possibly delirium). A RUDAS≤22 is suggestive of dementia, as is a Mini-Cog<3. Errors on the clock-drawing test are suggestive of dementia. Additional criteria need to be met to formally diagnose dementia based on the DSM-V (i.e. cognitive deficits interfere with daily activities and are not explained by delirium or another mental condition). *N=1507 included in analyses

Study-level risk of bias for hospital-wide and general medicine cohorts

I assessed risk of bias with a modified version of the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies and Cohort Studies.^{1,63} The items assessed for prevalence included (1) “Was the sample frame appropriate to address the target population and was sufficient coverage of the sample frame achieved?” (2) “Were study participants recruited appropriately?” (3) “Was the sample size adequate?” (4) “Were the study subjects and setting described in detail?” (5) “Were valid methods used for the identification of the condition?” (6) “Was the condition measured in a standard, reliable way for all participants?” (7) “Was the response rate adequate, and if not, was the low response rate managed appropriately?”⁶³

The items assessed for other outcomes included (1) “Were the two groups similar and recruited from the same population?” (2) “Were the exposures measured similarly to assign people to both exposed and unexposed groups?” (3) “Was the exposure measured in a valid and reliable way?” (4) “Were confounding factors identified and handled appropriately?” (5) For the outcome, “discharge to a location other than home” ONLY: “Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?” (6) “Were the outcomes measured in a valid and reliable way?” (7) “Was the follow up time reported and sufficient to be long enough for outcomes to occur? If the length of follow-up differed between groups, were appropriate strategies used to address it?” (8) “Was follow up complete, and if not, were the reasons to loss to follow up described and explored?” Also, “Was there appropriate statistical analysis for all relevant outcomes?”

Due to incomplete or unclear reporting of methods, some items were assessed as unclear and in other cases, inferences were made based on the author’s judgement.

Appendix Table 3.4 Study-level risk of bias for hospital-wide admissions

Appendix Table 1: Study 1: Risk of bias for hospital ward admissions																			
	JBI Prevalence Checklist								JBI Cohort Checklist								Statistical reporting	Rationale	
Author	1	2	3	4	5	6	7	Overall	1	2	3	4	5	6	7	8	Overall		1
Asmus-Szepesi et al., 2013	H	H	L	L	L	L	H	High		L	L	H		H	U	H	Moderate	H	The prevalence estimate is unlikely to be correct due to the large number of individuals who declined to participate, were deemed ineligible or were lost to follow-up and unclear recruitment strategy. The outcome data reported is likely to be correct, but outcomes were assessed by home visits. Illness severity was not controlled for and statistical reporting was poor.
Geriatric Medicine Research Collaborative 2019	H	H	L	H	L	L	L	High										L	The prevalence estimate is unlikely to be correct, because convenience sampling was used, sampling occurred on one day, participant characteristics were not well described, it is unclear if the method of frailty assessment was similar for all individuals (e.g. unlikely that assessors received the same training) and no statistical adjustments were made. No outcomes of interest were measured.
Gilbert et al., 2018	L	L	L	L	L	L	L	Low	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate and outcomes reported are very likely to be correct. Illness severity was not controlled for.
McAlister et al., 2018	L	L	L	L	L	L	L	Low	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate is very likely to be correct and outcomes reported are likely to be correct. The authors adjusted

																			outcomes (e.g. mortality) for age and sex, but not illness severity.
Romero-Ortuno et al., 2016a, Romero-Ortuno et al., 2016b	H	L	L	L	L	L	H	Moderate	L	L	L	L	L	L	L	L	Low	L	The prevalence estimate and outcomes reported are likely to be correct. A large number of participants missing frailty assessment data and these participants differed from those without missing data-although authors performed multiple imputation to address this concern. Characteristics of frail vs not frail patients were not well described. Only inpatient mortality was included, so deaths occurring after discharge are unknown.
Soong et al., 2015	L	L	L	H	H	L	L	Moderate										L	The prevalence estimate is likely to be correct. Sex and non-geriatric co-morbidities were not described. The method for frailty has not been validated. Confidence intervals were not reported. No other outcomes were measured.
Soong et al., 2019	L	L	L	H	U	L	L	Moderate	L	L	L	H		L	L	L	Moderate	H	The prevalence estimate and outcomes reported are likely to be correct. Nearly all eligible admissions were included, however, some details, e.g deaths in the validation cohort were unclear. In addition, the accuracy of the administrative data used was not reported and the measure was not compared to other frailty tools. Descriptive statistics were not provided. Illness severity and comorbidity were not controlled for.

Timmons et al., 2015	U	U	L	L	L	L	L	Low										L	The prevalence estimate is likely to be correct. The study provides adequate descriptions of the frailty assessment process, and participant characteristics. The frailty tool was validated in a community-based population, and confidence intervals are not reported. No other outcomes were measured.
Wallis et al., 2015	L	L	L	L	L	L	H	Moderate	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate is unlikely to be correct, but outcomes reported are likely to be correct. Over 20% of participants were missing frailty scores and these participants appeared to differ in terms of characteristics and outcomes than those with frailty scores available. Rates of comorbidity were much higher among frail participants, but were adjusted for in multivariate analyses. Illness severity was not controlled for.
Warnier et al., 2017, Warnier et al., 2019	H	L	L	H	L	L	L	Moderate	L	L	L	H	L	L	L	L	Moderate	L	The prevalence estimate is likely correct, but outcomes are unlikely to be correct. The studies did not describe participant's comorbidities, or account for age or sex or other confounders, such as illness severity in analyses. It was not clear to what extent loss to follow-up occurred. In addition, it was unclear what counted as a 'regular hospital ward.'
Street et al., 2021	L	L	L	L	L	L	L	Low	L	L	L	H		H	L	L	Moderate	L	The prevalence estimate is very likely to be correct and outcomes reported are likely to be correct. The authors did not adjust outcomes for illness severity and

																			results reflected admissions, instead of individual patients.
Hollinghurst et al., 2021	L	L	L	L	L	L	L	Low	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate is very likely to be correct and outcomes reported are likely to be correct. The authors did not adjust outcomes for illness severity.

Appendix Table 3.5 Study level risk of bias for general medicine admissions

Appendix Table 6: Study level risk of bias for general medicine admissions																			
	JBI Prevalence Checklist								JBI Cohort Checklist								Statistical reporting	Rationale	
Author	1	2	3	4	5	6	7	Overall	1	2	3	4	5	6	7	8	Overall	1	
Anani et al., 2020	H	L	L	L	L	L	U	High	L	L	L	H		U	U	U	Unclear	H	The prevalence estimate is unlikely to be correct, but there was insufficient information to assign a risk of bias to other outcomes. The authors excluded patients over 85 years of age and others with severe disease, because they assumed these individuals to be frail. It was not clear at what point during admissions frailty was measured, though the measure seemed likely to be reliable. It is unclear how outcomes were determined and how many participants were lost to follow-up or refused to participate. Illness severity was not controlled for.
Belga et al., 2016; Kahlon et al., 2015; McAlister et al., 2019	H	U	L	L	L	L	H	High	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate is unlikely to be correct and the outcomes reported were likely to be correct. It is unclear if potentially eligible patients who refused screening had similar characteristics to included patients or not. In addition, the sample frame was limited (e.g. people who were discharged to long-term care were excluded) and sampling method was not described clearly. Results were adjusted for age and sex, but not for other factors, e.g.

																			comorbidities that differed between groups and illness severity, although LACE score was adjusted for.
Bonjour et al., 2021	L	L	L	L	L	L	L	Low	L	L	L	H	U	L	L	L	Moderate	L	The prevalence estimate is very likely to be correct and outcomes reported are likely to be correct. Illness severity was not controlled for and it was not clear if participants were free from the outcome of institutionalisation at the start of the study.
Buurman et al., 2012	H	L	L	L	L	L	H	High	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate is unlikely to be correct, but outcomes are likely to be correct. Individual consent was required and a large number of eligible participants (>20%) refused participation. Non-participants differed in age and mortality than participants. Loss to follow up was unclear, but probably small for mortality (i.e. data were obtained from a municipal registry). Illness severity was not controlled for.
Dani et al., 2018	L	L	L	L	L	L	L	Low	L	L	L	H		L	L	L	Moderate	L	The outcomes are likely to be correct and prevalence very likely to be correct, but descriptive statistics were not provided for frail vs not frail participants, and mortality was only

																			adjusted for age and sex, but not comorbidity or illness severity.
Eckart et al., 2019	L	L	L	L	L	L	L	Low	L	L	L	H	L	L	L	H	Moderate	L	The prevalence estimate and outcomes reported are very likely to be correct. Variation in coding of ICD-10 scores could result in the misclassification of frailty, however, it is unclear how large this effect would be. In addition, the HFRS has been validated in similar settings previously. Follow-up was done by telephone and it was unclear how complete it was. Illness severity was measured, but not controlled for.
Eeles et al., 2012	L	L	H	L	L	L	H	Moderate	L	L	L	H		L	L	L	High	L	The prevalence estimate is likely to be correct, but outcomes reported are unlikely to be correct. Approximately 70% of eligible individuals were enrolled. Additional description of study participants could have been provided. No other major confounding factors, including age were adjusted for.
El-Sharkaway et al., 2015	H	U	H	L	L	L	H	High										L	The prevalence estimate is unlikely to be correct. A large number of individuals who were screened were excluded (n=1209/1409; 86%), including due to being severely ill and refusal to participate. The sampling method was unclear. No other

																			outcomes relevant to the review were reported.
Evans et al., 2014	U	H	L	L	L	L	H	High	L	L	L	H	H	L	L	L	Moderate	L	The prevalence estimate is unlikely to be correct and outcomes are likely to be correct. Even though probability sampling was not used, about 56% (n=950/1702) of the eligible sample was enrolled. It was unclear if sufficient coverage of sample frame was achieved, based on the information provided in the study. The modified method used by the authors has not been validated previously. Co-morbidities were reported and differed between frailty groups, but not included in multivariable models. Risk ratios for the association between age and sex and mortality adjusted for frailty were reported, but the full model including adjusted risk ratios for frailty was not reported. Illness severity was not controlled for. The authors did not distinguish between participants who were newly discharged vs returning to a care home (i.e. participants might have had the outcome at the start of the study).

Fitriana et al., 2021	U	L	H	L	L	L	U	High	L	L	L	H		H	L	U	High	M	The prevalence estimate and outcomes are unlikely to be correct due to small sample size, lack of adjustment for confounding by age, sex and comorbidity and only ascertaining readmissions at a single hospital site. Also, only those who survived to discharge were included.
Forti et al., 2014	L	L	L	L	U	L	H	Moderate	L	L	U	U		L	L	L	Moderate	L	The prevalence estimate and outcomes reported are likely to be correct, but were downgraded due to the poor response rate (n=252/685; 31%) and lack of adjustment for age, comorbidity and adjustment for comorbidity, respectively. It is not clear if the SOF-I has been validated in hospital settings, and how valid or reliable assessment was, given that participants were acutely ill and some details of measurement (e.g. timing) were not clearly described. It was unclear which confounding variables were controlled for.
Gregoravic et al., 2016	L	L	H	L	L	L	L	Moderate	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate and outcomes reported are likely to be correct. The study achieved near-complete coverage of the sample frame. No inter-rater reliability was reported, but the CFS, which was used in this study, generally performs well in this regard. Illness severity was not controlled for. Three-month mortality

																			data were obtained from hospital records, so deaths might have been under ascertained if people died outside of the hospital. It was not clear how many individuals were lost to follow-up.
Hernandez-Luis et al., 2018	H	L	H	L	L	L	L	High	L	L	L	H		H	L	U	High	L	The prevalence and outcomes are unlikely to be correct. People with a life expectancy <6 months and persisting delirium were excluded. Attrition and missing data were not reported. It is unclear who assessed frailty, and which point during the admission and it was unclear how mortality was assessed (i.e., using hospital records or government statistics). Although a multivariable model including frailty was described, the full model including the adjusted risk ratio for frailty was not reported. Illness severity was not controlled for.
Hoogerduijn et al., 2012	H	U	L	L	L	L	H	High	L	L	L	H		L	L	U	Moderate	L	The prevalence estimate is unlikely to be correct, and outcomes are unclear. A large number of eligible participants were excluded because the outcome of interest could not be assessed in them. People who were too ill to participate were also excluded. In addition, the description of sampling methods and coverage were insufficient. No other outcomes relevant to the review were reported. Confounding, including

																			illness severity, was not adequately accounted for and it was unclear if follow-up was complete.
Inouye et al., 2003	H	L	L	L	L	L	L	Moderate	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate and outcomes reported are likely to be correct. However, it is unclear if eligible non-participants who declined participation or were excluded for 'other' reasons were similar to included participants. People with terminal illness or severe dementia were also excluded. Some potential confounding factors associated with mortality were described, but not adjusted for with respect to the association between the BISEP score and mortality, e.g. illness severity.
Irina et al., 2018	H	L	H	L	L	L	L	High	L	L	L	H		H	L	U	High	L	Insufficient information was reported to assign a risk of bias for prevalence, but the risk of bias for other outcomes was high. It was not clear how many participants were excluded, in particular, those who were excluded because they were lost to follow-up and if these individuals differed from included participants. However, people with dementia/cognitive impairment, an elevated ALT or who were unable to complete the assessment were

																			excluded. No confounding factors were identified or adjusted for.
Juma et al., 2016	H	H	H	L	L	L	L	High	L	L	L	H	L	L	L	L	High	L	The prevalence estimates and outcomes are unlikely to be correct. The sample was small (n=75) and it was unclear how participants were recruited from the ongoing project cited. In addition, people who were deemed palliative had <1 chronic health conditions or were independently ambulating at baseline were excluded. It was unclear if sufficient coverage was achieved and what the response rate was. Outcomes were not adjusted for confounding, even though there were differences between age, sex and comorbidities between exposure groups, nor was illness severity controlled for.
Khandelwal et al., 2012	H	U	H	L	L	L	L	High	L	L	L	H		U	U	U	Unclear	H	The prevalence estimate reported is unlikely to be correct, and there was insufficient information available to assess the risk of bias for other outcomes. Characteristics of participants and eligible non-participants were not reported as well as the response rate, but people with neurologic deficits were excluded. The timing of frailty assessment with the Fried phenotype was not specified, but physical performance may be affected by illness acuity. No adjustment for

																			confounding variables was performed and it was unclear how outcomes (e.g. mortality) were assessed, as well as the degree to which complete follow-up was achieved.
Laura et al., 2022	H	L	L	L	L	U	Y	Moderate	L	L	U	H		L	L	L	Moderate	L	The prevalence estimate is likely to be correct or an underestimate, because patients from sheltered accommodation and care homes were excluded and 112 (7%) were excluded from the analysis because they could not be followed-up. It was also unclear who measured frailty and the CFS seemed to be applied in a non-standard way (i.e. taking into account comorbidity). The outcomes are likely to be correct for the target population, but the association between frailty and readmission was not adjusted for age, sex, comorbidity and illness severity.
McCrow et al., 2016	H	H	H	L	L	L	H	High										L	The prevalence estimate is unlikely to be correct. The sample size was small, response rate low, and convenience sampling was undertaken, which is susceptible to bias. People with severe/unstable comorbidities or who were moribund were excluded. No other outcomes of interest were reported.

Nardi et al., 2019	H	L	L	L	L	L	L	Moderate	L	L	L	H		L	U	U	High	L	It is unclear whether the prevalence estimate and outcomes reported are likely to be correct. The eligibility criteria were limited to people with 2+ chronic diseases. Confounding factors were not identified or adjusted for, and outcomes were assessed by calling participants, but loss to follow-up was not reported.
Noro et al., 2011	L	L	L	H	L	L	L	Moderate	L	L	L	H		L	L	L	Moderate	L	The prevalence estimate reported is likely correct, but there was insufficient information to assign a risk of bias for other outcomes. Additional information about participants could have been provided and no response rate or information on the completeness of follow-up was reported. Illness severity was not adequately controlled for.
Polidoro et al., 2013	L	L	H	L	L	L	L	Moderate										L	It is unclear whether the prevalence estimate is likely or unlikely to be correct. The method of frailty assessment was modified slightly by the authors, and it was not clear how the assessment was done. No other outcomes relevant to the review were reported.
Ramdass et al., 2018	H	U	L	L	L	L	H	High	L	L	L	H	L	L	L	L	Moderate	H	The prevalence estimate and outcomes are unlikely to be correct, and outcomes are likely to be correct. A large number of participants who were screened were not included (n=272/775) and those who died, were

																			not community-dwelling or were admitted under observation, which may impact the effect size reported. The sampling method was unclear. Also, outcomes were not adjusted for illness severity.
Rizza et al., 2022	H	H	H	L	L	U	L	High	L	L	U	H		U	L	U	High	L	The prevalence and outcomes are unlikely to be correct, because the sample was small, people with certain diagnoses (e.g., end-stage CKD, sepsis) were excluded, and consenting, sampling method and CGA details were unclear (e.g. timing). Adjusted outcomes for frailty were not available and it was not clear how deaths were followed-up.
Rose et al., 2014	L	L	H	L	L	L	L	Moderate	L	L	L	H	L	L	L	L	Low	M	The prevalence estimate is likely to be correct, but outcomes are unlikely to be correct. A number of participants were excluded due difficulty on the clock drawing test, which is part of the frailty assessment. The characteristics of these participants were not reported, so it was unclear if sufficient coverage of the sample was achieved. Important confounding factors were not described or adjusted for.
Sharma et al., 2022	H	L	H	L	L	U	L	High	L	L	U	H	U	U	L	H	High	L	The prevalence and outcomes are unlikely to be correct, because the sample was small and sampling method and details of frailty assessment (e.g., training of assessor)

																			not specified. In addition, adjusted outcomes for frailty were not available and it was not clear how follow-up was done. Presumably, people already living in nursing homes were not counted in nursing home admissions.
Subramanian et al., 2020	L	L	L	L	L	L	L	Low	L	L	L	H	H	L	L	L	Moderate	M	The prevalence estimate is very likely to be correct and outcomes reported are likely to be correct. It is not clear if the coding of the diagnostic codes used in frailty assessment was accurate. Important confounding variables were not adjusted for in the association between frailty and outcomes.

L = Low. M = Moderate. H = High. U = Unclear.

Appendix Table 3.6 Adjusted odds ratios and other measures for main study outcomes

Outcome	Measure	Study	Cut-point	Crude	Adjusted	Adjusted for
Mortality, in-hospital	OR (95% CIs)	Wallis (2015)	CFS (continuous?)	Not reported	1.60 (1.48 to 1.74)	Age, gender, Charlson comorbidity index, dementia or current cognitive concern
		Fujita (2022)	HFRS >15 (ref = <15)	Not reported	1.06 (1.05-1.08)	Age, gender
			eFI-AH >0.25 (ref = <0.25)		2.81 (2.49-3.17)	
	HR (95% CIs)	Hollinghurst (2021)	HFRS 5-15	Not reported	1.34 (1.29-1.38)	Age, sex
			HFRS >15 (ref = 0-5)		1.44 (1.37-1.51)	
		Soong (2019)	DF-GFS (continuous)	Not reported	1.06 (1.05 to 1.07)	Age, gender, country
		Romero-Ortuno (2016)	CFS 5 CFS 6 CFS 7-8 (ref = 1-4)*	Not reported	1.17 (0.84 to 1.61) 1.46 (1.09 to 1.96) 1.98 (1.47 to 2.66)	Age, sex, discharged by medical specialty, Charlson comorbidity index, history of dementia, current cognitive concern, illness acuity (ED-MEWS 4 or more)

			*Imputed data for missing CFS scores			
		Street (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	2.66 (2.61-2.70) 5.47 (5.32-5.62)	Age, sex, socioeconomic status, Charlson comorbidity, number of emergency admissions in preceding year, number of operation codes, ambulatory-care sensitive condition, national tariff for Healthcare Resource Group, care home resident, travel time from residence to hospital
Mortality, 30-day	OR (95% CIs)	Kahlon (2015)	CFS 5-8 (ref = 1-4)	2.46 (0.81 to 7.45)	2.18 (0.65 to 7.39)	Age, sex
		Gilbert (2018)	HFRS 5-15 HFRS >15 (ref = 0-5)	2.09 2.56	1.65 (1.62 to 1.68) 1.71 (1.68 to 1.75)	Age, sex, socioeconomic status, admission history, Charlson comorbidity and hospital variation
		Gilbert (2022)	HFRS 5-15 HFRS >15 (ref = 0-5)	1.79 (1.76-1.82) 2.29 (2.25-2.34)	1.34 (1.32-1.37) 1.38 (1.35-1.42)	Age, gender, hospital bed-days, primary care access, city median income and Charlson index categories
		Eckart (2019)	HFRS 5-15 HFRS >15	2.53 (2.09 to 3.06) 4.4 (2.94 to 6.57)	2.65 (2.17 to 3.25) 4.83 (3.17 to 7.37)	Age, sex, comorbidities not included in HFRS

			(ref = 0-5)			
	HR (95% CIs)	Bonjour (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.04 (0.95-1.14) 1.31 (1.16-1.47)	Year of discharge, gender, age group, Charlson index, ICU stay, previous hospitalizations, LOS
Mortality, 3-month		Gregoravic (2016)	CFS categories (1-3, 4-5, 7-8 and 9)	2.5 (1.19 to 5.3)	2.2 (0.1 to 4.67)	Gender, Charlson co-morbidity score, usual residence
	HR (95% CIs)	Bonjour (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.04 (0.97-1.12) 1.22 (1.12-1.34)	Year of discharge, gender, age group, Charlson index, ICU stay, previous hospitalizations, LOS
		Hollinghurst (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.29 (1.26-1.32) 1.41 (1.36-1.45)	Age, sex
Mortality, 1-year	HR (95% CIs)	Bonjour (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.05 (1.00-1.11) 1.21 (1.13-1.30)	Year of discharge, gender, age group, Charlson index, ICU stay, previous hospitalizations, LOS
Mortality, time-to-event	HR (95% CIs)	Romero-Ortuno (2017)	CFS 5 CFS 6 CFS 7-8 (ref = 1-4)	Not reported	1.08 (1.05 to 1.11) 1.31 (0.94 to 1.81) 2.10 (1.52 to 2.92)	Age, gender, discharged from medical vs. surgical specialty, Charlson co-morbidity, history of dementia, and current cognitive concern

		Dani (2018)	Increase per SD (0.96 points) on FI	5.9 (2.1 to 16)	3.5 (1.2 to 9.9)	Age, sex
		Noro (2011)	MAPLe-AC Mild Moderate High Very high (ref = Low)	Not reported	0.85 (0.38 to 1.94) 1.31 (0.76 to 2.25) 2.26 (1.29 to 3.94) 2.71 (1.44 to 5.09)	Age, sex, reason for hospitalization, diagnosis
		Buurman (2012)	Intermediate High (ref = Low risk)	1.15 (0.79 to 1.67) 1.81 (1.29 to 2.54)	1.10 (0.75 to 1.62) 1.62 (1.11 to 2.35)	Age, sex, comorbidity
Readmission, 30- day	OR (95% CIs)	Kahlon (2015)	CFS 5-8 (ref = 1-4)	1.82 (1.13 to 2.97)	1.90 (1.11 to 3.26)	Age, sex
		Fitriana (2021)	FRAIL (per-point)	Not reported	0.834 (0.455-1.528)	Function, malignancy, nutrition, depression, cognition (AMT), previous admission
		Wallis (2015)	CFS (per-point)	Not reported	1.04 (0.99 to 1.10)	Age, gender, Charlson comorbidity index, dementia or current cognitive concern
		Fujita (2022)	HFRS >15 (ref = <15)	Not reported	1.02 (1.01-1.04)	Age, gender

			eFI-AH >0.25 (ref = <0.25)		1111 (1.02-1.20)	
		Eckart (2019)	HFRS 5-15 HFRS >15 (ref = 0-5)	1.04 (0.88 to 1.24) 1.47 (0.95 to 2.26)	1.04 (0.87 to 1.24) 1.67 (1.08 to 2.59)	Age, sex, comorbidities not included in HFRS
		Gilbert (2018)	HFRS 5-15 HFRS >15 (ref = 0-5)	1.32 1.69	1.23 (1.22 to 1.25) 1.48 (1.46 to 1.50)	Age, sex, socioeconomic status, admission history, Charlson comorbidity and hospital variation
		Gilbert (2022)	HFRS 5-15 HFRS >15 (ref = 0-5)	1.24 (1.22-1.26) 1.48 (1.45-1.51)	1.04 (1.02-1.05) 1.00 (0.98-1.02)	Age, gender, hospital bed-days, primary care access, city median income and Charlson index categories
		Hollinghurst (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.31 (1.25-1.37) 1.52 (1.43-1.61)	Age, sex
		Soong (2019)	DF-GFS (continuous)	Not reported	1.02 (1.00 to 1.05)	Age, gender and country
	Average Marginal	Street (2021)	HFRS 5-15 HFRS >15	Not reported	-0.003 (-0.005, -0.001)	Age, sex, socioeconomic status, Charlson comorbidity, number of emergency admissions in

	Effect (95% CIs)		(ref = 0-5)		-0.027 (-0.031, -0.023)	preceding year, number of operation codes, ambulatory-care sensitive condition, national tariff for Healthcare Resource Group, care home resident, travel time from residence to hospital
Readmission, 90-day	HR (95% CIs)	Hollinghurst (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	1.37 (1.33-1.41) 1.67 (1.63-1.75)	1.29 (1.26-1.32) 1.41 (1.36-1.45)	Age, sex
Readmission, time-to-event	HR (95% CIs)	Anani (2020)	FRAIL scale ≥ 3 (ref = 0-2)	Not reported	1.59 (1.02 to 2.48)	Age, gender, diabetes mellitus, chronic kidney disease, an active malignancy and serum ALT
Long length of stay	OR (95% CIs)	Eckart (2019)	HFRS 5-15 HFRS >15 (ref = 0-5)	3.47 (2.99 to 4.02) 9.21 (6.51 to 13.01)	3.66 (3.14 to 4.28) 9.75 (6.83 to 13.92)	Age, sex, comorbidities not included in HFRS
		Gilbert (2018)	HFRS 5-15 HFRS >15 (ref = 0-5)	3.36 6.03	3.29 (3.25 to 3.30) 6.01 (5.92 to 6.10)	Age, sex, socioeconomic status, admission history, Charlson comorbidity and hospital variation
		Gilbert (2022)	HFRS 5-15	2.56 (2.54-2.59)	2.34 (2.32-2.37)	Age, gender, hospital bed-days, primary care access, city median

			HFRS >15 (ref = 0-5)	3.59 (3.55-3.64)	3.27 (3.22-3.32)	income and Charlson index categories
		Soong (2019)	DF-GFS (unclear)	Not reported	1.14 (1.13 to 1.14)	Age, gender and country
		Wallis (2015)	CFS (per-point)	Not reported	1.19 (1.14 to 1.23)	Age, gender, Charlson co-morbidity index, dementia or current cognitive concern
		Fujita (2022)	HFRS >15 (ref = <15) eFI-AH >0.25 (ref = <0.25)	Not reported	1.20 (1.18-1.21) 2.04 (1.91-2.17)	Age, gender
		Hollinghurst (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.68 (1.63-1.72) 2.07 (1.99-2.14)	Age, sex
		Street (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	2.66 (2.61-2.70) 5.47 (5.32-5.62)	Age, sex, socioeconomic status, Charlson comorbidity, number of emergency admissions in preceding year, number of operation codes, amulatory-care sensitive condition, national tariff for Healthcare Resource Group, care home resident, travel time from residence to hospital

	HR (95% CIs)	Anani (2020)	FRAIL scale ≥ 3 (ref = 0-2)	Not reported	1.55 (1.18 to 2.04)	Age, gender, diabetes mellitus, chronic kidney disease, an active malignancy and serum ALT
Discharge destination, (home)	OR (95% CIs)	Noro (2011)	MAPLe-AC Low Mild Moderate High (ref = Very high)	Not reported	11.63 (3.77 to 35.88) 8.77 (2.84 to 27.13) 3.67 (3.07 to 6.51) 1.69 (0.94 to 3.02)	Age, sex and reason for hospitalization
Care home admission, 1-year	HR (95% CIs)	Hollingshurst (2021)	HFRS 5-15 HFRS >15 (ref = 0-5)	Not reported	1.05 (1.00-1.11) 1.21 (1.13-1.30)	Age, sex
Living at home at one year	OR (95% CIs)	Noro (2011)	MAPLe-AC Low Mild Moderate	Not reported	3.51 (1.74 to 7.10) 6.14 (2.76 to 13.69) 2.95 (1.66 to 5.24)	Age, sex and reason for hospitalization

			High (ref = Very high)		1.79 (0.98 to 3.26)	

Appendix Table 3.7 Percent difference between crude and age/sex adjusted and most adjusted estimates (i.e. age/sex, comorbidity, others) for relative risk by outcome.

Outcome	Adjusted for	% Change, Mean/SD (range)		Studies (n)
		Moderate frailty	Severe frailty	
Mortality	Age/sex	-2.2/2.5 (-0.4 to -4)	3/7.1 (-8 to 2)	2
	Most adjusted (all studies)	-15.2/10.2 (1 to -25.1)	-19.5/15.9 (-3.6 to -39.8)	5
LOS	Age/sex	2.3 (NA)	2.3 (NA)	1
	Most adjusted	-3.9/4.1 (-0.9 to -8.6)	-3.5/4.7 (-0.3 to -8.9)	3
Readmission	Age/sex	1.9 (NA)	1.4 (NA)	1
	Most adjusted	-9.2/6 (-4.8 to -16.1)	-12.7/14.1 (-6.1 to -32.4)	3

Legend: % change was calculated as (adjusted - crude odds) / crude odds x 100. NA = not applicable. Most adjusted estimates included age/sex, comorbidity and any of illness severity, socio-economic status, median city income, primary care access, admission history, hospital bed-days, hospital variation, year of discharge, ICU stay and/or LOS. Sex and gender were used interchangeably.

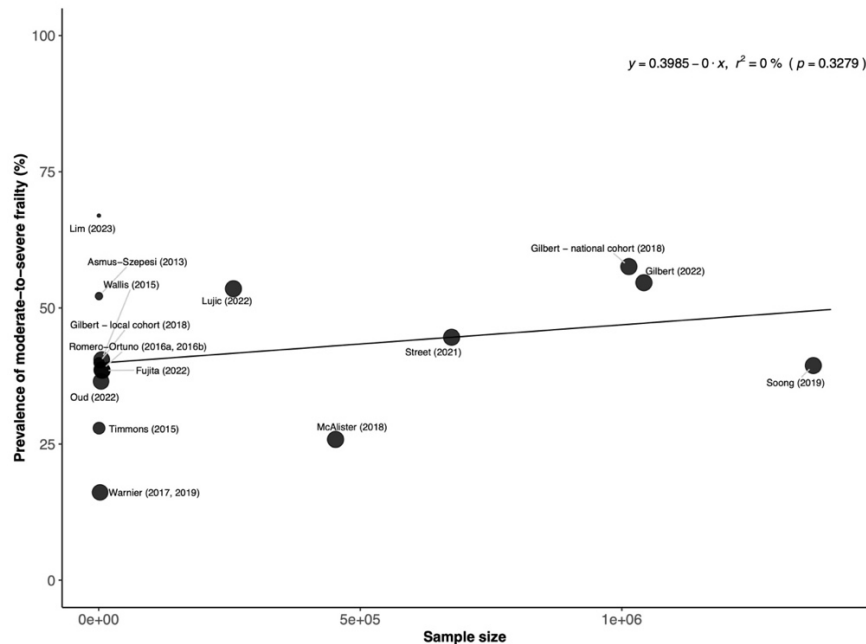
Appendix Table 3.8 C-statistic (area-under-the-receiver-operator-curve) and 95% CIs for study outcomes

		C-statistic (95% CI)						
Study name / type of measure	Frailty tool	Mortality			Length of stay (LOS)		Discharge destination	
		Dichotomous	Ordinal (3 categories)	Ordinal (4-5 categories)	Dichotomous	Ordinal (3 categories)	Dichotomous	Ordinal (3 categories)
Prospective tools								
Brief								
Asmus-Szepesi (2013)	ISAR-HP	0.63 (0.57-0.68)	0.66 (0.6- 0.72)	0.66 (0.6-0.73)	NA	NA	NA	NA
Buurman (2012)	ISAR-HP	0.55 (0.51-0.59)	0.57 (0.52- 0.62)	NA	NA	NA	NA	NA
Warnier (2017, 2019)	VMS	0.7 (0.67-0.73)	NA	NA	NA	NA	0.6 (0.58-0.62)	NA
CFS								
Hernandez-Luis (2018)	CFS	0.65 (0.57-0.73)	NA	NA	NA	NA	NA	NA
Gregoravic (2016)	CFS	0.61 (0.48-0.74)	NA	NA	NA	NA	NA	NA
Kahlon (2015)	CFS	0.61 (0.47-0.75)	NA	NA	NA	NA	NA	NA
Romero-Ortuno (2016a, 2016b)	CFS	0.6 (0.57-0.63)	0.62 (0.59- 0.65)	0.66 (0.63- 0.69)	NA	NA	NA	NA
Wallis (2015)	CFS	0.66 (0.64-0.69)	0.69 (0.66- 0.72)	0.74 (0.71- 0.76)	NA	NA	NA	NA
Phenotype								
Hernandez-Luis (2018)	Fried	0.67 (0.59-0.75)	NA	NA	NA	NA	NA	NA
Irina (2018)	FRAIL	0.6 (0.48-0.73)	NA	NA	NA	NA	NA	NA
Multidimensional								
Inouye et al (2003)	BISEP	0.59 (0.64-0.69)	0.8 (0.76- 0.84)	0.82 (0.78- 0.86)	NA	NA	NA	NA
Ramdass (2018)	REFS	NA	NA	NA	NA	NA	0.58 (0.54- 0.62)	0.63 (0.59- 0.68)

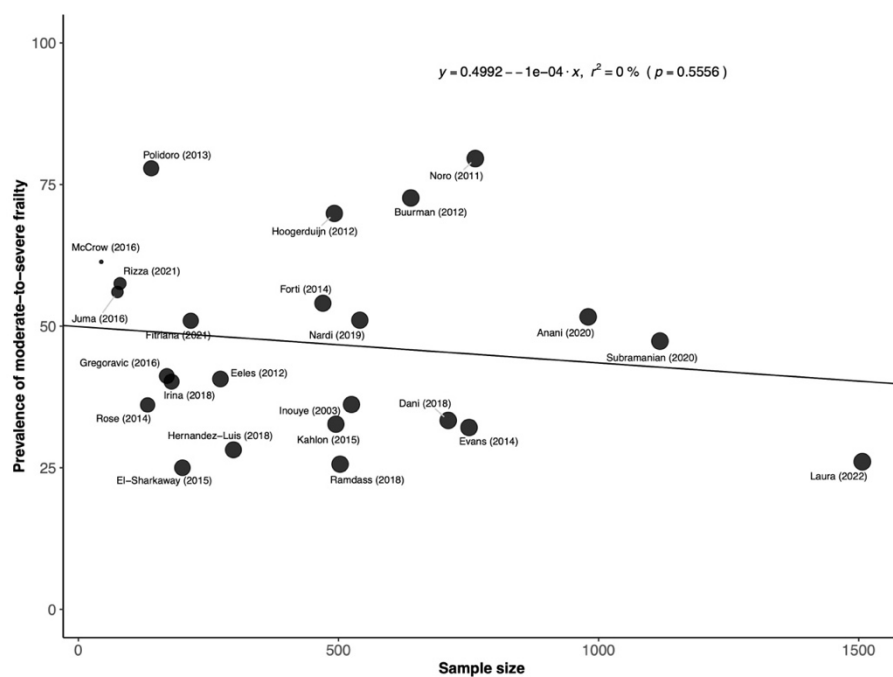
Warnier (2017, 2019)	MFST-HP	0.61 (0.56-0.65)	NA	NA	NA	NA	0.63 (0.61-0.65)	NA
Retrospective or unclear HFRS								
Bonjour (2021)	HFRS	0.51 (0.5-0.53)	NA	NA	NA	NA	0.63 (0.62-0.63)	NA
Eckart (2019)	HFRS	0.62 (0.6-0.64)	0.62 (0.6-0.65)	NA	0.66 (0.64-0.68)	0.67 (0.65-0.68)	0.62 (0.60-0.63)	0.62 (0.6-0.64)
Gilbert - national cohort (2018)	HFRS	0.59 (0.59-0.59)	0.6 (0.6-0.6)	NA	0.65 (0.65-0.65)	0.68 (0.68-0.68)	NA	NA
Gilbert (2022)	HFRS	0.58 (0.58-0.58)	0.59 (0.59-0.59)	NA	0.62 (0.62-0.62)	0.63 (0.63-0.64)	NA	NA
Lujic (2022)	HFRS	0.61 (0.61-0.61)	NA	NA	0.65 (0.64-0.65)	NA	NA	NA
McAlister (2018)	HFRS	0.53 (0.53-0.53)	0.53 (0.53-0.53)	NA	0.64 (0.64-0.64)	0.64 (0.64-0.65)	NA	NA
Street (2021)	HFRS	0.58 (0.57-0.58)	0.63 (0.63-0.63)	NA	0.68 (0.68-0.68)	0.7 (0.7-0.7)	NA	NA
Subramanian (2020)	HFRS	0.64 (0.59-0.69)	NA	NA	NA	NA	NA	NA
Other deficit accumulation								
Dani (2018) – 3 year mortality	FI	0.55 (0.51-0.58)	0.55 (0.51-0.59)	NA	NA	NA	NA	NA
Evans (2014)	FI-CGA	0.64 (0.6-0.69)	0.66 (0.62-0.71)	0.69 (0.64-0.73)	NA	NA	NA	NA
Rizza (2022)	MPI	0.68 (0.58-0.79)	0.70 (0.59-0.82)	NA	NA	NA	NA	NA

Appendix Figure 3.1 Prevalence of moderate-to-severe frailty plotted against sample size and meta-regression equation stratified by setting

(A) Studies of hospital-wide unplanned admissions

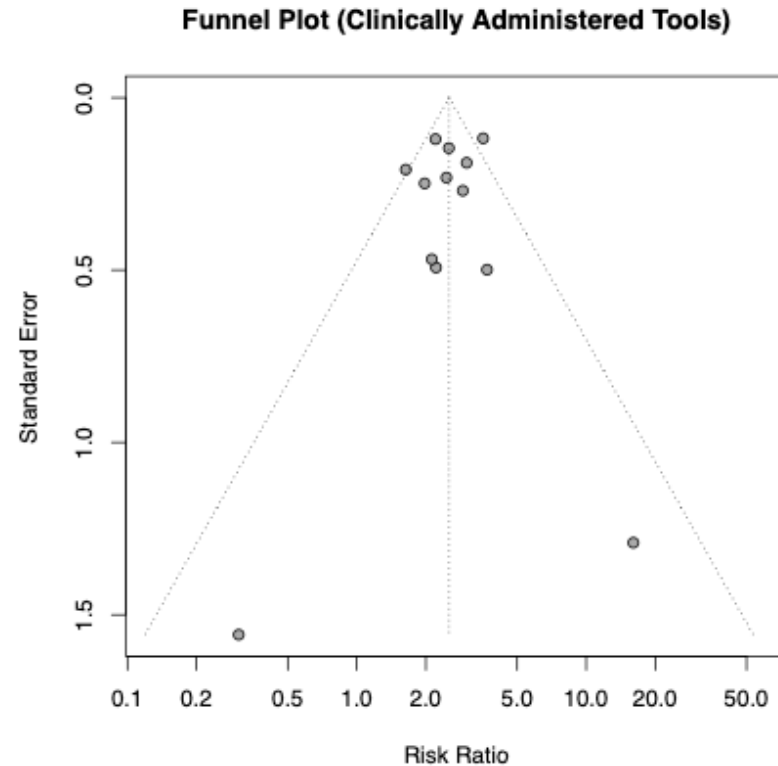


(B) Studies of general medicine admissions

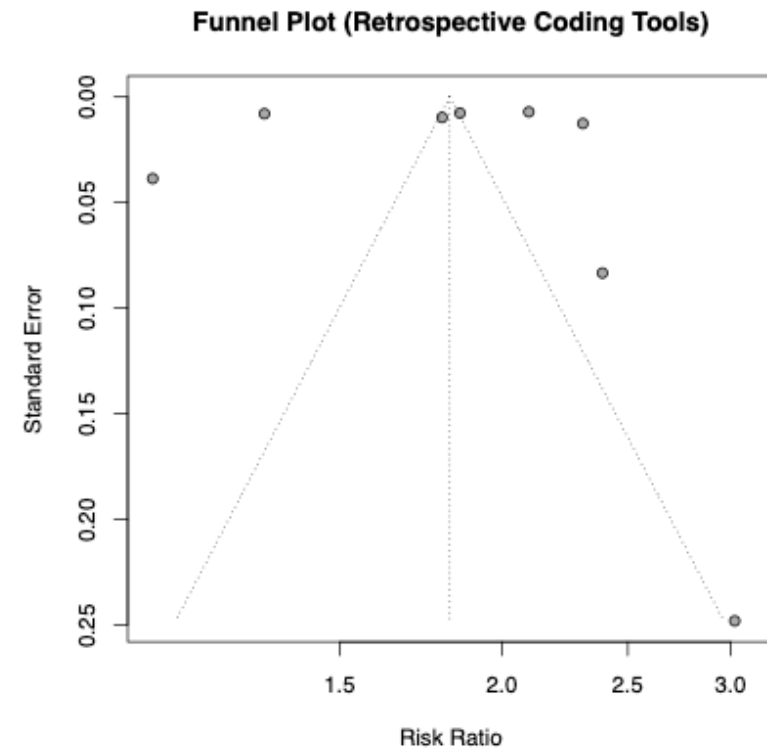


Note: Outliers (sample size > Q3 + 1.5*IQR) were removed from analysis, i.e. Bonjour (2021) and Eckart (2019).

Appendix Figure 3.2 Funnel plots with Egger's test for the unadjusted relative risks of mortality for moderate/severe versus no/mild frailty stratified by type of measure

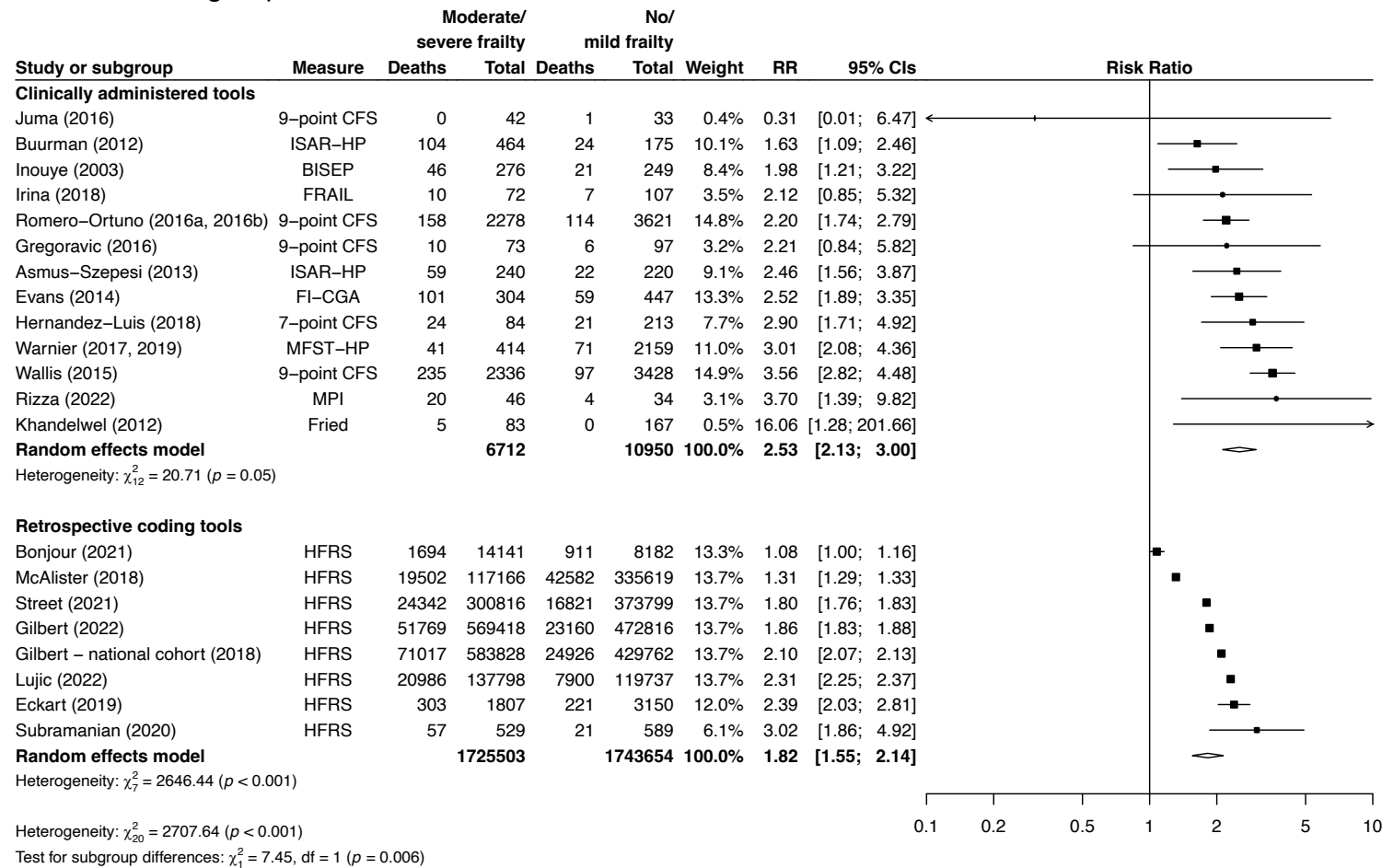


Egger's test: Intercept (95% CIs) = -0.33 (-1.75-1.08), p-value = 0.6527, $df = 12$.



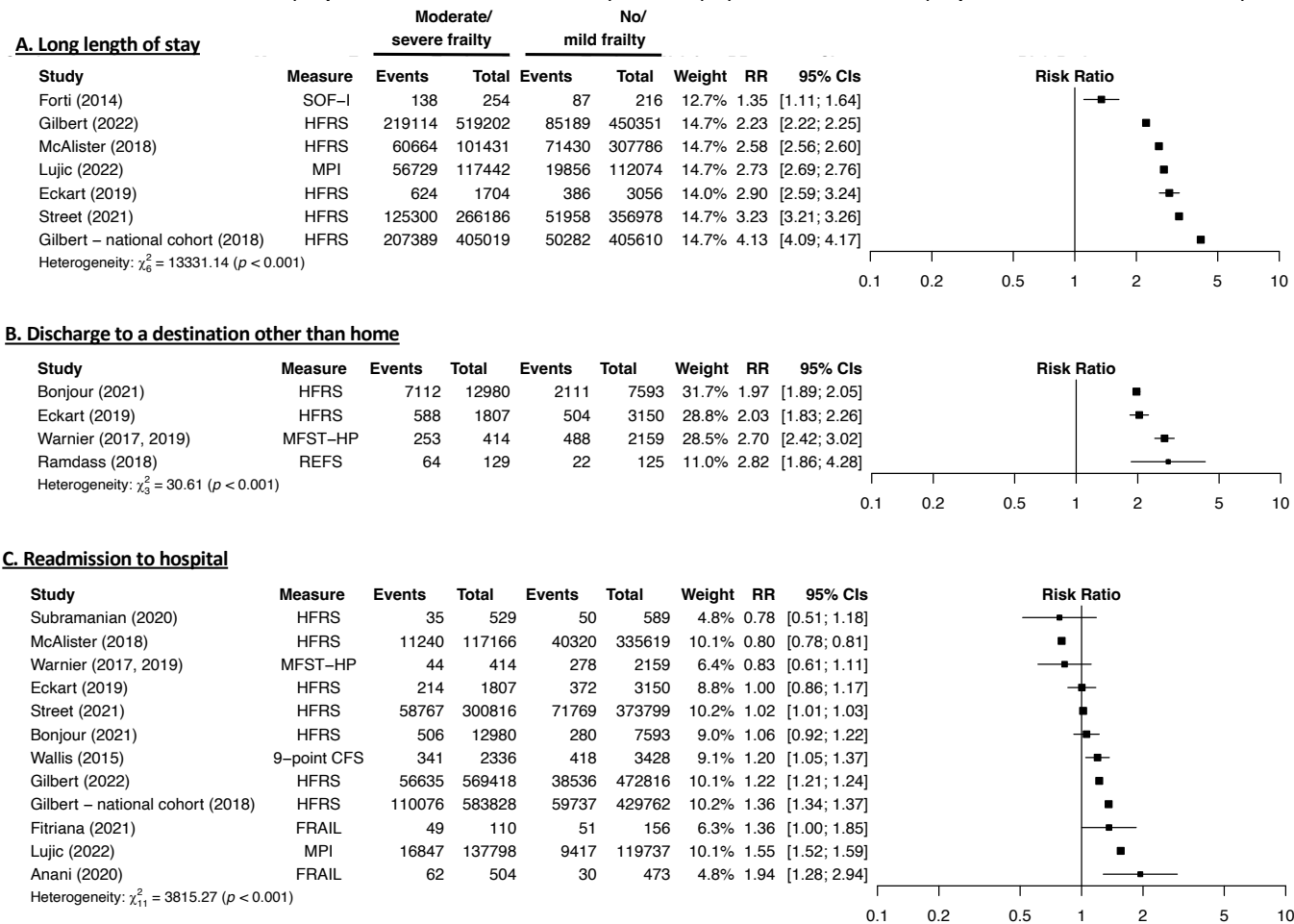
Egger's test: Intercept (95% CIs) = -0.35 (-26.28-25.58), p-value = 0.8666, $df = 7$ (Note: due to the small sample size the test is underpowered, and results cannot be relied on).

Appendix Figure 3.3 Unadjusted relative risks of mortality for moderate/severe versus no/mild frailty stratified by frailty tool type, including studies with no events in either group



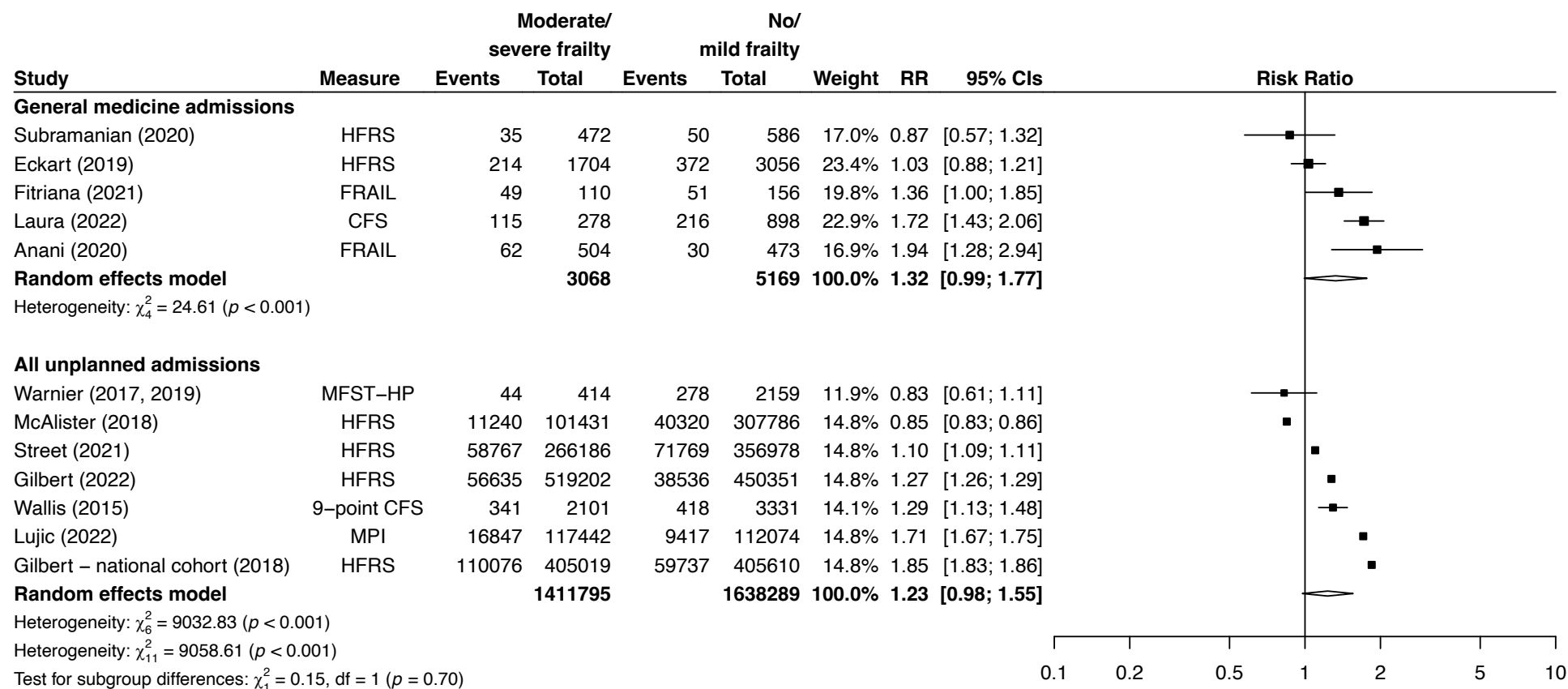
Legend: To avoid artificially reducing the standard error, when multiple estimates were reported for the same cohort, the estimate with the best validity was included in the pooled estimate. Estimates not included were Warnier et al. (2017, 2019), which reported a RR for 30-day mortality of 8.97 (95% CI 4.71 to 17.10).

Appendix Figure 3.4 Sensitivity analysis: Unadjusted RRs for (A) length of stay >8-10 days (excluding those who died in hospital), (B) discharge to a destination other than home (reported denominators), and (C) readmission (reported denominators)



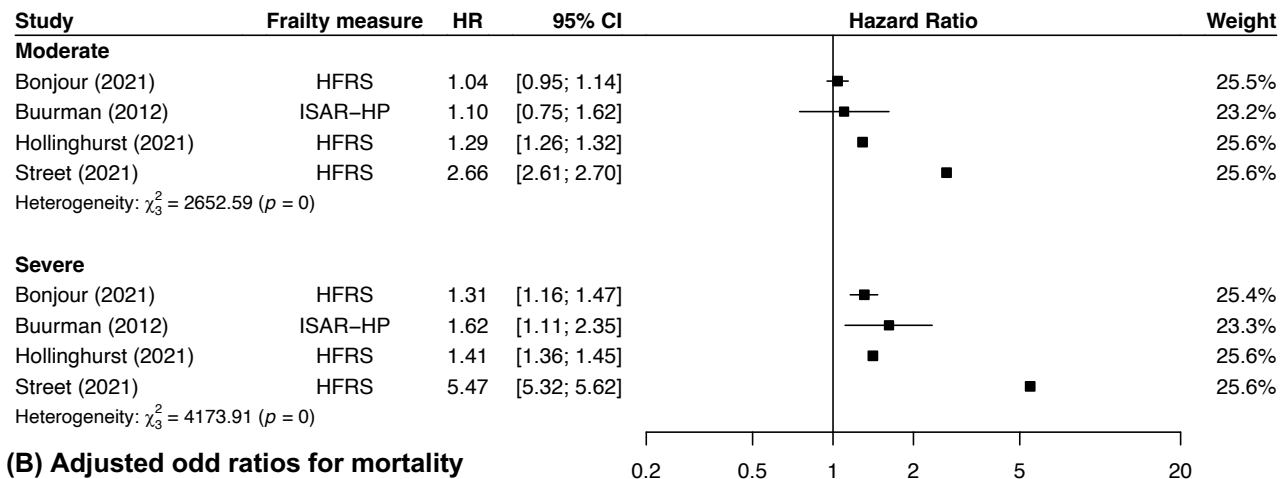
Legend: To avoid artificially reducing the standard error, when multiple estimates were reported for the same cohort, the estimate judged to have the best validity was retained. Warnier et al. (2017, 2019) also reported, using the VMS, a relative risk of 1.85 (95% CI 1.60 to 2.14) days for discharge to a nursing home or post-acute care facility and a relative risk for 30-day readmission of 1.09 (95% CI 0.89 to 1.34), but these estimates were not included in meta-analyses for this reason.

Appendix Figure 3.5 Unadjusted relative risks of readmission for moderate/severe versus no/mild frailty in people who survived to discharge, stratified by setting

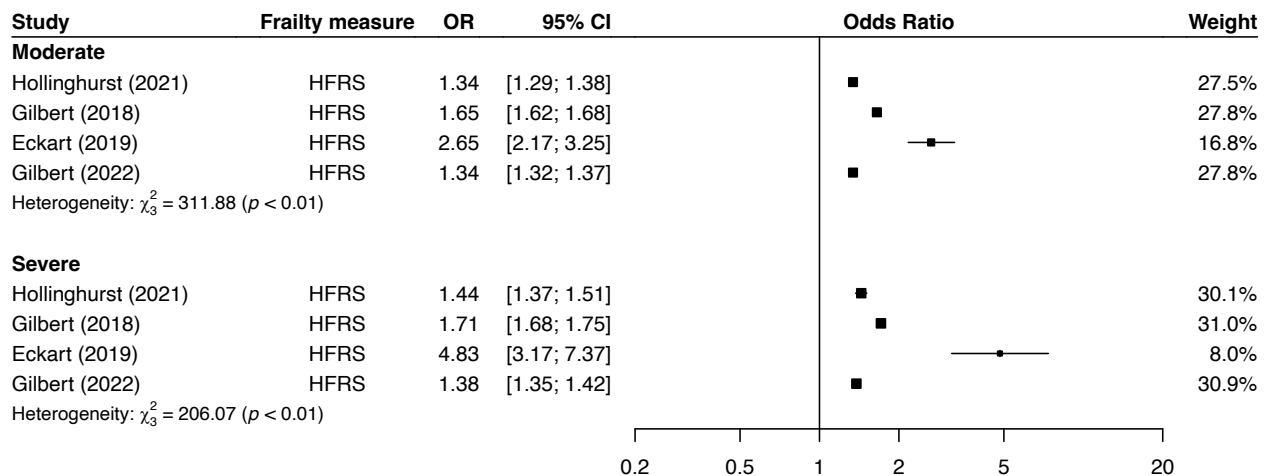


Appendix Figure 3.6 Adjusted hazard (A) and odds (B) ratios for mortality by degree of frailty

(A) Adjusted hazard ratios for mortality



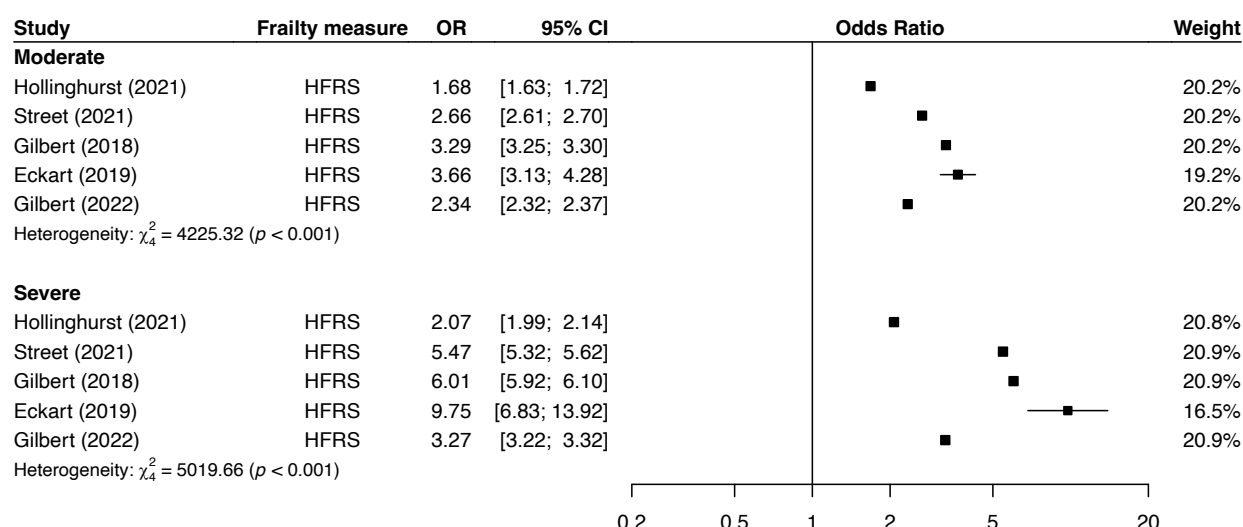
(B) Adjusted odd ratios for mortality



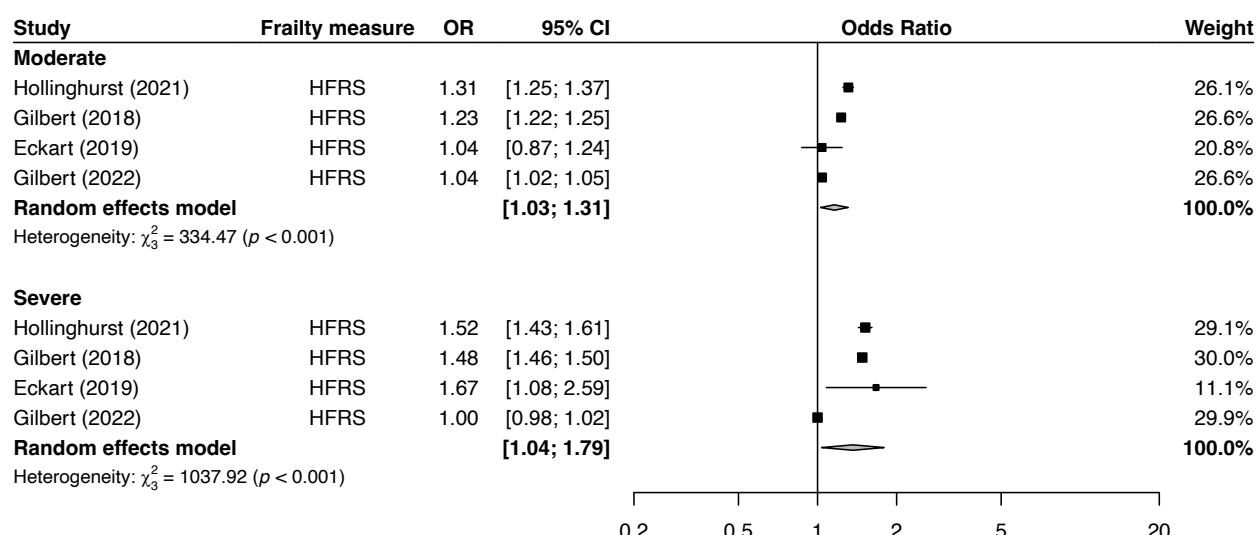
Legend: Hollinghurst et al. (2021) adjusted odds and hazard ratios for age and sex. Gilbert et al. (2018) adjusted odds ratios for age, sex, socioeconomic status, admission history, Charlson comorbidity and hospital variation. Eckart et al. (2019) adjusted for age, sex and comorbidities not included in the HFRS. Bonjour et al. (2021) adjusted hazard ratios for age group, gender, year of discharge, Charlson index, ICU stay, previous hospitalisations and length of stay. Buurman et al. (2012) adjusted hazard ratios for age, sex and comorbidity. Street et al. (2021) adjusted hazard ratios for age, sex, socioeconomic status, Charlson comorbidity, number of emergency admissions in preceding year, number of operation codes, ambulatory care sensitive condition, national tariff for Healthcare Resource Group, care home resident, travel time from residence to hospital.

Appendix Figure 3.7 Adjusted odds ratios for (A) long length of stay and (B) 30-day readmission

(A) Adjusted odds ratios for length of stay >8-10 days



(B) Adjusted odds ratios for 30-day readmission



Legend: Hollinghurst et al. (2021) adjusted odds ratios for age and sex. Gilbert et al. (2018) adjusted odds ratios for age, sex, socioeconomic status, admission history, Charlson comorbidity and hospital variation. Eckart et al. (2019) adjusted for age, sex and comorbidities not included in the HFRS. Street et al. (2021) adjusted hazard ratios for age, sex, socioeconomic status, Charlson comorbidity, number of emergency admissions in preceding year, number of operation codes, ambulatory care sensitive condition, national tariff for Healthcare Resource Group, care home resident, travel time from residence to hospital

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Appendix 4 Supplementary material for Chapter 4

Appendix Table 4.1 NHS Digital SHMI Charlson Comorbidity Index weights

Condition Name	ICD-10 codes	Weight
Acute myocardial infarction	I21, I22, I23, I252, I258	5
Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
Congestive heart failure	I50	13
Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
Dementia	F00, F01, F02, F03, F051	14
Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
Liver disease	K702, K703, K717, K73, K74	8
Peptic ulcer	K25, K26, K27, K28	9
Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
Pulmonary disease	J40-J47, J60-J67	4
Cancer	C00-C76, C81-C97	8
Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
Paraplegia	G041, G81, G820, G821, G822	1
Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10
Metastatic cancer	C77, C78, C79, C80	14
Severe liver disease	K721, K729, K766, K767	18
HIV	B20, B21, B22, B23, B24, O987	2

Legend: Table adapted from *NHS Digital. IAP00385 Summary Hospital-level Mortality Indicator (SHMI). In: Health and Social Care. p. 81-4, Appendix D.1.*

Appendix Table 4.2 Gilbert et al. Lancet 2018 Hospital Frailty Risk Score weights

ICD-10	Description	Weight
F00	Dementia in Alzheimer's disease	7.10
G81	Hemiplegia	4.40
G30	Alzheimer's disease	4.00
I69	Sequelae of cerebrovascular disease (secondary codes)	3.70
R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29.6 Tendency to fall)	3.60
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.20
F05	Delirium, not induced by alcohol and other psychoactive substances	3.20
W19	Unspecified fall	3.20
S00	Superficial injury of head	3.20
R31	Unspecified haematuria	3.00
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.90
R41	Other symptoms and signs involving cognitive functions and awareness	2.70
R26	Abnormalities of gait and mobility	2.60
I67	Other cerebrovascular diseases	2.60
R56	Convulsions, not elsewhere classified	2.60
R40	Somnolence, stupor and coma	2.50
T83	Complications of genitourinary prosthetic devices, implants and grafts	2.40
S06	Intracranial injury	2.40
S42	Fracture of shoulder and upper arm	2.30
E87	Other disorders of fluid, electrolyte and acid-base balance	2.30
M25	Other joint disorders, not elsewhere classified	2.30
E86	Volume depletion	2.30
R54	Senility	2.20
Z50	Care involving use of rehabilitation procedures	2.10
F03	Unspecified dementia	2.10
W18	Other fall on same level	2.10
Z75	Problems related to medical facilities and other health care	2.00
F01	Vascular dementia	2.00
S80	Superficial injury of lower leg	2.00
L03	Cellulitis	2.00
H54	Blindness and low vision	1.90
E53	Deficiency of other B group vitamins	1.90
Z60	Problems related to social environment	1.80
G20	Parkinson's disease	1.80
R55	Syncope and collapse	1.80
S22	Fracture of rib(s), sternum and thoracic spine	1.80

K59	Other functional intestinal disorders	1.80
N17	Acute renal failure	1.80
L89	Decubitus ulcer	1.70
Z22	Carrier of infectious disease	1.70
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.70
L97	Ulcer of lower limb, not elsewhere classified	1.60
R44	Other symptoms and signs involving general sensations and perceptions	1.60
K26	Duodenal ulcer	1.60
I95	Hypotension	1.60
N19	Unspecified renal failure	1.60
A41	Other septicaemia	1.60
Z87	Personal history of other diseases and conditions	1.50
J96	Respiratory failure, not elsewhere classified	1.50
X59	Exposure to unspecified factor	1.50
M19	Other arthrosis	1.50
G40	Epilepsy	1.50
M81	Osteoporosis without pathological fracture	1.40
S72	Fracture of femur	1.40
S32	Fracture of lumbar spine and pelvis	1.40
E16	Other disorders of pancreatic internal secretion	1.40
R94	Abnormal results of function studies	1.40
N18	Chronic renal failure	1.40
R33	Retention of urine	1.30
R69	Unknown and unspecified causes of morbidity	1.30
N28	Other disorders of kidney and ureter, not elsewhere classified	1.30
R32	Unspecified urinary incontinence	1.20
G31	Other degenerative diseases of nervous system, not elsewhere classified	1.20
Y95	Nosocomial condition	1.20
S09	Other and unspecified injuries of head	1.20
R45	Symptoms and signs involving emotional state	1.20
G45	Transient cerebral ischaemic attacks and related syndromes	1.20
Z74	Problems related to care-provider dependency	1.10
M79	Other soft tissue disorders, not elsewhere classified	1.10
W06	Fall involving bed	1.10
S01	Open wound of head	1.10
A04	Other bacterial intestinal infections	1.10
A09	Diarrhoea and gastroenteritis of presumed infectious origin	1.10
J18	Pneumonia, organism unspecified	1.10
J69	Pneumonitis due to solids and liquids	1.00

R47	Speech disturbances, not elsewhere classified	1.00
E55	Vitamin D deficiency	1.00
Z93	Artificial opening status	1.00
R02	Gangrene, not elsewhere classified	1.00
R63	Symptoms and signs concerning food and fluid intake	0.90
H91	Other hearing loss	0.90
W10	Fall on and from stairs and steps	0.90
W01	Fall on same level from slipping, tripping and stumbling	0.90
E05	Thyrotoxicosis [hyperthyroidism]	0.90
M41	Scoliosis	0.90
R13	Dysphagia	0.80
Z99	Dependence on enabling machines and devices	0.80
U80	Agent resistant to penicillin and related antibiotics	0.80
M80	Osteoporosis with pathological fracture	0.80
K92	Other diseases of digestive system	0.80
I63	Cerebral Infarction	0.80
N20	Calculus of kidney and ureter	0.70
F10	Mental and behavioural disorders due to use of alcohol	0.70
Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.70
R00	Abnormalities of heart beat	0.70
J22	Unspecified acute lower respiratory infection	0.70
Z73	Problems related to life-management difficulty	0.60
R79	Other abnormal findings of blood chemistry	0.60
Z91	Personal history of risk-factors, not elsewhere classified	0.50
S51	Open wound of forearm	0.50
F32	Depressive episode	0.50
M48	Spinal stenosis (secondary code only)	0.50
E83	Disorders of mineral metabolism	0.40
M15	Polyarthrosis	0.40
D64	Other anaemias	0.40
L08	Other local infections of skin and subcutaneous tissue	0.40
R11	Nausea and vomiting	0.30
K52	Other noninfective gastroenteritis and colitis	0.30
R50	Fever of unknown origin	0.10

Legend: Table adapted from Table A2, 'List of 109 ICD-10 codes included in logistic regression model and number of points awarded for each to create the hospital frailty risk score,' in Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018; 391(10132): 1775-82, (Supplement): 6-10.

Appendix Table 4.3 Royal College of Physicians National Early Warning Score (NEWS) version 1

Criteria	Point Value
Respiratory Rate	
≤8	3
9-11	1
12-20	0
21-24	2
≥25	3
Oxygen Saturation (%)	
≤91	3
92-93	2
94-95	1
≥96	0
Temperature in °C	
≤35.0	3
35.1-36.0	1
36.1-38.0	0
38.1-39.0	1
≥39.1	2
Systolic blood pressure	
≤90	3
91-100	2
101-110	1
111-219	0
≥220	3
Heart Rate (beats per minute)	
≤40	3
41-50	1
51-90	0
91-110	1
111-130	2
≥131	3
AVPU	
Alert	0
Verbal, Voice, Pain, Unresponsive	3
Any Supplemental Oxygen (not scored)	
Yes	2
No	0

Legend: Table adapted from *The Royal College of Physicians. National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS. London: The Royal College of Physicians, 2012.* 'Any Supplemental Oxygen,' was not recorded reliably in ORCHARD-EPR and therefore was not scored. NEWS scores were categorised as follows: scores of <4 were categorised as 'Low' (unless, one of temperature, AVPU, heart rate, systolic blood pressure, oxygen saturation or respiratory rate was scored as 3), scores of 5-6 were 'Medium' and ≥7 were 'High.'

Appendix Table 4.4 ICD-10 codes list for infection

ICD10	Description
Y95	Hospital-acquired infection
T880	Infection following immunization
T857	Infection due to internal prosthetic devices, implants and grafts
T846	Infection and inflammatory reaction due to internal fixation device [any site]
T845	Prosthetic joint infection
T836	Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract
T827	Infections due to cardiac and vascular devices
T826	Infection and inflammatory reaction due to cardiac valve prosthesis
T802	Infections following infusion, transfusion and therapeutic injection
R651	Systemic Inflammatory Response Syndrome of infectious origin with organ failure
R650	Systemic Inflammatory Response Syndrome of infectious origin without organ failure
R572	Septic shock
O98	Maternal infectious and parasitic diseases
O91	Infections of breast associated with childbirth
O86	Other puerperal infections
O85X	Puerperal sepsis
O753	Other infection during labour
O411	Infection of amniotic sac and membranes
O23	Infections of genitourinary tract in pregnancy
N61	Abscess, carbuncle, mastitis of breast
N45	Orchitis and epididymitis
N431	Infected hydrocele
N41	Prostatitis and abscess of prostate
N390	Urinary tract infections, unspecified
N34	Urethritis and urethral abscess
N300	Acute cystitis
N291	Other disorders of kidney and ureter in infectious and parasitic diseases classified elsewhere
N290	Late syphilis of kidney
N159	Kidney infection, unspecified
N151	Renal abscess
N10 N12 N136	Acute pyelonephritis/pyonephrosis
N080	Glomerular disorders in infectious and parasitic diseases classified elsewhere
M902	Osteopathy in other infectious diseases classified elsewhere
M901	Periostitis in other infectious diseases classified elsewhere
M600 [M][6][5][0-1] [M][7][1][0-1]	Infective myositis, synovitis and bursitis
M01	Direct infections of joint in infectious and parasitic diseases classified elsewhere
M00	Pyogenic arthritis
K810 K819	Cholecystitis, acute or unspecified
K65	Peritonitis
K61 K630 K750	Abscess of anal and rectal regions, intestine, and liver
K57	Diverticulitis of intestine
K37	Unspecified appendicitis
K36	Other appendicitis

K35	Acute appendicitis
K122	Cellulitis and abscess of mouth
K113	Abscess of salivary gland
K102 K122	Infections of the jaws and mouth
K052	Acute periodontitis
K050 K102 K122	Infections of the jaws and mouth
K047	Periapical abscess without sinus
K046	Periapical abscess with sinus
J853	Abscess of mediastinum
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection
J392	Other diseases of pharynx
J36 J390 J391	Deep neck space infections
J350	Chronic tonsillitis
J340	Abscess, furuncle and carbuncle of nose
J09 [J][1][0-8]+	Influenza and pneumonia
J051	Acute epiglottitis
J01	Acute sinusitis
I681	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
I400	Infective myocarditis
I33 T826	Infective endocarditis
H70	Mastoiditis
H031	Involvement of eyelid in other infectious diseases
H00 H050	Infections of the eye or orbit
G00 G02 G042 G049 G06	Bacterial, parasitic or other infectious meningitis, encephalitis, and intracranial abscess
D733	Abscess of spleen
[N][7][0-3]+ N751 [N][7][6][0-4] T835	Catheter-associated urinary tract infections
[N][3][0][8-9]	Cystitis, other or unspecified
[M][4][6][2-5] M86	Osteomyelitis, infection of intervertebral disc or nonspecific discitis, and other infective spondylopathies
[L][0][0-8]+ T814	Infections of other skin and subcutaneous tissue including cellulitis, cutaneous abscess, furuncle, carbuncle, impetigo, acute lymphadenitis, folliculitis, mastitis
[K][6][7][0-8]	Disorders of peritoneum in infectious diseases, classified elsewhere
[J][8][5-6]+	Abscess of lung and mediastinum; Pyothorax
[J][2][0-2]+	Other acute lower respiratory infections
[J][0][0-6]+	Acute upper respiratory infections
[H][6][5-6]+	Nonsuppurative, and suppurative and unspecified otitis media
[H][6][0][0-3] H620 H623	Infective otitis externa
[A][1-3][0-9]+ [A][4][2-9]+ [A][5-9][0-9]+	Other infections [A00-A99], not classified separately
[A][4][0-1]+	Sepsis, Staphylococcus or other bacterial
[A][0][0-9]+	Intestinal infectious diseases
[B][0-9][0-9]+	Other infections [B00-B99]

Legend: ICD codes are written as “regular expressions” to help facilitate coding. I developed this list by handsearching the ICD-10 code book for codes related to infection (see Chapter 4).

Appendix 5 Supplementary material for Chapter 5

Appendix Table 5.1 Characteristics of general medicine admissions in ORCHARD 2017-2019 with versus without at least one of a completed cognitive screen and/or ≥ 1 ICD-10 code(s) for dementia or delirium

	First admissions (N=18,614)		
Characteristic	No cognitive data, N = 4,612 ¹ (25%)	Yes cognitive data, N = 14,002 ¹ (75%)	p-value ²
Age	80.8 (7.4)	83.6 (7.2)	<0.001
Female sex	2,381 / 4,612 (51%)	7,393 / 14,002 (53%)	0.054
CCI	7.1 (7.9)	11.6 (10.9)	<0.001
Frailty markers			
HFRS	4.8 (4.3)	8.9 (6.5)	<0.001
Fall history	1,077 / 3,565 (30%)	5,229 / 11,500 (45%)	<0.001
Incontinence	411 / 3,557 (12%)	3,060 / 11,540 (27%)	<0.001
Braden score	19.0 (3.3)	17.5 (3.6)*	<0.001
Observations and labs			
SIRS $\geq 2^{**}$	1,692 / 4,507 (38%)	5,454 / 13,824 (39%)	0.022
Low oxygen saturation	1,315 / 4,604 (29%)	4,059 / 13,981 (29%)	0.5
CRP >6 mm/L	2,912 / 3,968 (73%)	10,165 / 13,026 (78%)	<0.001
Na <135 mm/L	1,416 / 4,519 (31%)	4,352 / 13,875 (31%)	0.9
Length of stay (days)	2 (1, 5)	4 (2, 11)	<0.001
In-hospital death	319 / 4,612 (6.9%)	1,496 / 14,002 (11%)	<0.001
¹ Mean (SD); n (%); Median (IQR) for length of stay ² t-test; Pearson's Chi-squared test, Fisher's exact test, Wilcoxon rank sum test for length of stay. Significant p-values bolded (<0.01). *Missing from denominator: No cognitive data = 614, Yes cognitive data = 1,249 **P-values for each criterion: abnormal tympanic temperature (0.2), WBCC (<0.001), HR>90 (0.4) and RR>20 (0.8)			

Appendix Table 5.2 Cross-tabulation of coded dementia and delirium cases vs those identified on the cognitive screen alone

Cognitive screen	ICD-10 codes	Total
Does the patient have a diagnosis of dementia?	<i>Dementia: F00X, F01X, F02X, F03X, G03X, Other</i>	
Yes	1,992 (91%)	2,180
Uncertain	204 (19%)	1,068
No	403 (4.3%)	9,415
Not done	850 (14%)	5,951
Total	3,449 (19%)	18,614
Does the patient have delirium?	<i>Delirium: F05X, Other</i>	
Yes	951 (53%)	1,783
Uncertain	473 (19%)	2,480
No	431 (5.1%)	8,400
Not done	390 (6.6%)	5,951
Total	2,245 (12%)	18,614

Appendix Table 5.3 Frequency of dementia (N=4,799) and delirium (N=2,245) ICD-10 codes

Three-digit ICD-10 code	N (%)	Four-digit ICD-10 code	N (%)
Dementia			
F00X - Dementia in Alzheimer Disease	759 (16%)	F009 - Dementia in Alzheimer Disease, unspecified	702 (15%)
		Other (<2%): • F000 (n=4), • F001 (n=4), • F002 (n=49)	57 (1%)
F01X - Vascular dementia	574 (12%)	F019 - Vascular dementia, unspecified	564 (12%)
		Other (<2%): • F010 (n=2), • F011 (n=4), • F012 (n=2), • F013 (n=1), • F018 (n=1)	10 (0.2%)
F02X - Dementia in other diseases classified elsewhere	208 (4.3%)	F028 - Dementia in other <i>specified</i> diseases classified elsewhere	123 (2.6%)
		Other (<2%): • F020 (n=18), • F022 (n=2), • F023 (n=65)	85 (1.8%)
F03X - Unspecified dementia	1,582 (33%)	NA	NA
G30X - Alzheimer disease	1,053 (22%)	G309 – Alzheimer disease, unspecified	997 (21%)
		Other (<2%): • G300 (n=6), • G301 (n=3), • G308 (n=47)	56 (1.2%)
Other	623 (13%)	F051 - Delirium superimposed on dementia	612 (13%)
		F107 - Residual and late-onset psychotic disorder (alcohol)	11 (0.2%)
Delirium			
F05X	2,245 (100%)	F050 - Delirium not superimposed on dementia, so described	338 (15%)
		F051 – Delirium superimposed on dementia	1,612 (27%)
		F058 – Other delirium	62 (2.8%)
		F059 - Delirium, unspecified	1,233 (55%)
Other	0 (0%)	F194 – Withdrawal state with delirium (alcohol)	0 (0%)

Appendix Table 5.4 Proportion of AMT-10 questions answered correctly in ORCHARD and the audit cohort

AMT-10 Question	ORCHARD 2017-2019, N = 10,098 ¹	Audit 2010-2018, N = 327 ¹	p-value ²
Date of birth	9,405 (93%)	298 (91%)	0.2
Monarch	8,837 (88%)	276 (84%)	0.10
Location	8,738 (87%)	276 (84%)	0.3
Recognise two people	8,716 (86%)	276 (84%)	0.3
Age	8,538 (85%)	264 (81%)	0.061
Count backwards (from 20 to 1)	7,865 (78%)	247 (76%)	0.3
Time (nearest hour)	7,730 (77%)	244 (75%)	0.4
Current year	7,338 (73%)	216 (66%)	0.008
Year of WWII	7,182 (71%)	227 (69%)	0.5
Recall 42 W street	5,443 (54%)	171 (52%)	0.6
¹ n (%); Median (IQR)			
² Pearson's Chi-squared test; Wilcoxon rank sum test			

Appendix Table 5.5 Results for full model for outcomes associated with delirium certain or uncertain compared to no delirium. Unadjusted and models adjusted for age/sex, comorbidity and illness severity are shown

Unadjusted and models adjusted for age, sex, comorbidity, and illness severity are shown.														
Characteristic	Event N	N	M1 (unadjusted)			M2 (age + sex)			M3 (+ comorbidity)			M4 (+ illness severity)		
			OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value
During admission														
Delirium														
None	1022	13,425	—	—		—	—		—	—		—	—	
Certain	451	3,056	2.1	1.86, 2.36	<0.001	1.93	1.71, 2.18	<0.001	1.74	1.54, 1.96	<0.001	1.71	1.51, 1.94	<0.001
Uncertain	313	1,989	2.27	1.97, 2.59	<0.001	2.13	1.85, 2.44	<0.001	1.92	1.67, 2.21	<0.001	1.79	1.55, 2.06	<0.001
Age	1786	18,470				1.04	1.03, 1.04	<0.001	1.03	1.02, 1.04	<0.001	1.03	1.03, 1.04	<0.001
Sex						1.36	1.23, 1.50	<0.001	1.28	1.16, 1.42	<0.001	1.29	1.16, 1.43	<0.001
CCI														
0	278	5,174							—	—		—	—	
1-5	176	3,152							1.07	0.88, 1.30	0.5	0.95	0.78, 1.16	0.6
>5	1332	10,144							2.36	2.06, 2.70	<0.001	2.17	1.89, 2.49	<0.001
NEWS	1022	13,425	—	—		—	—		—	—		—	—	
Low	451	3,056	2.1	1.86, 2.36	<0.001	1.93	1.71, 2.18	<0.001	1.74	1.54, 1.96	<0.001	1.71	1.51, 1.94	<0.001
Low-Medium	313	1,989	2.27	1.97, 2.59	<0.001	2.13	1.85, 2.44	<0.001	1.92	1.67, 2.21	<0.001	1.79	1.55, 2.06	<0.001
Medium	1786	18,470				1.04	1.03, 1.04	<0.001	1.03	1.02, 1.04	<0.001	1.03	1.03, 1.04	<0.001
High						1.36	1.23, 1.50	<0.001	1.28	1.16, 1.42	<0.001	1.29	1.16, 1.43	<0.001

After discharge (<=30 days)														
Delirium														
None	655	12,403	—	—		—	—		—	—		—	—	
Certain	207	2,605	1.55	1.31, 1.82	<0.001	1.37	1.16, 1.62	<0.001	1.25	1.05, 1.47	0.009	1.24	1.05, 1.46	0.012
Uncertain	163	1,676	1.93	1.61, 2.31	<0.001	1.77	1.47, 2.12	<0.001	1.6	1.33, 1.92	<0.001	1.57	1.30, 1.88	<0.001
Age	1025	16,684				1.05	1.04, 1.06	<0.001	1.05	1.04, 1.06	<0.001	1.05	1.04, 1.06	<0.001
Sex						1.31	1.15, 1.49	<0.001	1.24	1.09, 1.42	<0.001	1.25	1.09, 1.42	<0.001
CCI														
0	169	4,896							—	—		—	—	
1-5	119	2,976							1.22	0.96, 1.55	0.11	1.17	0.92, 1.48	0.2
>5	737	8,812							2.33	1.97, 2.78	<0.001	2.26	1.91, 2.70	<0.001
NEWS														
Low	136	1,263										—	—	
Low-Medium	628	11,655										0.48	0.39, 0.58	<0.001
Medium	104	1,721										0.52	0.39, 0.68	<0.001
High	157	2,045										0.69	0.54, 0.88	0.003

After discharge (30 days to 1 year)														
Delirium														
None	2089	11,748	—	—		—	—		—	—		—	—	
Certain	587	2,398	1.5	1.35, 1.66	<0.001	1.37	1.23, 1.52	<0.001	1.24	1.11, 1.38	<0.001	1.24	1.11, 1.38	<0.001
Uncertain	367	1,513	1.48	1.30, 1.68	<0.001	1.38	1.22, 1.57	<0.001	1.26	1.10, 1.43	<0.001	1.24	1.09, 1.41	0.001
Age	3043	15,659				1.04	1.03, 1.05	<0.001	1.04	1.03, 1.04	<0.001	1.04	1.03, 1.04	<0.001
Sex						1.36	1.26, 1.48	<0.001	1.3	1.20, 1.41	<0.001	1.3	1.20, 1.41	<0.001
CCI														
0	588	4,727							—	—		—	—	
1-5	403	2,857							1.2	1.04, 1.37	0.011	1.18	1.02, 1.35	0.021
>5	2052	8,075							2.24	2.03, 2.48	<0.001	2.22	2.00, 2.45	<0.001
NEWS														
Low	286	1,127										—	—	
Low-Medium	2056	11,027										0.67	0.58, 0.78	<0.001
Medium	322	1,617										0.71	0.59, 0.85	<0.001
High	379	1,888										0.74	0.62, 0.89	0.001

LOS>7 days															
Delirium															
None	3249	13,425	—	—			—	—		—	—		—	—	
Certain	1467	3,056	2.89	2.67, 3.14	<0.001	2.77	2.55, 3.01	<0.001	2.63	2.42, 2.85	<0.001	2.62	2.41, 2.84	<0.001	
Uncertain	801	1,989	2.11	1.91, 2.33	<0.001	2.04	1.85, 2.25	<0.001	1.93	1.75, 2.13	<0.001	1.92	1.74, 2.12	<0.001	
Age	5517	18,470				1.02	1.01, 1.02	<0.001	1.01	1.01, 1.02	<0.001	1.01	1.01, 1.02	<0.001	
Sex						1.03	0.97, 1.10	0.3	1	0.93, 1.06	>0.9	1	0.94, 1.07	>0.9	
CCI															
0	1179	5,174							—	—		—	—		
1-5	805	3,152							1.2	1.08, 1.34	<0.001	1.19	1.08, 1.33	<0.001	
>5	3533	10,144							1.62	1.50, 1.76	<0.001	1.61	1.49, 1.75	<0.001	
NEWS															
Low	547	1,735										—	—		
Low-Medium	3559	12,415										0.95	0.85, 1.06	0.3	
Medium	632	1,936										1.08	0.94, 1.25	0.3	
High	779	2,384										1.11	0.97, 1.27	0.14	

Discharge to new residence (survivors)

Delirium														
None	1768	12,230	—	—		—	—		—	—		—	—	
Certain	851	2,528	3	2.73, 3.31	<0.001	2.69	2.43, 2.96	<0.001	2.6	2.35, 2.87	<0.001	2.6	2.36, 2.87	<0.001
Uncertain	443	1,642	2.19	1.94, 2.46	<0.001	2.01	1.77, 2.26	<0.001	1.94	1.71, 2.19	<0.001	1.95	1.72, 2.20	<0.001
Age	3062	16,400				1.04	1.04, 1.05	<0.001	1.04	1.04, 1.05	<0.001	1.04	1.04, 1.05	<0.001
Sex						0.88	0.81, 0.95	0.002	0.87	0.80, 0.94	<0.001	0.87	0.80, 0.94	<0.001
CCI														
0	778	4,820							—	—		—	—	
1-5	427	2,924							0.95	0.84, 1.09	0.5	0.96	0.85, 1.10	0.6
>5	1857	8,656							1.26	1.14, 1.38	<0.001	1.27	1.15, 1.39	<0.001
NEWS														
Low	198	1,236										—	—	
Low-Medium	2155	11,442										1.22	1.04, 1.45	0.015
Medium	351	1,705										1.29	1.06, 1.57	0.013
High	358	2,017										1.12	0.92, 1.36	0.3

Discharge delayed >2 days (survivors)

Delirium														
None	1161	12,403	—	—		—	—		—	—		—	—	

Certain	638	2,605	3.14	2.82, 3.50	<0.001	2.88	2.58, 3.21	<0.001	2.76	2.47, 3.08	<0.001	2.76	2.47, 3.08	<0.001
Uncertain	311	1,676	2.21	1.92, 2.53	<0.001	2.06	1.79, 2.36	<0.001	1.97	1.71, 2.26	<0.001	1.97	1.71, 2.26	<0.001
Age	2110	16,684				1.03	1.03, 1.04	<0.001	1.03	1.03, 1.04	<0.001	1.03	1.03, 1.04	<0.001
Sex						0.94	0.85, 1.03	0.2	0.92	0.83, 1.01	0.067	0.92	0.83, 1.01	0.068
CCI														
0	465	4,896							—	—		—	—	
1-5	322	2,976							1.23	1.06, 1.43	0.008	1.23	1.06, 1.43	0.008
>5	1323	8,812							1.48	1.32, 1.67	<0.001	1.48	1.32, 1.67	<0.001
NEWS														
Low	162	1,263										—	—	
Low-Medium	1454	11,655										1	0.84, 1.20	>0.9
Medium	234	1,721										1.04	0.83, 1.29	0.8
High	260	2,045										0.99	0.80, 1.23	>0.9

Readmission within 30 days discharge (survivors)

Delirium														
None	1435	11,997	—	—		—	—		—	—		—	—	
Certain	362	2,497	1.25	1.10, 1.41	<0.001	1.19	1.05, 1.35	0.006	1.16	1.02, 1.31	0.024	1.15	1.02, 1.31	0.027

Uncertain	215	1,635	1.11	0.95, 1.30	0.2	1.08	0.92, 1.25	0.3	1.04	0.89, 1.21	0.6	1.03	0.88, 1.20	0.7
Age	2012	16,129				1.02	1.01, 1.02	<0.001	1.02	1.01, 1.02	<0.001	1.02	1.01, 1.02	<0.001
Sex						1.11	1.01, 1.21	0.038	1.08	0.98, 1.18	0.12	1.08	0.98, 1.18	0.12
CCI														
0	458	4,733							—	—		—	—	
1-5	373	2,877							1.42	1.22, 1.64	<0.001	1.4	1.21, 1.62	<0.001
>5	1181	8,519							1.45	1.30, 1.63	<0.001	1.44	1.28, 1.62	<0.001
NEWS														
Low	182	1,215										—	—	
Low-Medium	1349	11,279										0.79	0.67, 0.93	0.005
Medium	209	1,665										0.82	0.66, 1.02	0.069
High	272	1,970										0.91	0.75, 1.12	0.4

¹ OR = Odds Ratio, CI = Confidence Interval

Appendix Table 5.6 Descriptive outcomes in people with and without certain dementia

	Certain dementia (N=3,584)					No certain dementia (N=14,769)				
Characteristic	N total ¹	No delirium N = 1,638 ² (46%)	Uncertain delirium N = 763 ² (21%)	Certain delirium N = 1,183 ² (33%)	p- value ³	N total ¹	No delirium N = 11,692 ² (79%)	Uncertain delirium N = 1,219 ² (8.2%)	Certain delirium N = 1,858 ² (13%)	p- value ³
Death										
In hospital	3,584	160 (9.8%)	127 (17%)	158 (13%)	<0.001	14,769	859 (7.3%)	184 (15%)	290 (16%)	<0.001
30 days PD	3,139	113 (7.6%)	80 (13%)	102 (10.0%)	0.001	13,436	542 (5.0%)	83 (8.0%)	103 (6.6%)	<0.001
30-365 days PD	2,844	331 (24%)	155 (28%)	242 (26%)	0.2	12,708	1,749 (17%)	212 (22%)	345 (24%)	<0.001
Other										
LOS >7 days	3,584	451 (28%)	291 (38%)	587 (50%)	<0.001	14,769	2,778 (24%)	508 (42%)	873 (47%)	<0.001
DTOC ≥2 days	3,139	206 (14%)	110 (17%)	274 (27%)	<0.001	13,436	950 (8.8%)	201 (19%)	362 (23%)	<0.001
Discharge to new residence	3,081	350 (24%)	181 (29%)	386 (39%)	<0.001	13,210	1,393 (13%)	261 (26%)	459 (30%)	<0.001
Readmissions within 30 days PD	3,034	202 (14%)	89 (14%)	134 (14%)	>0.9	12,991	1,226 (12%)	126 (13%)	227 (15%)	<0.001
¹ N at risk: includes either the full cohort, those who survived to discharge or 30 days PD. *Discharge destination was unknown for 58 admissions with dementia and 226 without. ² n (%); Median (IQR); ³ Pearson's Chi-squared test; Kruskal-Wallis rank sum test										

Appendix Table 5.7 Delirium outcomes (reference=no delirium) including an interaction term for dementia. Adjusted for age, sex, CCI, HFRS, NEWS

	No delirium (OR=1)	Uncertain delirium					Certain delirium					P-value uncertain vs certain ²
Outcome	Events/N	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	p-value
Death												
In hospital	1,019 / 13,330	311 / 1,982	2.24	1.94	1.61, 2.32	<0.001	448 / 3,041	2.33	2	1.72, 2.32	<0.001	0.8
30 days	655 / 12,311	163 / 1,671	1.66	1.46	1.14, 1.85	0.002	205 / 2,593	1.33	1.15	0.91, 1.42	0.2	0.12
1 year	2,080 / 11,656	367 / 1,508	1.4	1.28	1.08, 1.51	0.003	587 / 2,388	1.5	1.35	1.18, 1.54	<0.001	0.6
Other												
LOS >7 days	3,229 / 13,330	799 / 1,982	2.29	2.2	1.95, 2.49	<0.001	1,460 / 3,041	2.84	2.69	2.42, 2.97	<0.001	0.008
DTOC >2 days	1,156 / 12,311	311 / 1,671	2.51	2.36	1.99, 2.79	<0.001	636 / 2,593	3.12	2.85	2.48, 3.26	<0.001	0.059
Discharge to new residence	1,743 / 12,138	442 / 1,637	2.31	2.17	1.86, 2.52	<0.001	845 / 2,516	2.9	2.59	2.28, 2.93	<0.001	0.054
Readmission <30 days	1,428 / 11,910	215 / 1,630	1.08	1.03	0.84, 1.25	0.8	361 / 2,485	1.34	1.27	1.09, 1.48	0.002	0.08

Appendix Table 5.8 Delirium outcomes (reference=no delirium) in people with dementia. Adjusted for age, sex, CCI and NEWS category

Dementia	No delirium (OR=1)	Uncertain delirium					Certain delirium					P-value uncertain vs certain
Outcome	Events/N	Events/N	Crude OR	Adjusted OR	95% CI	p-value	Events/N	Crude OR	Adjusted OR	95% CI	p-value	p-value
Death												
In hospital	160/1638	127/763	1.84	1.7	1.30, 2.20	<0.001	158/1183	1.42	1.44	1.13, 1.84	0.003	0.2
30 days	113/1478	80/636	1.74	1.7	1.25, 2.31	<0.001	102/1025	1.33	1.34	1.00, 1.77	0.046	0.14
1 year	331/1365	155/556	1.21	1.21	0.96, 1.51	0.1	242/923	1.11	1.11	0.92, 1.35	0.3	0.5
Other												
LOS >7 days	451/1638	291/763	1.62	1.64	1.37, 1.97	<0.001	587/1183	2.59	2.58	2.21, 3.03	<0.001	<0.001
DTOC >2 days	206/1478	110/636	1.29	1.29	1.00, 1.67	0.046	274/1025	2.25	2.25	1.84, 2.76	<0.001	<0.001
Discharge to new residence	350/1457	181/623	1.3	1.29	1.05, 1.60	0.017	386/1001	1.99	1.98	1.67, 2.37	<0.001	<0.001
Readmission <30 days	202/1434	89/624	1.01	1	0.76, 1.31	>0.9	134/976	0.97	0.97	0.76, 1.22	0.8	0.8

Appendix Table 5.9 Delirium outcomes (reference=no delirium) in people without dementia. Adjusted for age, sex, CCI and NEWS category

No dementia	No delirium (OR=1)		Uncertain delirium				Certain delirium				P-value uncertain vs certain	
Outcome	Events/N	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p- value	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p- value	p-value
Death												
In hospital	859/11692	184/1219	2.24	1.94	1.62, 2.32	<0.001	290/1858	2.33	2	1.72, 2.33	<0.001	0.8
30 days	542/10833	83/1035	1.66	1.46	1.14, 1.86	0.002	103/1568	1.33	1.14	0.91, 1.42	0.2	0.11
1 year	1749/10291	212/952	1.4	1.27	1.07, 1.49	0.005	345/1465	1.5	1.33	1.16, 1.52	<0.001	0.6
Other												
LOS >7 days	2778/11692	508/1219	2.29	2.17	1.92, 2.46	<0.001	873/1858	2.84	2.65	2.39, 2.94	<0.001	0.009
DTOC >2 days	950/10833	201/1035	2.51	2.31	1.94, 2.73	<0.001	362/1568	3.12	2.76	2.40, 3.17	<0.001	0.072
Discharge to new residence	1393/10833	261/1014	2.31	2.14	1.83, 2.49	<0.001	459/1515	2.9	2.54	2.24, 2.87	<0.001	0.067
Readmission <30 days	1226/10476	126/1006	1.08	1.03	0.84, 1.25	0.8	227/1509	1.34	1.27	1.09, 1.48	0.002	0.077

Appendix Table 5.10 Descriptive outcomes by delirium status for HFRS $\geq$ 5 (moderate or high risk) or HFRS $<$ 5 (low risk), excluding coded delirium

	Moderate or high risk (N=11,266)					Low risk (N=7,087)				
Characteristic	N at risk ¹	No delirium N = 6,891 ² (61%)	Uncertain delirium N = 1,565 ² (14%)	Certain delirium N = 2,810 ² (25%)	p-value ³	N at risk ¹	No delirium N = 6,439 ² (91%)	Uncertain delirium N = 417 ² (5.9%)	Certain delirium N = 231 ² (3.3%)	p-value ³
Death										
In hospital	11,266	696 (10%)	262 (17%)	411 (15%)	<0.001	7,087	323 (5.0%)	49 (12%)	37 (16%)	<0.001
30 days PD	9,897	408 (6.6%)	134 (10%)	195 (8.1%)	<0.001	6,678	247 (4.0%)	29 (7.9%)	10 (5.2%)	0.002
30-365 days PD	9,160	1,196 (21%)	306 (26%)	540 (25%)	<0.001	6,392	884 (15%)	61 (18%)	47 (26%)	<0.001
Other										
LOS >7 days	11,266	2,356 (34%)	714 (46%)	1,403 (50%)	<0.001	7,087	873 (14%)	85 (20%)	57 (25%)	<0.001
DTOC $\geq$ 2 days	9,897	964 (16%)	278 (21%)	617 (26%)	<0.001	6,678	192 (3.1%)	33 (9.0%)	19 (9.8%)	<0.001
Discharge to new residence	9,664	1,299 (21%)	387 (30%)	806 (35%)	<0.001	6,627	444 (7.3%)	55 (15%)	39 (21%)	<0.001
Readmissions within 30 days PD	9,540	765 (13%)	176 (14%)	334 (15%)	0.1	6,485	663 (11%)	39 (11%)	27 (14%)	0.4
¹ N at risk: includes either the full cohort, those who survived to discharge or 30 days PD. *Discharge destination information was not known for 234 admissions with moderate-severe frailty and 51 without ² n (%); Median (IQR); ³ Pearson's Chi-squared test; Kruskal-Wallis rank sum test										

Appendix Table 5.11 Delirium outcomes (reference=no delirium) including an interaction term for modified HFRS excluding coded delirium. Adjusted for age, sex, CCI, HFRS, NEWS

Outcome	No delirium (OR=1)		Uncertain delirium				Certain delirium				P-value uncertain vs certain ²	
	Events/N	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p- value	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p- value	p-value
Death												
In hospital	1,019 / 13,330	311 / 1,982	2.87	2.32	1.76, 3.04	<0.001	448 / 3,041	2.48	2.15	1.68, 2.74	<0.001	0.7
30 days	655 / 12,311	163 / 1,671	2.12	1.72	1.21, 2.42	0.002	205 / 2,593	1.55	1.25	0.90, 1.74	0.2	0.2
1 year	2,080 / 11,656	367 / 1,508	1.4	1.18	0.92, 1.50	0.2	587 / 2,388	1.73	1.47	1.19, 1.80	<0.001	0.2
Other												
LOS >7 days	3,229 / 13,330	799 / 1,982	2.06	2.03	1.66, 2.48	<0.001	1,460 / 3,041	2.63	2.61	2.20, 3.10	<0.001	0.041
DTOC >2 days	1,156 / 12,311	311 / 1,671	2.85	2.76	2.07, 3.66	<0.001	636 / 2,593	4.23	4.02	3.19, 5.05	<0.001	0.024
Discharge to new residence	1,743 / 12,138	442 / 1,637	2.55	2.4	1.88, 3.04	<0.001	845 / 2,516	3.06	2.73	2.22, 3.34	<0.001	0.4
Readmission <30 days	1,428 / 11,910	215 / 1,630	1.24	1.15	0.86, 1.53	0.3	361 / 2,485	1.77	1.65	1.29, 2.09	<0.001	0.048

Notes: The interaction term for HFRS was highly correlated with delirium, increasing the standard error. Therefore, a modified HFR excluding coded delirium was used.

Appendix Table 5.12 Delirium outcomes (reference=no delirium) in the moderate/high risk modified HFRS group. Adjusted for age, sex, CCI, NEWS

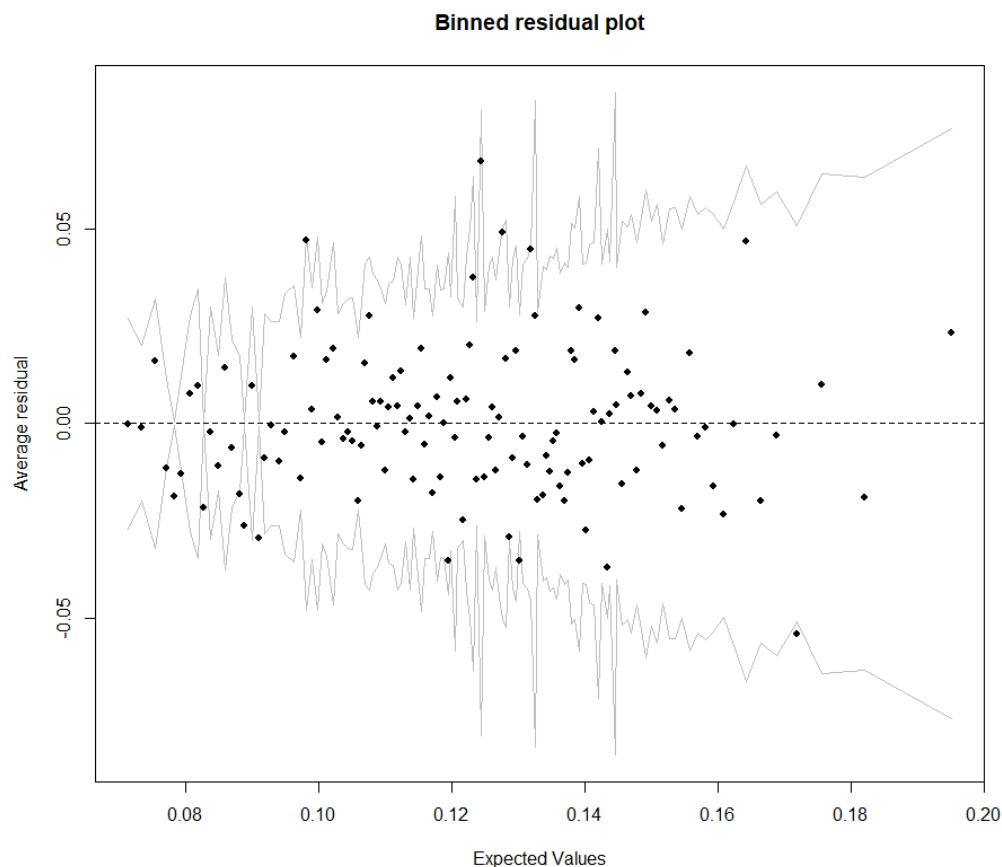
HFRS _≥ 5	No delirium (OR=1)	Uncertain delirium					Certain delirium					P-value uncertain vs certain ²
Outcome	Events/N	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	p-value
Death												
In hospital	696/6891	262/1565	1.79	1.51	1.28, 1.77	<0.001	411/2810	1.52	1.37	1.19, 1.56	<0.001	0.3
30 days	408/6195	134/1303	1.63	1.44	1.17, 1.77	<0.001	195/2399	1.25	1.14	0.95, 1.36	0.2	0.045
1 year	1196/5787	306/1169	1.36	1.25	1.08, 1.45	0.003	540/2204	1.25	1.15	1.02, 1.29	0.022	0.3
Other												
LOS >7 days	2356/6891	714/1565	1.61	1.57	1.40, 1.75	<0.001	1403/2810	1.92	1.87	1.71, 2.05	<0.001	0.005
DTOC >2 days	964/6195	278/1303	1.47	1.42	1.22, 1.65	<0.001	617/2399	1.88	1.82	1.62, 2.04	<0.001	0.003
Discharge to new residence	1299/6066	387/1270	1.61	1.55	1.35, 1.78	<0.001	806/2328	1.94	1.85	1.67, 2.06	<0.001	0.018
Readmission <30 days	765/5973	176/1269	1.1	1.07	0.89, 1.27	0.5	334/2298	1.16	1.14	0.99, 1.31	0.068	0.5

Appendix Table 5.13 Delirium outcomes (reference=no delirium) in the low risk modified HFRS group. Adjusted for age, sex, CCI and NEWS

HFRS<5	No delirium (OR=1)		Uncertain delirium				Certain delirium					P-value uncertain vs certain ²
Outcome	Events/N	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	Events/N	Crude OR ¹	Adjusted OR ¹	95% CI ¹	p-value	p-value
Death												
In hospital	323/6439	49/417	2.52	2.05	1.45, 2.85	<0.001	37/231	3.61	2.93	1.95, 4.31	<0.001	0.2
30 days	247/6116	29/368	2.03	1.72	1.12, 2.54	0.009	10/194	1.29	1.09	0.53, 2.01	0.8	0.2
1 year	884/5869	61/339	1.24	1.05	0.77, 1.39	0.8	47/184	1.93	1.7	1.19, 2.39	0.003	0.033
Other												
LOS >7 days	873/6439	85/417	1.63	1.55	1.20, 1.99	<0.001	57/231	2.09	1.98	1.44, 2.68	<0.001	0.2
DTOC >2 days	192/6116	33/368	3.04	2.76	1.84, 4.03	<0.001	19/194	3.35	2.84	1.67, 4.58	<0.001	>0.9
Discharge to new residence	444/6072	55/367	2.23	2.05	1.49, 2.76	<0.001	39/188	3.32	2.97	2.02, 4.26	<0.001	0.11
Readmission <30 days	663/5937	39/361	0.96	0.88	0.62, 1.23	0.5	27/187	1.34	1.23	0.79, 1.84	0.3	0.2

Appendix Figure 5.1 Logistic regression model diagnostics (example)

In the figure below, residuals were binned. The number of bins was determined by the square root of N as recommended by Gelman and Hill and those that fell outside the 95% confidence boundaries of the fitted values determined, in addition to inspection of the distribution of points on the plots.¹ The plot below shows binned residuals from the saturated model for death 30 days after admission, which has weak evidence of poor fit with 93% of binned residuals (observed-expected values) within the 95% error bounds.



I also assessed for multicollinearity: in the saturated model, VIFS were 1.03 for delirium, 1.05 for age, 1.03 for sex, 1.02 for Charlson Comorbidity and 1.01 for NEWS score categories.

Coding details for ward round observations at John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust

As per the Methods, I recorded ‘field notes’ during ward rounds at the John Radcliffe Hospital with an emphasis on understanding the patient population included in ORCHARD and also real-world use of the cognitive screen. I did not record identifiable details to maintain confidentiality and added memos to my notes later, because it was not possible to transcribe all relevant information during the ward round due to the speed/pace of activities. I performed descriptive coding in three iterations to enable myself to become familiar with the data.

Appendix Table 5.14 Coding frame

A	B	C
A1. Patient	B1.1 Acute factor	C1.1.1 Delirium precipitants C1.1.2 Hypoactive delirium C1.1.3 Hyperactive delirium C1.1.4 Other features of delirium C1.1.5 Variation in presentation of delirium C1.1.6 Illness severity C1.1.7 Fluctuation in condition before/during hospital stay C1.1.8 other acute factors impacting assessment
	B1.2 Pre-existing factor	C1.2.1 Polypharmacy C1.2.2 Baseline cognition C1.2.3 Age C1.2.4 Comorbidity C1.2.5 Sensory problems, e.g., hearing C1.2.6 Mental illness
A2. Hospital	B2.1 Individual hospital staff	C2.1.1 Training level of staff C2.1.2 Specialty of staff C2.1.3 Character attributes of individual staff (e.g., dedication and attentiveness)
	B2.2 Groups and social structures	C2.2.1 Ward round C2.2.2 MDT and roles of different staff
	B2.3 Health services and systems	C2.3.1 Supply/demand C2.3.2 Interdependence of care systems (e.g., secondary-primary)
	B2.4 Physical environment	B2.4.1 Location of patients B2.4.2 Noise B2.4.3 Privacy
IRR = irrelevant; UNC = uncertain		

Legend: Notes are shown in the table below, along with the most specific code applicable. Content in brackets was added after the ward round.

Appendix Table 5.15 Application of codes to field notes

Source	Notes	Codes
Emergency Assessment Unit, Post Take Ward Round #1 (PM)	Team of ~3 (other people doing other tasks) About 14 patients and very busy [Most patients had not been seen prior to the ward round therefore first cognitive assessments were done on the ward round]	A2 B2.3 C2.3.1
	Importance of seeing the patient, e.g., someone with terminal illness who has good function [cognitive assessment, particularly for delirium, often required a good history and physical exam and 'expert' input from the consultant/registrar was sometimes needed to diagnose cognitive problems]	A1 B1.1 C1.1.7 A2 B2.2 C2.1.1
	Variability as a sign of vulnerability [value of ward round, repeated assessments; including in cognition]	A1 B1.1 C1.1.7 A2 B2.2 C2.2.1
	Interaction or relationship between frailty and illness severity (i.e., general appearance, management, prognosis, etc.) [unclear if any points relevant to the research question were intended here – perhaps factors to be weighed in weighing the risk of delirium?]	UNC
	Variable levels of engagement & assessing delirium (quick assessment) [patient engagement impacted the speed of assessment, particularly for the AMTS or its feasibility; it also <i>appeared</i> difficult to tell apart 'low engagement' from hypoactive delirium – perhaps part of a spectrum? Curious about engagement and DSD [*delirium superimposed on dementia], but did not report any notes on this]	A1 B1.1/B2.1
	Younger patients with frailty	UNC
	Pain management (e.g., fractures) and SOB [*shortness of breath] impacting quality of assessment [Cognitive assessment appeared expedited or perhaps was not fully completed in two patients, each with one of these conditions due to the burden on the patient perceived by the team/their difficulty participating]	A1 B1.1 C1.1.8
Emergency Assessment Unit,	Team of ~7 [Considered 'big' by staff] About 20 patients and very busy	A2 B2.3

Post Take Ward Round #2 (AM)		C2.3.1
	Not feasible to do the cognitive assessment on lots of patients [due to time constraints; reasons why were not recorded systematically and the team split up at time so not all patients were observed]	A2 B2.3 C2.3.1
	Number of people with concern for infection (bacterial, viral), including based on delirium [the identification of an acute medical cause appeared to increase the speed (not measured) and confidence with which staff, especially junior staff, identified delirium]	A1 B1.1 C1.1.1
	Lot of variability in things like cognition and mobility by age [unclear what was intended here; several implications could be drawn] Mix of age range of patients & comparison of older versus younger and comorbidity, diagnostic process, etc. [insinuated that the process of screening for delirium was again attuned to patient risk factors – some patients were too young and not eligible] Breadth of presentations [physical and mental illness, acute and chronic]	A1 B1.2 C1.2.2 C1.2.3 C1.2.4 A2 B2.1
	Amount of polypharmacy and contribution to problems [Comment from a doctor on the team. Problems = delirium or impaired cognition. Drugs could be a predisposing or precipitating factor, but it was sometimes difficult to determine which]	A1 B1.2 C1.2.1
	Skin conditions that seem like they could have been treated earlier [wondering what led treatment to be delayed]	IRR
	Moving, e.g., corridor to room, to other rooms to ward [additional time spent looking for patients in other areas of A&E or other hospital floors; more difficult to monitor and disruptive to the round]	A2 B2.4 B2.4.1 (related to B2.3)
	Subtlety of delirium (could see it being missed by other doctors or in other settings), i.e. hypoactive [I believe that delirium was not recorded by the A&E doctor in several cases] Breadth of presentations [repeat]	A1 B1.1 C1.1.2 C1.1.4 C1.1.5 A2 B2.1 C2.1.2
	Use of CRP, lymphocytes in informing perception of illness severity – lack of use of NEWS, etc. Illness severity linked to infection, so maybe not accounted for as well in non-infection delirium? The caveat being that NEWS is probably not sufficient, especially in older people]	A1 B1.1 C1.1.6
	Have not seen nutrition, Braden score, etc. come up, i.e. markers of vulnerability	IRR

Complex Medicine Unit Ward Rounds #1-2 and Multidisciplinary Team Meeting (MDT)	Inpatient unit (I think there are four) [i.e., one of four units; number of staff/patients varied, but were 'overstaffed' on at least two days]	A2 B2.3 C2.3.1
	Mostly old/very old patients [but not quite all – cognitive screening was more cursory/check-box in a young-old patient with no/few risk factors]	A2 B2.1 B1.2.3
	Low engaged-ness of some patients is difficult to distinguish from delirium without expertise [i.e., from registrar or consultant in specialty]	A1 B1.1 C1.1.2 C1.1.4 C1.1.5 A2 B2.1 C2.1.2
	Complex medical background and needs, including range of mental illnesses [faded from memory, wish I recorded more detail but recall two more disruptive, agitated and loud patients – 1 younger and 1 older]	A1 B1.2 C1.2.6
	Impressed by effort to carefully diagnose patients (e.g., hypothyroid vs just delirium)	A2 B2.1 C2.1.3
	Impact of frailty and cognition on discharge and staffing very apparent (and also value of screening for planning these things) [There was potentially a motivation beyond impressing the consultant to complete assessments, because they were used by other staff and could be brought up in MDT meetings if needed - accountability]	A2 B2.2 C2.2.2 B2.3 C2.3.1 C2.3.2
	Need to take a good history to assess frailty, not just how the patient looks [discussed above – i.e., role of expertise and need for time; includes cognitive frailty]	A2 B2.3 C2.3.1 A1 B1.1 C1.1.7 A2 B2.2 C2.1.1
	Difficulty of cognitive screen, e.g., raise voice, engaging patients, noisy setting, sensory problems [discussed above]	A2 B2.4 C2.4.2 C2.4.3

		A1 B1.2 C1.2.5

Notes on reflexivity: To improve the *credibility* of this work, the consultant who led the ward round (STP) provided feedback on the results. Inclusion of related results from ORCHARD in this chapter, including reasons the AMTS was not completed and the investigation of patient characteristics which might be associated with uncertain delirium diagnosis allows for evaluation of the *reliability* of findings. With regards to the *objectivity* of the work, multiple potential sources of contamination were present. First, STP is my DPhil supervisor and also the OUFT Clinical Lead for Dementia and Delirium and Principal Investigator of ORCHARD, so the ward rounds may represent a ‘best-case scenario,’ (e.g., if the medical teams that I observed were unusually skilled at cognitive assessment, although this is made less likely by the frequent turnover/rotation of doctors. Second, I am a medical student with limited knowledge of real-world clinical practice. It was not possible to record full details every clinical encounter, so I could have missed clinically important information, although the consultant reviewed my results to mitigate this concern. Although the scope of this work is limited, it may provide useful context and help with hypothesis-generation.

Appendix 6 Supplementary materials for Chapter 6

Appendix Table 6.1 Characteristics of people with cognitive data vs missing cognitive data

Characteristic	No cognitive data, N = 13,724 ¹	Yes cognitive screen and/or ICD codes, N = 37,478 ¹	p-value ²
Age	80 (7)	83 (7)	<0.001
Female sex*	6,511 (48%)	19,347 (52%)	<0.001
Care home resident	1,545 (11%)	9,396 (25%)	<0.001
CCI	8 (8)	12 (10)	<0.001
HFRS	5 (4)	9 (7)	<0.001
Abnormal NEWS score*	3,621 (26%)	10,951 (29%)	<0.001

¹Mean (SD); n / N (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test

*Missing data: Sex missing for 147 with no cognitive data and 361 with cognitive data.

NEWS score missing for 206 with no cognitive data and 283 with cognitive data

Appendix Table 6.2 Age- and cause-specific prevalence of cognitive frailty

Age group	Delirium	DSD	Dementia	AMTS<8, no known dementia or delirium	Any cognitive frailty
70-74	974/9,675 10.1% [9.48-10.7%]	260/9,675 2.69% [2.38-3.03%]	271/9,675 2.80% [2.49-3.15%]	120/9,675 1.24% [1.03-1.49%]	1,625/9,675 16.8% [16.1-17.6%]
75-79	1,304/10,216 12.8% [12.1-13.4%]	509/10,216 4.98% [4.57-5.43%]	537/10,216 5.26% [4.84-5.71%]	257/10,216 2.52% [2.22-2.84%]	2,607/10,216 25.5% [24.7-26.4%]
80-84	1,574/11,424 13.8% [13.2-14.4%]	1,130/11,424 9.89% [9.35-10.5%]	890/11,424 7.79% [7.31-8.30%]	331/11,424 2.90% [2.60-3.23%]	3,925/11,424 34.4% [33.5-35.2%]
85-89	1,777/10,747 16.5% [15.8-17.3%]	1,472/10,747 13.7% [13.1-14.4%]	1,123/10,747 10.4% [9.88-11.0%]	390/10,747 3.63% [3.29-4.00%]	4,762/10,747 44.3% [43.4-45.3%]
>=90	1,855/9,140 20.3% [19.5-21.1%]	1,434/9,140 15.7% [15.0-16.5%]	1,000/9,140 10.9% [10.3-11.6%]	436/9,140 3.00% [2.85-3.15%]	4,725/9,140 51.7% [50.7-52.7%]

Appendix Table 6.3 Specialty-specific prevalence of cognitive frailty subtypes (specialties with n>50; n=50,950)

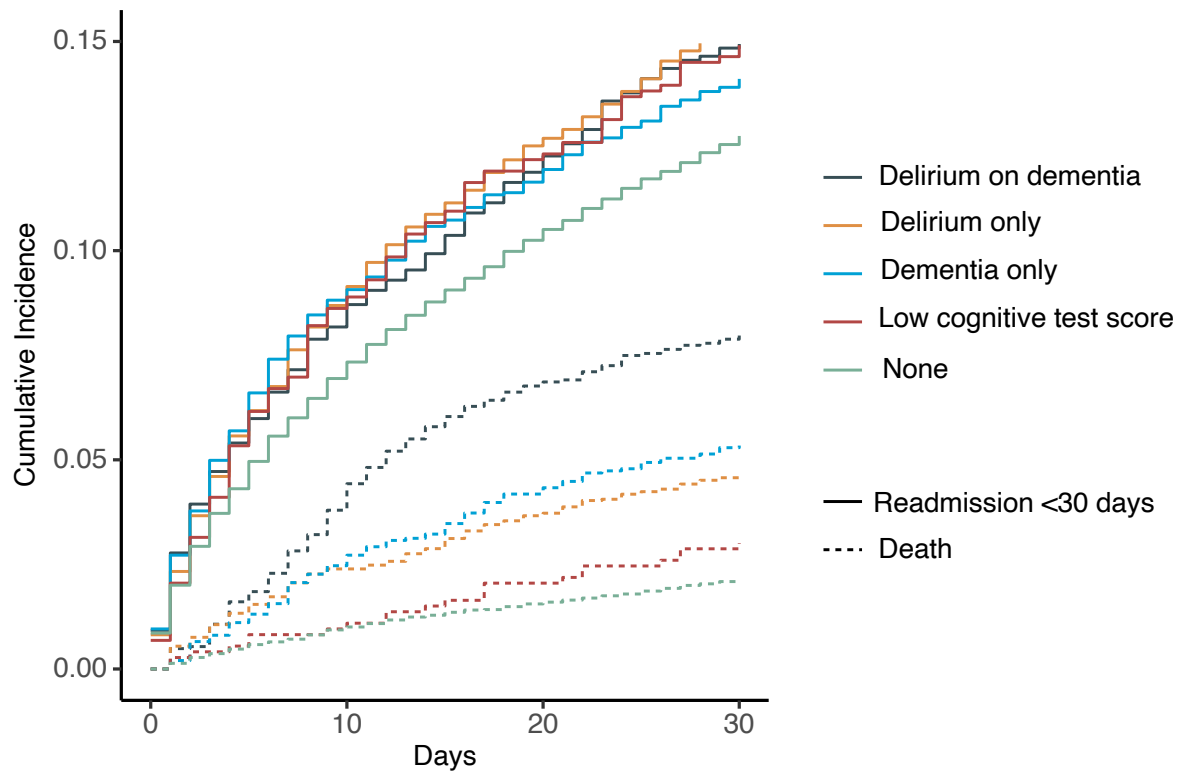
Characteristic	Delirium	Delirium on dementia	Dementia	AMTS<8
100 - General Surgery	308/3,819 8.06% [7.23-8.98%]	118/3,819 3.09% [2.57-3.70%]	241/3,819 6.31% [5.57-7.14%]	134/3,819 3.51% [2.96-4.15%]
101 - Urology	29/856 3.39% [2.32-4.89%]	16/856 1.87% [1.11-3.09%]	53/856 6.19% [4.71-8.08%]	17/856 1.99% [1.20-3.23%]
102 - Transplant Surgery Service	4/185 2.16% [0.69-5.80%]	0/185 0% [0-2.54%]	0/185 0% [0-2.54%]	0/185 0% [0-2.54%]
106 - Upper Gastrointestinal Surgery	3/59 5.08% [1.32-15.1%]	0/59 0% [0-7.62%]	1/59 1.69% [0.09-10.3%]	1/59 1.69% [0.09-10.3%]
107 - Vascular Surgery	51/773 6.60% [5.00-8.64%]	15/773 1.94% [1.13-3.26%]	51/773 6.60% [5.00-8.64%]	19/773 2.46% [1.53-3.88%]
108 - Spinal Surgery Service	17/200 8.50% [5.18-13.5%]	1/200 0.50% [0.03-3.18%]	11/200 5.50% [2.92-9.89%]	1/200 0.50% [0.03-3.18%]
110 - Trauma and Orthopaedics	477/3,673 13.0% [11.9-14.1%]	446/3,673 12.1% [11.1-13.3%]	291/3,673 7.92% [7.08-8.86%]	89/3,673 2.42% [1.96-2.99%]
120 - Ear Nose and Throat	25/685 3.65% [2.42-5.42%]	12/685 1.75% [0.95-3.13%]	45/685 6.57% [4.88-8.76%]	3/685 0.44% [0.11-1.39%]
130 - Ophthalmology	2/117 1.71% [0.30-6.65%]	1/117 0.85% [0.04-5.36%]	13/117 11.1% [6.29-18.6%]	7/117 5.98% [2.65-12.4%]
144 - Maxillo Facial Surgery	4/91 4.40% [1.42-11.5%]	3/91 3.30% [0.86-10.0%]	4/91 4.40% [1.42-11.5%]	2/91 2.20% [0.38-8.47%]
150 - Neurosurgical Service	116/702 16.5% [13.9-19.5%]	10/702 1.42% [0.73-2.69%]	24/702 3.42% [2.25-5.12%]	4/702 0.57% [0.18-1.56%]

160 - Plastic Surgery	9/386 2.33% [1.14-4.54%]	7/386 1.81% [0.80-3.87%]	28/386 7.25% [4.96-10.4%]	2/386 0.52% [0.09-2.07%]
172 - Cardiac Surgery	19/254 7.48% [4.68-11.6%]	3/254 1.18% [0.31-3.70%]	5/254 1.97% [0.73-4.79%]	2/254 0.79% [0.14-3.12%]
173 - Thoracic Surgery	3/86 3.49% [0.91-10.6%]	4/86 4.65% [1.50-12.1%]	5/86 5.81% [2.16-13.7%]	2/86 2.33% [0.40-8.94%]
300 - General Internal Medicine	5,819/33,512 17.4% [17.0-17.8%]	4,037/33,512 12.0% [11.7-12.4%]	2,861/33,512 8.54% [8.24-8.84%]	1,162/33,512 3.47% [3.28-3.67%]
301 - Gastroenterology	16/183 8.74% [5.24-14.1%]	4/183 2.19% [0.70-5.86%]	9/183 4.92% [2.42-9.42%]	2/183 1.09% [0.19-4.31%]
303 - Clinical Haematology	55/708 7.77% [5.95-10.1%]	6/708 0.85% [0.34-1.93%]	13/708 1.84% [1.02-3.20%]	9/708 1.27% [0.62-2.49%]
306 - Hepatology	10/67 14.9% [7.77-26.2%]	0/67 0% [0-6.76%]	2/67 2.99% [0.52-11.3%]	1/67 1.49% [0.08-9.14%]
315 - Palliative Medicine	109/356 30.6% [25.9-35.7%]	5/356 1.40% [0.52-3.44%]	3/356 0.84% [0.22-2.65%]	11/356 3.09% [1.63-5.62%]
320 - Cardiology	66/1,462 4.51% [3.53-5.74%]	15/1,462 1.03% [0.60-1.73%]	53/1,462 3.63% [2.75-4.75%]	11/1,462 0.75% [0.40-1.39%]
328 - Stroke Medicine	72/468 15.4% [12.3-19.0%]	26/468 5.56% [3.73-8.14%]	31/468 6.62% [4.62-9.37%]	6/468 1.28% [0.52-2.91%]
340 - Respiratory Medicine	14/220 6.36% [3.66-10.7%]	3/220 1.36% [0.35-4.26%]	7/220 3.18% [1.40-6.72%]	3/220 1.36% [0.35-4.26%]
350 - Infectious Diseases	15/152 9.87% [5.82-16.0%]	9/152 5.92% [2.92-11.3%]	12/152 7.89% [4.33-13.7%]	5/152 3.29% [1.22-7.91%]

361 - Renal Medicine	32/311 10.3% [7.25-14.3%]	4/311 1.29% [0.41-3.49%]	5/311 1.61% [0.59-3.93%]	4/311 1.29% [0.41-3.49%]
370 - Medical Oncology	81/853 9.50% [7.65-11.7%]	9/853 1.06% [0.52-2.07%]	7/853 0.82% [0.36-1.76%]	15/853 1.76% [1.02-2.95%]
400 - Neurology	8/141 5.67% [2.66-11.2%]	2/141 1.42% [0.25-5.55%]	2/141 1.42% [0.25-5.55%]	2/141 1.42% [0.25-5.55%]
430 - Elderly Medicine Service	65/301 21.6% [17.2-26.8%]	32/301 10.6% [7.49-14.8%]	26/301 8.64% [5.83-12.5%]	10/301 3.32% [1.70-6.22%]
502 - Gynaecology	4/96 4.17% [1.34-10.9%]	4/96 4.17% [1.34-10.9%]	4/96 4.17% [1.34-10.9%]	0/96 0% [0-4.79%]
800 - Clinical Oncology (Radiotherapy)	26/234 11.1% [7.52-16.0%]	1/234 0.43% [0.02-2.73%]	4/234 1.71% [0.55-4.61%]	6/234 2.56% [1.05-5.76%]
n/N and % [95% CI]				

Appendix 7 Supplementary analysis for Chapter 7

Appendix Figure 7.1 Cumulative incidence for 30-day readmissions and death



Appendix Table 7.1 Summary of cohort outcomes by type of cognitive frailty

Characteristic	None, N = 19,453	Delirium only, N = 3,845	Delirium on dementia, N = 2,352	Dementia only, N = 2,156	Low cognitive test score, N = 784	p-value ¹
Death in hospital, n / N (%)	1,074 / 19,453 (5.5%)	558 / 3,845 (15%)	319 / 2,352 (14%)	191 / 2,156 (8.9%)	55 / 784 (7.0%)	<0.001
Death up to 1 year post-discharge, n / N (%)	3,120 / 18,379 (17%)	865 / 3,287 (26%)	682 / 2,033 (34%)	535 / 1,965 (27%)	202 / 729 (28%)	<0.001
LoS >10 days, n / N (%)	3,746 / 19,453 (19%)	1,546 / 3,845 (40%)	941 / 2,352 (40%)	542 / 2,156 (25%)	252 / 784 (32%)	<0.001
LoS, Median (IQR) days	4.0 (6.0)	8.0 (13.0)	8.0 (14.0)	4.0 (8.3)	6.0 (11.0)	<0.001
Discharge other than to home, n / N (%)	2,291 / 17,989 (13%)	1,015 / 3,158 (32%)	728 / 1,977 (37%)	505 / 1,911 (26%)	183 / 710 (26%)	<0.001
DTOC >2 days, n / N (%)	1,476 / 18,379 (8.0%)	819 / 3,287 (25%)	566 / 2,033 (28%)	307 / 1,965 (16%)	151 / 729 (21%)	<0.001
Readmitted <30 days, n / N (%)	2,329 / 17,994 (13%)	505 / 3,192 (16%)	301 / 1,993 (15%)	279 / 1,930 (14%)	109 / 706 (15%)	<0.001

¹Pearson's Chi-squared test; Kruskal-Wallis rank sum test (LoS only)

²Death up to 1 year PD, discharge other than to home, DTOC >2 and readmissions were reported in survivors. Discharge destination was not known for 650 admissions, who were excluded. Readmissions data were not available for patients discharged after December 1, 2019, who were excluded.

Appendix Table 7.2 ORs for in hospital death by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p
Delirium only	2.91 (2.60 to 3.24)	<0.001	2.58 (2.31 to 2.89)	<0.001	2.44 (2.18 to 2.73)	<0.001	2.23 (1.98 to 2.50)	<0.001
Dementia only	1.66 (1.41 to 1.95)	<0.001	1.43 (1.21 to 1.68)	<0.001	1.52 (1.28 to 1.79)	<0.001	1.45 (1.22 to 1.71)	<0.001
Delirium on dementia	2.69 (2.35 to 3.06)	<0.001	2.26 (1.97 to 2.59)	<0.001	2.36 (2.05 to 2.71)	<0.001	2.14 (1.86 to 2.47)	<0.001
Low cognitive test score	1.29 (0.96 to 1.69)	0.075	1.11 (0.83 to 1.46)	0.48	1.04 (0.77 to 1.38)	0.77	1.11 (0.82 to 1.48)	0.48
Age			1.04 (1.03 to 1.05)	<0.001	1.04 (1.03 to 1.04)	<0.001	1.04 (1.03 to 1.04)	<0.001
Sex			1.33 (1.22 to 1.46)	<0.001	1.21 (1.10 to 1.32)	<0.001	1.22 (1.11 to 1.34)	<0.001
mCCI					1.06 (1.05 to 1.06)	<0.001	1.05 (1.05 to 1.06)	<0.001
NEWS category								
Low							—	
Low-Medium							1.90 (1.64 to 2.20)	<0.001
Medium							2.68 (2.36 to 3.05)	<0.001
High							5.94 (5.24 to 6.73)	<0.001
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.3 ORs for death up to 1 year after discharge in those surviving to discharge by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p
Delirium only	1.75 (1.60 to 1.90)	<0.001	1.54 (1.41 to 1.69)	<0.001	1.48 (1.35 to 1.62)	<0.001	1.44 (1.32 to 1.58)	<0.001
Dementia only	1.83 (1.64 to 2.03)	<0.001	1.55 (1.39 to 1.73)	<0.001	1.65 (1.47 to 1.84)	<0.001	1.64 (1.46 to 1.83)	<0.001
Delirium on dementia	2.47 (2.23 to 2.73)	<0.001	2.07 (1.86 to 2.29)	<0.001	2.16 (1.95 to 2.40)	<0.001	2.12 (1.90 to 2.35)	<0.001
Low cognitive test score	1.87 (1.58 to 2.21)	<0.001	1.59 (1.34 to 1.88)	<0.001	1.55 (1.30 to 1.84)	<0.001	1.57 (1.32 to 1.87)	<0.001
Age			1.04 (1.04 to 1.05)	<0.001	1.04 (1.04 to 1.05)	<0.001	1.04 (1.04 to 1.05)	<0.001
Sex			1.46 (1.37 to 1.55)	<0.001	1.35 (1.27 to 1.44)	<0.001	1.36 (1.28 to 1.45)	<0.001
mCCI					1.06 (1.05 to 1.06)	<0.001	1.05 (1.05 to 1.06)	<0.001
NEWS category								
Low							—	
Low-Medium							1.14 (1.02 to 1.27)	0.015
Medium							1.33 (1.20 to 1.47)	<0.001
High							1.73 (1.52 to 1.95)	<0.001
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.4 Time-varying HRs Cox regression models for death over the entire study period by type of cognitive frailty
PH = Cox proportional hazards regression. TV = Time varying Cox regression. $P < 0.001$ unless otherwise specified.

Characteristic	HRs (95% CI) [†]							
	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	PH	TV	PH	TV	PH	TV	PH	TV
Delirium only*	1.78 (1.69 to 1.87)	2.01 (1.88 to 2.14)	1.56 (1.48 to 1.64)	1.76 (1.64 to 1.88)	1.49 (1.42 to 1.57)	1.66 (1.55 to 1.77)	1.42 (1.35 to 1.49)	1.56 (1.46 to 1.67)
Dementia only	1.67 (1.57 to 1.78)	1.67 (1.57 to 1.78)	1.41 (1.32 to 1.50)	1.41 (1.32 to 1.50)	1.45 (1.36 to 1.55)	1.45 (1.36 to 1.54)	1.43 (1.34 to 1.52)	1.43 (1.34 to 1.52)
Delirium on dementia*	2.07 (1.96 to 2.20)	2.38 (2.21 to 2.56)	1.71 (1.61 to 1.81)	1.97 (1.83 to 2.13)	1.72 (1.62 to 1.82)	1.99 (1.84 to 2.15)	1.65 (1.56 to 1.75)	1.89 (1.75 to 2.04)
Low cognitive test score	1.48 (1.33 to 1.64)	1.48 (1.34 to 1.65)	1.24 (1.12 to 1.38)	1.24 (1.12 to 1.38)	1.19 (1.07 to 1.32)	1.20 (1.08 to 1.33)	1.21 (1.09 to 1.34)	1.21 (1.09 to 1.35)
Age			1.04 (1.04 to 1.05)	1.04 (1.04 to 1.05)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)
Sex			1.37 (1.32 to 1.42)	1.37 (1.32 to 1.42)	1.28 (1.23 to 1.33)	1.28 (1.23 to 1.33)	1.28 (1.23 to 1.33)	1.28 (1.23 to 1.33)
mCCI*					1.04 (1.04 to 1.04)	1.05 (1.04 to 1.05)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.05)
NEWS category (ref = low)								
Low-Medium							1.27 (1.20 to 1.35)	1.28 (1.20 to 1.36)
Medium*							1.44 (1.36 to 1.53)	1.67 (1.55 to 1.80)
High*							2.09 (1.96 to 2.23)	2.81 (2.60 to 3.04)

[†] HR = Hazard Ratio, CI = Confidence Interval
* $p \leq 0.001$ for time interaction with variable in all models where included

Appendix Table 7.5 Landmark HRs Cox regression models for death by type of cognitive frailty

M1 = unadjusted. M2 = age- and sex-adjusted. M3 = M2 and comorbidity adjusted. M4 = M3 and NEWS. $P < 0.001$ unless specified.

	Landmark ≤ 90 days HRs (95% CI) ¹				Landmark > 90 days HRs (95% CI) ¹			
	M1	M2 (+age, sex)	M3 (+CCI)	M4 (+NEWS)	M1	M2 (+age, sex)	M3 (+CCI)	M4 (+NEWS)
Delirium only	2.19 (2.03 to 2.36)	1.92 (1.78 to 2.07)	1.81 (1.67 to 1.95)	NA	1.52 (1.42 to 1.63)	1.32 (1.23 to 1.41)	1.28 (1.19 to 1.37)	1.25 (1.17 to 1.34)
Dementia only	1.67 (1.50 to 1.85)	1.41 (1.27 to 1.56)	1.47 (1.33 to 1.64)	NA	1.68 (1.55 to 1.82)	1.40 (1.29 to 1.52)	1.43 (1.32 to 1.55)	1.42 (1.31 to 1.54)
Delirium on dementia	2.54 (2.33 to 2.76)	2.10 (1.92 to 2.29)	2.13 (1.95 to 2.33)	NA	1.78 (1.64 to 1.92)	1.45 (1.34 to 1.58)	1.45 (1.34 to 1.57)	1.43 (1.32 to 1.55)
Low cognitive test score	1.28 (1.07 to 1.54) ²	1.11 (0.93 to 1.33) ³	1.06 (0.88 to 1.27) ⁴	NA	1.61 (1.42 to 1.83)	1.33 (1.16 to 1.51)	1.28 (1.12 to 1.46)	1.29 (1.13 to 1.47)
Age		1.04 (1.04 to 1.04)	1.04 (1.03 to 1.04)	NA		1.05 (1.04 to 1.05)	1.04 (1.04 to 1.05)	1.04 (1.04 to 1.05)
Sex		1.32 (1.25 to 1.40)	1.21 (1.14 to 1.29)	NA		1.40 (1.33 to 1.46)	1.32 (1.26 to 1.39)	1.32 (1.26 to 1.39)
mCCI			1.05 (1.05 to 1.05)	NA			1.04 (1.03 to 1.04)	1.04 (1.03 to 1.04)
NEWS category (ref = low)								
Low-Medium				NA				1.15 (1.06 to 1.24) ⁵
Medium				NA				1.19 (1.10 to 1.29)
High				NA				1.34 (1.22 to 1.48)

¹ HR = Hazard Ratio, CI = Confidence Interval
² $p = 0.007$
³ $p = 0.27$
⁴ $p = 0.53$
⁵ $p = 0.001$

Appendix Table 7.6 ORs for Length of Stay >10 days by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p
Delirium only	2.82 (2.62 to 3.03)	<0.001	2.66 (2.47 to 2.87)	<0.001	2.59 (2.40 to 2.80)	<0.001	2.62 (2.43 to 2.82)	<0.001
Dementia only	1.41 (1.27 to 1.56)	<0.001	1.30 (1.17 to 1.45)	<0.001	1.33 (1.20 to 1.48)	<0.001	1.34 (1.20 to 1.49)	<0.001
Delirium on dementia	2.80 (2.56 to 3.06)	<0.001	2.56 (2.34 to 2.81)	<0.001	2.61 (2.38 to 2.86)	<0.001	2.64 (2.40 to 2.89)	<0.001
Low cognitive test score	1.99 (1.70 to 2.31)	<0.001	1.84 (1.57 to 2.15)	<0.001	1.81 (1.55 to 2.11)	<0.001	1.80 (1.54 to 2.10)	<0.001
Age			1.02 (1.01 to 1.02)	<0.001	1.01 (1.01 to 1.02)	<0.001	1.01 (1.01 to 1.02)	<0.001
Sex			0.93 (0.88 to 0.98)	0.01	0.89 (0.84 to 0.94)	<0.001	0.89 (0.84 to 0.94)	<0.001
mCCI					1.03 (1.02 to 1.03)	<0.001	1.03 (1.02 to 1.03)	<0.001
NEWS category								
Low							—	
Low-Medium							1.0 (0.90 to 1.09)	0.92
Medium							0.94 (0.85 to 1.03)	0.16
High							0.80 (0.71 to 0.89)	<0.001
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.7 RR for Length of Stay (count) by type of cognitive frailty using Negative Binomial regression

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	RR (95% CI) ¹	p	RR (95% CI) ¹	p	RR (95% CI) ¹	p	RR (95% CI) ¹	p
Delirium only	1.82 (1.76 to 1.89)	<0.001	1.79 (1.73 to 1.86)	<0.001	1.77 (1.71 to 1.84)	<0.001	1.77 (1.71 to 1.83)	<0.001
Dementia only	1.30 (1.24 to 1.36)	<0.001	1.27 (1.21 to 1.33)	<0.001	1.29 (1.23 to 1.35)	<0.001	1.29 (1.23 to 1.35)	<0.001
Delirium on dementia	1.91 (1.83 to 1.99)	<0.001	1.86 (1.78 to 1.94)	<0.001	1.88 (1.80 to 1.97)	<0.001	1.88 (1.80 to 1.97)	<0.001
Low cognitive test score	1.60 (1.49 to 1.72)	<0.001	1.56 (1.45 to 1.68)	<0.001	1.55 (1.45 to 1.67)	<0.001	1.55 (1.44 to 1.67)	<0.001
Age			1.01 (1.00 to 1.01)	<0.001	1.00 (1.00 to 1.01)	<0.001	1.00 (1.00 to 1.01)	<0.001
Sex			0.96 (0.94 to 0.99)	0.003	0.94 (0.91 to 0.96)	<0.001	0.94 (0.91 to 0.96)	<0.001
mCCI					1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001
NEWS category								
Low							—	
Low-Medium							1.03 (0.98 to 1.07)	0.25
Medium							1.01 (0.97 to 1.06)	0.53
High							0.97 (0.92 to 1.01)	0.16
¹ RR = Risk Ratio, CI = Confidence Interval								

Appendix Table 7.8 ORs for DTOC>2 days by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p	OR (95% CI) ¹	p
Delirium only	3.67 (3.33 to 4.05)	<0.001	3.12 (2.83 to 3.45)	<0.001	3.07 (2.78 to 3.39)	<0.001	3.06 (2.77 to 3.38)	<0.001
Dementia only	2.12 (1.85 to 2.42)	<0.001	1.69 (1.48 to 1.94)	<0.001	1.72 (1.50 to 1.97)	<0.001	1.72 (1.50 to 1.97)	<0.001
Delirium on dementia	4.13 (3.69 to 4.62)	<0.001	3.25 (2.89 to 3.65)	<0.001	3.27 (2.91 to 3.68)	<0.001	3.27 (2.91 to 3.67)	<0.001
Low cognitive test score	2.96 (2.44 to 3.56)	<0.001	2.38 (1.95 to 2.87)	<0.001	2.35 (1.93 to 2.84)	<0.001	2.35 (1.93 to 2.84)	<0.001
Age			1.05 (1.04 to 1.05)	<0.001	1.05 (1.04 to 1.05)	<0.001	1.05 (1.04 to 1.05)	<0.001
Sex			0.82 (0.76 to 0.88)	<0.001	0.79 (0.73 to 0.86)	<0.001	0.80 (0.74 to 0.86)	<0.001
mCCI					1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001
NEWS category								
Low							—	
Low-Medium							1.13 (1.00 to 1.29)	0.055
Medium							1.03 (0.91 to 1.17)	0.62
High							0.96 (0.81 to 1.13)	0.62
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.9 ORs for DTOC>2 days by type of cognitive frailty, care home residents

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p
Delirium only	2.03 (1.62 to 2.55)	<0.001	2.05 (1.63 to 2.57)	<0.001	2.05 (1.63 to 2.58)	<0.001	2.08 (1.65 to 2.61)	<0.001
Dementia only	1.02 (0.79 to 1.32)	0.85	1.03 (0.80 to 1.32)	0.83	1.08 (0.83 to 1.39)	0.56	1.09 (0.84 to 1.40)	0.52
Delirium on dementia	1.64 (1.32 to 2.02)	<0.001	1.64 (1.33 to 2.03)	<0.001	1.69 (1.37 to 2.09)	<0.001	1.72 (1.39 to 2.13)	<0.001
Low cognitive test score	1.78 (1.17 to 2.66)	0.006	1.80 (1.18 to 2.69)	0.005	1.85 (1.21 to 2.76)	0.003	1.82 (1.20 to 2.73)	0.004
Age			1.00 (0.98 to 1.01)	0.55	1.00 (0.98 to 1.01)	0.54	1.00 (0.99 to 1.01)	0.63
Sex			1.07 (0.91 to 1.27)	0.41	1.05 (0.89 to 1.24)	0.55	1.05 (0.88 to 1.24)	0.6
mCCI					1.02 (1.01 to 1.03)	<0.001	1.02 (1.01 to 1.03)	<0.001
NEWS category								
Low							—	
Low-Medium							0.98 (0.74 to 1.28)	0.86
Medium							0.93 (0.70 to 1.21)	0.58
High							0.42 (0.26 to 0.65)	<0.001
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.10 ORs for DTOC>2 days by type of cognitive frailty, non-care home residents

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p
Delirium only	3.81 (3.42 to 4.24)	<0.001	3.18 (2.85 to 3.55)	<0.001	3.12 (2.79 to 3.49)	<0.001	3.09 (2.76 to 3.45)	<0.001
Dementia only	2.17 (1.84 to 2.54)	<0.001	1.65 (1.39 to 1.95)	<0.001	1.66 (1.40 to 1.96)	<0.001	1.66 (1.40 to 1.95)	<0.001
Delirium on dementia	4.64 (4.03 to 5.33)	<0.001	3.46 (3.00 to 4.00)	<0.001	3.49 (3.01 to 4.02)	<0.001	3.45 (2.99 to 3.99)	<0.001
Low cognitive test score	2.98 (2.39 to 3.68)	<0.001	2.31 (1.85 to 2.86)	<0.001	2.27 (1.82 to 2.82)	<0.001	2.28 (1.82 to 2.82)	<0.001
Age			1.06 (1.05 to 1.06)	<0.001	1.06 (1.05 to 1.06)	<0.001	1.06 (1.05 to 1.06)	<0.001
Sex			0.76 (0.70 to 0.83)	<0.001	0.74 (0.67 to 0.81)	<0.001	0.74 (0.67 to 0.81)	<0.001
mCCI					1.02 (1.01 to 1.02)	<0.001	1.02 (1.01 to 1.02)	<0.001
NEWS category								
Low							—	
Low-Medium							1.19 (1.03 to 1.37)	0.02
Medium							1.06 (0.91 to 1.23)	0.42
High							1.18 (0.98 to 1.42)	0.08
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.11 ORs for discharge destination other than home by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p
Delirium only	3.25 (2.98 to 3.54)	<0.001	2.76 (2.52 to 3.01)	<0.001	2.73 (2.50 to 2.99)	<0.001	2.74 (2.50 to 2.99)	<0.001
Dementia only	2.46 (2.20 to 2.75)	<0.001	1.97 (1.76 to 2.20)	<0.001	1.98 (1.77 to 2.22)	<0.001	1.99 (1.77 to 2.22)	<0.001
Delirium on dementia	3.99 (3.61 to 4.42)	<0.001	3.13 (2.82 to 3.48)	<0.001	3.14 (2.83 to 3.49)	<0.001	3.15 (2.84 to 3.50)	<0.001
Low cognitive test score	2.38 (2.00 to 2.83)	<0.001	1.90 (1.59 to 2.26)	<0.001	1.89 (1.58 to 2.25)	<0.001	1.88 (1.57 to 2.24)	<0.001
Age			1.05 (1.04 to 1.05)	<0.001	1.05 (1.04 to 1.05)	<0.001	1.05 (1.04 to 1.05)	<0.001
Sex			0.82 (0.76 to 0.87)	<0.001	0.81 (0.75 to 0.86)	<0.001	0.81 (0.75 to 0.86)	<0.001
mCCI					1.01 (1.00 to 1.01)	<0.001	1.01 (1.01 to 1.01)	<0.001
NEWS category								
Low							—	
Low-Medium							1.13 (1.01 to 1.26)	0.031
Medium							0.93 (0.83 to 1.04)	0.23
High							0.86 (0.73 to 0.99)	0.045
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.12 ORs for 30-day readmission by type of cognitive frailty

Characteristic	M1 (unadjusted)		M2 (age + sex)		M3 (+ comorbidity)		M4 (+ NEWS)	
	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p	OR (95% CI) [†]	p
Delirium only	1.26 (1.14 to 1.40)	<0.001	1.24 (1.11 to 1.38)	<0.001	1.21 (1.09 to 1.34)	<0.001	1.19 (1.07 to 1.33)	0.001
Dementia only	1.14 (0.99 to 1.30)	0.061	1.10 (0.96 to 1.26)	0.15	1.13 (0.98 to 1.29)	0.091	1.10 (0.96 to 1.26)	0.16
Delirium on dementia	1.20 (1.05 to 1.36)	0.007	1.16 (1.02 to 1.32)	0.027	1.17 (1.02 to 1.34)	0.021	1.15 (1.00 to 1.31)	0.043
Low cognitive test score	1.23 (0.99 to 1.51)	0.054	1.19 (0.96 to 1.47)	0.1	1.17 (0.94 to 1.44)	0.14	1.18 (0.95 to 1.45)	0.13
Age			1.01 (1.00 to 1.01)	<0.001	1.01 (1.00 to 1.01)	0.003	1.01 (1.00 to 1.01)	0.003
Sex			1.20 (1.12 to 1.29)	<0.001	1.16 (1.08 to 1.25)	<0.001	1.16 (1.08 to 1.25)	<0.001
mCCI					1.02 (1.02 to 1.03)	<0.001	1.02 (1.02 to 1.03)	<0.001
NEWS category								
Low							—	
Low-Medium							1.08 (0.95 to 1.22)	0.24
Medium							1.24 (1.10 to 1.40)	<0.001
High							1.28 (1.10 to 1.49)	0.001
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 7.13 Cause-specific and subdistribution HRs for readmissions (continued on next page)

Characteristic	M1 (unadjusted)				M2 (age + sex)			
	Cause-specific		Subdistribution		Cause-specific		Subdistribution	
	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value
Delirium only	1.26 (1.14 to 1.38)	<0.001	1.24 (1.13 to 1.36)	<0.001	1.23 (1.11 to 1.35)	<0.001	1.21 (1.10 to 1.33)	<0.001
Dementia only	1.14 (1.01 to 1.29)	0.037	1.12 (0.99 to 1.27)	0.069	1.10 (0.97 to 1.25)	0.12	1.09 (0.96 to 1.24)	0.18
Delirium on dementia	1.22 (1.09 to 1.38)	<0.001	1.19 (1.05 to 1.34)	0.005	1.18 (1.05 to 1.34)	0.007	1.15 (1.02 to 1.30)	0.022
Low cognitive test score	1.19 (0.98 to 1.44)	0.077	1.18 (0.98 to 1.43)	0.082	1.15 (0.95 to 1.39)	0.16	1.15 (0.95 to 1.40)	0.16
Age					1.01 (1.01 to 1.01)	<0.001	1.01 (1.00 to 1.01)	<0.001
Sex					1.20 (1.13 to 1.29)	<0.001	1.20 (1.12 to 1.28)	<0.001
mCCI								
NEWS category								
Low								
Low-Medium								
Medium								
High								

[†] HR = Hazard Ratio, CI = Confidence Interval

Cause-specific and subdistribution HRs for readmissions (continued from previous page)

Characteristic	M3 (+ comorbidity)				M4 (+ NEWS)			
	Cause-specific		Subdistribution		Cause-specific		Subdistribution	
	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value
Delirium only	1.20 (1.09 to 1.32)	<0.001	1.18 (1.07 to 1.30)	<0.001	1.18 (1.07 to 1.30)	<0.001	1.17 (1.06 to 1.29)	0.002
Dementia only	1.12 (0.99 to 1.27)	0.074	1.11 (0.98 to 1.26)	0.11	1.10 (0.97 to 1.25)	0.13	1.09 (0.96 to 1.24)	0.2
Delirium on dementia	1.19 (1.05 to 1.34)	0.006	1.16 (1.03 to 1.30)	0.018	1.17 (1.03 to 1.32)	0.013	1.14 (1.01 to 1.28)	0.036
Low cognitive test score	1.13 (0.93 to 1.37)	0.22	1.13 (0.93 to 1.37)	0.22	1.13 (0.93 to 1.38)	0.2	1.13 (0.93 to 1.38)	0.2
Age	1.01 (1.00 to 1.01)	<0.001	1.01 (1.00 to 1.01)	0.001	1.01 (1.00 to 1.01)	<0.001	1.01 (1.00 to 1.01)	0.001
Sex	1.16 (1.09 to 1.25)	<0.001	1.16 (1.08 to 1.24)	<0.001	1.16 (1.09 to 1.24)	<0.001	1.15 (1.08 to 1.23)	<0.001
mCCI	1.02 (1.02 to 1.03)	<0.001	1.02 (1.02 to 1.02)	<0.001	1.02 (1.02 to 1.02)	<0.001	1.02 (1.02 to 1.02)	<0.001
NEWS category								
Low					—		—	
Low-Medium					1.07 (0.95 to 1.20)	0.27	1.06 (0.95 to 1.20)	0.29
Medium					1.22 (1.10 to 1.36)	<0.001	1.21 (1.08 to 1.34)	<0.001
High					1.28 (1.12 to 1.46)	<0.001	1.24 (1.09 to 1.42)	0.002

[†] HR = Hazard Ratio, CI = Confidence Interval

Appendix Table 7.14 Cause-specific HRs for readmissions, adjusted and full models (age, sex, CCI and NEWS-adjusted) stratified by care home residence prior to admission

Characteristic	Non-care home residents				Care home residents			
	Non-adjusted		Full model (M4)		Non-adjusted		Full model (M4)	
	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value	HR (95% CI) [†]	p-value
Delirium only	1.26 (1.14 to 1.40)	<0.001	1.18 (1.06 to 1.32)	0.002	1.00 (0.79 to 1.27)	0.99	1.01 (0.80 to 1.28)	0.94
Dementia only	1.15 (1.0 to 1.34)	0.059	1.11 (0.95 to 1.28)	0.19	0.86 (0.67 to 1.10)	0.22	0.86 (0.67 to 1.11)	0.25
Delirium on dementia	1.32 (1.14 to 1.53)	<0.001	1.25 (1.08 to 1.45)	0.004	0.81 (0.65 to 1.02)	0.076	0.83 (0.66 to 1.04)	0.1
Low cognitive test score	1.22 (0.99 to 1.51)	0.065	1.15 (0.93 to 1.42)	0.2	0.87 (0.55 to 1.37)	0.54	0.91 (0.58 to 1.44)	0.7
Age			1.01 (1.00 to 1.01)	<0.001			0.99 (0.98 to 1.01)	0.34
Sex			1.16 (1.08 to 1.25)	<0.001			1.17 (0.99 to 1.39)	0.071
mCCI			1.02 (1.02 to 1.03)	<0.001			1.01 (1.00 to 1.02)	0.094
NEWS category								
Low			—				—	
Low-Medium			1.08 (0.95 to 1.22)	0.24			1.00 (0.75 to 1.34)	>0.99
Medium			1.20 (1.07 to 1.35)	0.002			1.30 (1.00 to 1.69)	0.049
High			1.23 (1.06 to 1.43)	0.006			1.54 (1.11 to 2.13)	0.01

[†] HR = Hazard Ratio, CI = Confidence Interval

Appendix Table 7.15 Sensitivity analysis: ORs and RRs for any cognitive frailty versus none for main outcomes, model 2 (age, sex, mCCI- and NEWS-adjusted)

RRs were calculated using Poisson regression models without robust variance due to large sample size (i.e., bias likely to be <2% of values shown based on Zou et al., 2003 – see citation below). Binomial regression with a log-link was not used due to non-convergence.

Any cognitive frailty				
Outcome and strata	OR (95% CI) ¹	p-value	RR (95% CI) ²	p-value
In hospital death	1.90 (1.73 to 2.09)	<0.001	1.72 (1.58 to 1.88)	<0.001
Death up to 1 year	1.62 (1.52 to 1.74)	<0.001	1.43 (1.35 to 1.51)	<0.001
LoS >10 days	2.25 (2.12 to 2.38)	<0.001	1.79 (1.70 to 1.88)	<0.001
DTOC >2 days	2.71 (2.51 to 2.94)	<0.001	2.33 (2.17 to 2.51)	<0.001
Discharge destination	2.55 (2.38 to 2.73)	<0.001	2.06 (1.94 to 2.18)	<0.001
Readmission within 30 days	1.16 (1.07 to 1.26)	<0.001	1.13 (1.05 to 1.22)	<0.001
¹ OR = Odds Ratio, CI = Confidence Interval ² RR = Risk Ratio, CI = Confidence Interval; See Zou, G., 2004. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. American Journal of Epidemiology 159, 702–706 for more detail on Poisson versus Modified Poisson regression approaches.				

Appendix Table 7.16 Sensitivity analysis: Cohort characteristics using certain delirium as the case definition

Characteristic	Overall, N = 28,590	Delirium on dementia, N = 1,439	Delirium only, N = 2,290	Dementia only, N = 3,069	Low AMTS, N = 1,309	None, N = 20,483	p-value ¹
Age, Mean (SD)	81.8 (7.4)	85.7 (6.5)	84.6 (7.4)	85.4 (6.6)	84.8 (7.2)	80.5 (7.1)	<0.001
Sex, n (%)							<0.001
Female	14,813 (52%)	817 (57%)	1,257 (55%)	1,776 (58%)	759 (58%)	10,204 (50%)	
Male	13,777 (48%)	622 (43%)	1,033 (45%)	1,293 (42%)	550 (42%)	10,279 (50%)	
NEWS category, n (%)							<0.001
Low	21,396 (75%)	1,004 (70%)	1,530 (67%)	2,174 (71%)	972 (74%)	15,716 (77%)	
Low-Medium	2,548 (8.9%)	160 (11%)	284 (12%)	297 (9.7%)	138 (11%)	1,669 (8.1%)	
Medium	2,789 (9.8%)	161 (11%)	286 (12%)	315 (10%)	131 (10%)	1,896 (9.3%)	
High	1,857 (6.5%)	114 (7.9%)	190 (8.3%)	283 (9.2%)	68 (5.2%)	1,202 (5.9%)	
CCI, Mean (SD)	8.9 (9.2)	19.4 (9.0)	8.4 (8.8)	18.5 (9.0)	8.0 (8.7)	6.8 (7.9)	<0.001
HFRS category, n (%)							<0.001
Low risk	13,098 (46%)	56 (3.9%)	217 (9.5%)	489 (16%)	420 (32%)	11,916 (58%)	
Moderate risk	12,134 (42%)	570 (40%)	1,349 (59%)	1,732 (56%)	750 (57%)	7,733 (38%)	
High risk	3,358 (12%)	813 (56%)	724 (32%)	848 (28%)	139 (11%)	834 (4.1%)	High risk
Care home resident, n (%)	3,594 (13%)	497 (35%)	371 (16%)	986 (32%)	234 (18%)	1,506 (7.4%)	<0.001
mCCI, Mean (SD)	7.0 (8.0)	6.9 (7.9)	8.4 (8.8)	6.2 (7.7)	8.0 (8.7)	6.8 (7.9)	<0.001

¹Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Appendix Table 7.17 Sensitivity analysis: ORs using certain delirium as the case definition for main outcomes, most adjusted model (age, sex, CCI and NEWS-adjusted; continued on next page)

Characteristic	None	Delirium only			Delirium on dementia		
	n/N (%)	n/N (%)	OR (95% CI) ¹	p	n/N (%)	OR (95% CI) ¹	p
Death in hospital	1,249 / 20,483 (6.1%)	331 / 2,290 (14%)	1.98 (1.72 to 2.27)	<0.001	180 / 1,439 (13%)	1.80 (1.50 to 2.14)	<0.001
Death up to 1 year post-discharge	3,339 / 19,234 (17%)	516 / 1,959 (26%)	1.38 (1.23 to 1.54)	<0.001	409 / 1,259 (32%)	1.94 (1.71 to 2.21)	<0.001
LoS >10 days	4,136 / 20,483 (20%)	963 / 2,290 (42%)	2.61 (2.38 to 2.86)	<0.001	659 / 1,439 (46%)	3.12 (2.79 to 3.48)	<0.001
DTOC >2 days	1,661 / 20,483 (8.1%)	538 / 2,290 (23%)	3.18 (2.83 to 3.57)	<0.001	405 / 1,439 (28%)	3.70 (3.23 to 4.23)	<0.001
Discharge other than to home	2,541 / 18,812 (14%)	634 / 1,880 (34%)	2.65 (2.38 to 2.95)	<0.001	493 / 1,227 (40%)	3.42 (3.01 to 3.87)	<0.001
Readmitted <30 days	2,281 / 17,751 (13%)	497 / 3,148 (16%)	1.30 (1.14 to 1.48)	<0.001	294 / 1,970 (15%)	1.16 (0.98 to 1.37)	0.11

¹ OR = Odds Ratio, CI = Confidence Interval

Continued from previous page

Characteristic	Dementia only			Low cognitive test score		
	n/N (%)	OR (95% CI) [†]	<i>p</i>	n/N (%)	OR (95% CI) [†]	<i>p</i>
Death in hospital	330 / 3,069 (11%)	1.56 (1.36 to 1.79)	<0.001	107 / 1,309 (8.2%)	1.04 (1.03 to 1.04)	<0.001
Death up to 1 year post-discharge	808 / 2,739 (29%)	1.78 (1.61 to 1.95)	<0.001	332 / 1,202 (28%)	1.51 (1.32 to 1.73)	<0.001
LoS >10 days	824 / 3,069 (27%)	1.37 (1.25 to 1.50)	<0.001	445 / 1,309 (34%)	1.84 (1.63 to 2.08)	<0.001
DTOC >2 days	468 / 3,069 (15%)	1.73 (1.54 to 1.94)	<0.001	247 / 1,309 (19%)	2.11 (1.80 to 2.45)	<0.001
Discharge other than to home	740 / 2,661 (28%)	1.97 (1.78 to 2.17)	<0.001	314 / 1,165 (27%)	1.89 (1.64 to 2.16)	<0.001
Readmitted <30 days	274 / 1,913 (14%)	1.10 (0.98 to 1.24)	0.075	106 / 701 (15%)	1.05 (0.88 to 1.24)	0.58

Appendix Table 7.18 Sensitivity analysis: ORs using the original CCI including coded dementia for main outcomes, adjusted model (M3: age, sex, CCI-adjusted)

Variables	Death in hospital		Death discharge to 1 year		LOS >10 days		DTC >2 days		Discharge to place other than home		30-day readmission	
	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value
Delirium only	2.44 (2.18 to 2.73)	<0.001	1.48 (1.35 to 1.62)	<0.001	2.59 (2.41 to 2.80)	<0.001	3.07 (2.78 to 3.39)	<0.001	2.73 (2.50 to 2.98)	<0.001	1.21 (1.09 to 1.35)	<0.001
Dementia only	0.75 (0.63 to 0.90)	0.002	0.87 (0.77 to 0.98)	0.019	0.96 (0.86 to 1.08)	0.51	1.36 (1.18 to 1.58)	<0.001	1.75 (1.55 to 1.98)	<0.001	0.86 (0.74 to 1.00)	0.045
Delirium on dementia	1.15 (0.99 to 1.33)	0.066	1.11 (1.0 to 1.25)	0.061	1.87 (1.69 to 2.06)	<0.001	2.57 (2.26 to 2.92)	<0.001	2.76 (2.46 to 3.09)	<0.001	0.89 (0.77 to 1.02)	0.1
Low cognitive test score	1.04 (0.78 to 1.38)	0.76	1.55 (1.30 to 1.84)	<0.001	1.81 (1.55 to 2.11)	<0.001	2.35 (1.93 to 2.84)	<0.001	1.89 (1.58 to 2.25)	<0.001	1.17 (0.95 to 1.44)	0.14
Age	1.04 (1.03 to 1.04)	<0.001	1.04 (1.04 to 1.05)	<0.001	1.01 (1.01 to 1.02)	<0.001	1.05 (1.04 to 1.05)	<0.001	1.05 (1.04 to 1.05)	<0.001	1.01 (1.00 to 1.01)	0.003
Sex	1.21 (1.10 to 1.32)	<0.001	1.36 (1.27 to 1.45)	<0.001	0.89 (0.84 to 0.94)	<0.001	0.79 (0.73 to 0.86)	<0.001	0.80 (0.75 to 0.86)	<0.001	1.17 (1.08 to 1.25)	<0.001
CCI	1.06 (1.05 to 1.06)	<0.00	1.05 (1.05 to 1.06)	<0.001	1.03 (1.02 to 1.03)	<0.001	1.02 (1.01 to 1.02)	<0.001	1.01 (1.01 to 1.01)	<0.001	1.02 (1.02 to 1.03)	<0.001

¹ OR = Odds Ratio, CI = Confidence Interval

Appendix Table 7.19 Sensitivity analysis: ORs for main outcomes stratified by specialty groups, most adjusted model (age, sex, CCI and NEWS-adjusted) in *general medicine*

Variables	None	Delirium alone		Dementia alone			Delirium superimposed on dementia			Low AMTS			
	n/N	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
Death in hospital	697/10601	400/2868	1.93 (1.68 to 2.22)	<0.001	148/1570	1.36 (1.12 to 1.65)	0.002	270/1885	2.10 (1.79 to 2.47)	<0.001	42/554	1.09 (0.77 to 1.51)	0.62
Death discharge to 1 year	1905/9904	675/2468	1.38 (1.24 to 1.54)	<0.001	419/1422	1.60 (1.40 to 1.82)	<0.001	548/1615	1.95 (1.73 to 2.19)	<0.001	150/512	1.49 (1.22 to 1.83)	<0.001
LOS >10 days	1787/10601	994/2868	2.47 (2.25 to 2.71)	<0.001	369/1570	1.47 (1.29 to 1.67)	<0.001	688/1885	2.75 (2.46 to 3.07)	<0.001	165/554	1.91 (1.58 to 2.31)	<0.001
DTOC >2 days	860/9904	552/2468	2.76 (2.45 to 3.11)	<0.001	216/1422	1.70 (1.44 to 2.00)	<0.001	383/1615	2.95 (2.57 to 3.38)	<0.001	100/512	2.22 (1.75 to 2.79)	<0.001
Discharge to place other than home	1306/9763	709/2413	2.41 (2.17 to 2.69)	<0.001	355/1395	1.89 (1.65 to 2.17)	<0.001	563/1585	3.08 (2.73 to 3.47)	<0.001	121/501	1.73 (1.39 to 2.14)	<0.001
30-day readmission	1407/9642	409/2392	1.17 (1.03 to 1.32)	0.012	221/1392	1.09 (0.93 to 1.27)	0.3	252/1584	1.09 (0.94 to 1.27)	0.24	87/493	1.22 (0.95 to 1.54)	0.11
¹ OR = Odds Ratio, CI = Confidence Interval													

Appendix Table 7.20 Sensitivity analysis: ORs for main outcomes stratified by specialty groups, most adjusted model (age, sex, CCI and NEWS-adjusted) in *general surgery*

Variables	None	Delirium alone			Dementia alone			Delirium superimposed on dementia			Low AMTS		
	n/N	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
Death in hospital	160/2304	34/170	3.50 (2.17 to 5.54)	<0.001	17/133	2.42 (1.31 to 4.26)	0.003	12/57	3.54 (1.58 to 7.41)	0.001	7/81	1.03 (0.39 to 2.33)	0.95
Death discharge to 1 year	297/2144	28/136	1.53 (0.95 to 2.41)	0.073	23/116	1.48 (0.88 to 2.41)	0.13	15/45	3.15 (1.55 to 6.13)	0.001	15/74	1.32 (0.69 to 2.38)	0.38
LOS >10 days	457/2304	76/170	3.55 (2.54 to 4.94)	<0.001	26/133	1.09 (0.68 to 1.68)	0.72	19/57	2.12 (1.17 to 3.74)	0.011	14/81	0.89 (0.47 to 1.57)	0.69
DTOC >2 days	100/2144	24/136	5.81 (3.32 to 9.94)	<0.001	10/116	2.43 (1.11 to 4.85)	0.017	9/45	5.82 (2.37 to 13.0)	<0.001	8/74	2.83 (1.17 to 6.09)	0.012
Discharge to place other than home	135/2114	22/129	3.60 (2.09 to 5.99)	<0.001	16/113	2.81 (1.51 to 4.95)	<0.001	9/42	4.58 (1.94 to 9.84)	<0.001	9/74	2.14 (0.95 to 4.33)	0.047
30-day readmission	270/2087	26/136	1.54 (0.96 to 2.41)	0.053	17/113	1.19 (0.67 to 1.99)	0.54	4/41	0.73 (0.22 to 1.87)	0.56	8/73	0.77 (0.34 to 1.56)	0.51
¹ OR = Odds Ratio, CI = Confidence Interval													

Appendix Table 7.21 Sensitivity analysis: ORs for main outcomes stratified by specialty groups, most adjusted model (age, sex, CCI and NEWS-adjusted) in *trauma and orthopaedics*

Variables	None	Delirium alone		Dementia alone			Delirium superimposed on dementia			Low AMTS			
	n/N	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
Death in hospital	26/1737	22/330	3.07 (1.64 to 5.69)	<0.001	4/180	1.34 (0.37 to 3.66)	0.61	22/299	3.55 (1.88 to 6.65)	<0.001	2/68	1.60 (0.25 to 5.70)	0.53
Death discharge to 1 year	127/1711	53/308	1.57 (1.06 to 2.28)	0.02	28/176	2.12 (1.31 to 3.34)	0.002	89/277	4.06 (2.89 to 5.69)	<0.001	16/66	2.97 (1.54 to 5.45)	<0.001
LOS >10 days	647/1737	230/330	2.96 (2.28 to 3.87)	<0.001	91/180	1.43 (1.04 to 1.96)	0.028	177/299	1.81 (1.39 to 2.35)	<0.001	43/68	2.40 (1.45 to 4.05)	<0.001
DTOC >2 days	357/1711	147/308	2.35 (1.79 to 3.07)	<0.001	54/176	1.17 (0.82 to 1.66)	0.38	108/277	1.52 (1.14 to 2.01)	0.004	26/66	1.75 (1.02 to 2.95)	0.039
Discharge to place other than home	447/1620	153/278	2.27 (1.73 to 2.99)	<0.001	83/167	1.96 (1.40 to 2.74)	<0.001	121/259	1.47 (1.11 to 1.96)	0.007	36/63	2.66 (1.57 to 4.55)	<0.001
30-day readmission	137/1679	30/294	1.16 (0.74 to 1.77)	0.5	14/169	1.08 (0.58 to 1.88)	0.79	31/270	1.37 (0.87 to 2.09)	0.16	5/61	0.95 (0.33 to 2.22)	0.92
¹ OR = Odds Ratio, CI = Confidence Interval													

Appendix Table 7.22 Sensitivity analysis: ORs for main outcomes stratified by specialty groups, most adjusted model (age, sex, CCI and NEWS-adjusted) in *specialty surgery*

Variables	None	Delirium alone			Dementia alone			Delirium superimposed on dementia			Low AMTS		
	n/N	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
Death in hospital	87/2676	30/197	3.54 (2.15 to 5.70)	<0.001	9/174	1.29 (0.57 to 2.60)	0.51	4/46	2.24 (0.61 to 6.33)	0.17	0/36	0.00 (0.00 to 104)	0.97
Death discharge to 1 year	262/2589	29/167	1.57 (1.00 to 2.40)	0.044	33/165	1.79 (1.16 to 2.70)	0.007	10/42	2.15 (0.97 to 4.39)	0.044	3/36	0.59 (0.14 to 1.70)	0.39
LOS >10 days	501/2676	112/197	5.35 (3.93 to 7.31)	<0.001	36/174	1.15 (0.77 to 1.69)	0.48	19/46	3.38 (1.80 to 6.25)	<0.001	11/36	2.07 (0.95 to 4.22)	0.053
DTOC >2 days	65/2589	21/167	4.81 (2.76 to 8.11)	<0.001	10/165	1.96 (0.91 to 3.82)	0.063	6/42	4.99 (1.79 to 11.9)	<0.001	2/36	1.65 (0.26 to 5.72)	0.51
Discharge to place other than home	250/2498	74/145	8.22 (5.73 to 11.8)	<0.001	38/155	2.38 (1.57 to 3.54)	<0.001	19/41	6.27 (3.25 to 12.0)	<0.001	6/33	1.61 (0.59 to 3.75)	0.31
30-day readmission	242/2551	13/160	0.86 (0.46 to 1.50)	0.62	13/161	0.80 (0.42 to 1.40)	0.47	4/40	0.98 (0.29 to 2.51)	0.97	3/36	0.78 (0.19 to 2.23)	0.69
¹ OR = Odds Ratio, CI = Confidence Interval													

Note: only 54% had cognitive data reported.

Appendix Table 7.23 Sensitivity analysis: ORs for main outcomes stratified by specialty groups, most adjusted model (age, sex, CCI and NEWS-adjusted) in *specialty medicine*

Variables	None	Delirium alone		Dementia alone			Delirium superimposed on dementia			Low AMTS			
	n/N	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value
Death in hospital	174/2576	72/280	4.02 (2.88 to 5.58)	<0.001	13/99	1.76 (0.89 to 3.21)	0.083	11/65	2.14 (1.00 to 4.21)	0.036	4/45	1.45 (0.42 to 3.76)	0.49
Death discharge to 1 year	610/2402	80/208	1.67 (1.23 to 2.27)	0.001	32/86	1.69 (1.06 to 2.68)	0.026	20/54	1.68 (0.92 to 3.00)	0.082	18/41	2.54 (1.32 to 4.82)	0.005
LOS >10 days	489/2576	134/280	3.49 (2.69 to 4.53)	<0.001	20/99	0.95 (0.56 to 1.56)	0.85	38/65	5.51 (3.30 to 9.31)	<0.001	19/45	2.90 (1.55 to 5.32)	<0.001
DTOC >2 days	104/2402	36/208	4.04 (2.64 to 6.09)	<0.001	9/86	2.14 (0.97 to 4.24)	0.041	21/54	10.7 (5.78 to 19.5)	<0.001	10/41	5.94 (2.65 to 12.3)	<0.001
Discharge to place other than home	209/2352	57/193	3.62 (2.53 to 5.12)	<0.001	13/81	1.55 (0.79 to 2.81)	0.17	16/50	3.38 (1.75 to 6.30)	<0.001	11/39	3.08 (1.41 to 6.27)	0.003
30-day readmission	328/2384	27/205	0.93 (0.60 to 1.41)	0.75	14/90	1.18 (0.62 to 2.10)	0.59	10/53	1.57 (0.73 to 3.08)	0.22	6/41	1.14 (0.43 to 2.57)	0.77
[†] OR = Odds Ratio, CI = Confidence Interval													

Note: only 54% had cognitive data reported.

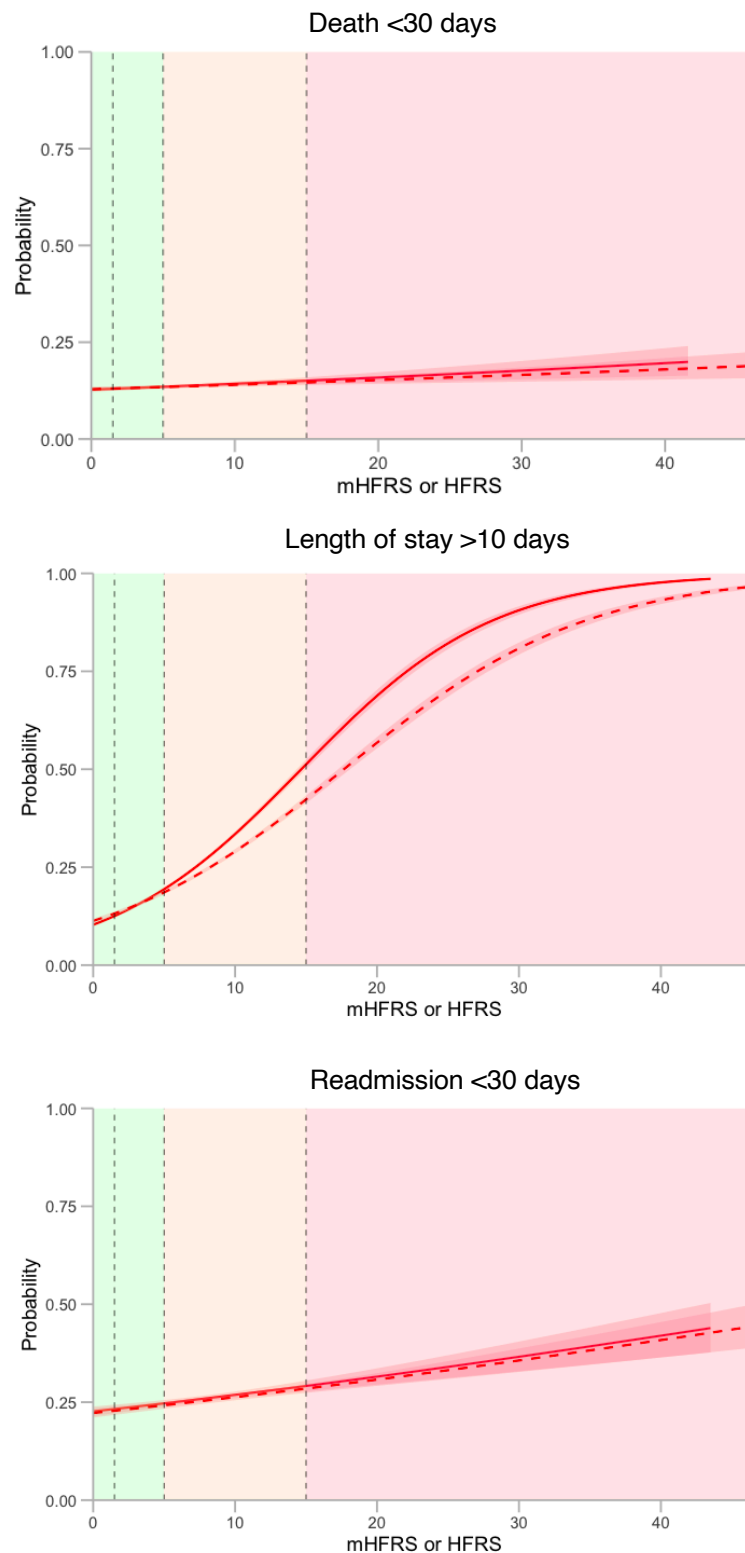
Appendix 8 Supplementary material for Chapter 8

Appendix Table 8.0 Cross tabulation of mHFRS versus HFRS in ORCHARD-EPR

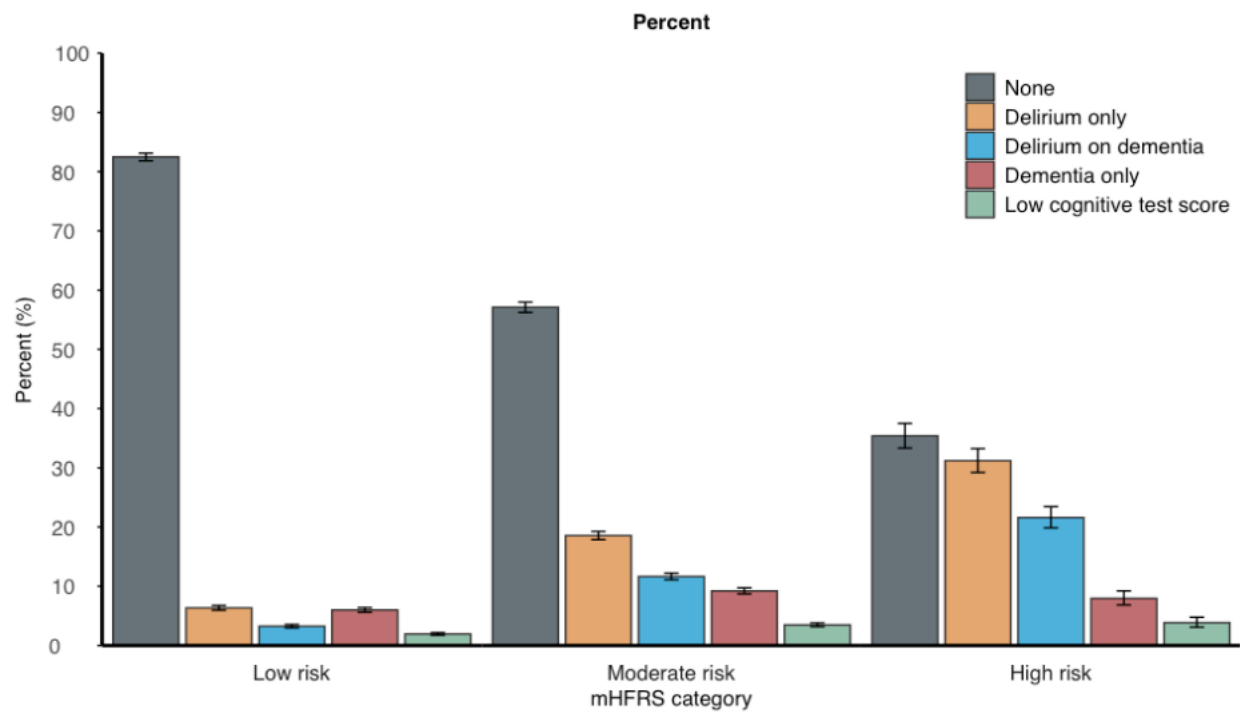
Appendix Table 3.3 Cross tabulation of mHFRS versus HFRS in CHORR AND ET				
	mHFRS			Total
	Low risk	Moderate risk	High risk	
HFRS, n (%)				
Low risk	13,098 (100%)	0 (0%)	0 (0%)	13,098 (100%)
Moderate risk	863 (7.1%)	11,271 (93%)	0 (0%)	12,134 (100%)
High risk	85 (2.5%)	1,250 (37%)	2,023 (60%)	3,358 (100%)
Total, n (%)	14,046 (49%)	12,521 (44%)	2,023 (7.1%)	28,590 (100%)

Appendix Figure 8.0 HFERS versus mHFERS and outcomes (similar to original validation of HFERS in a national cohort Figure 1 in Gilbert et al., 2018)

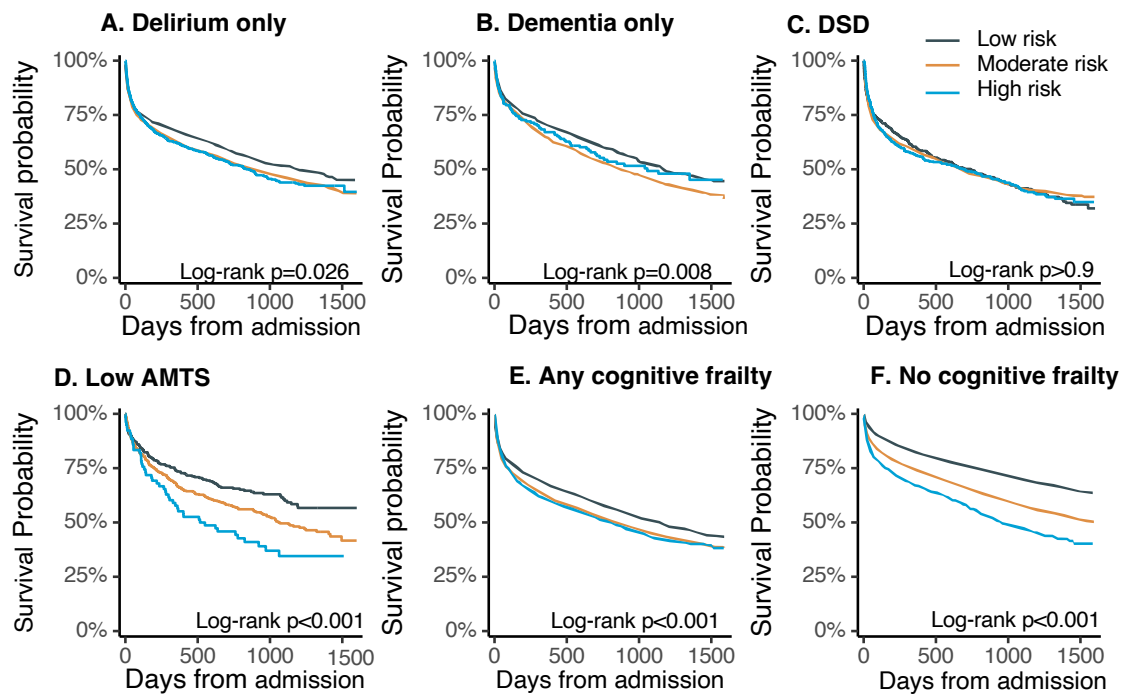
Red lines indicate probabilities associated with mHFERS (solid) or HFERS (dotted) scores (logistic regression with 95% CIs in pink). Black dashed lines indicate scores of 1.5, 5 and 15 on the mHFERS or HFERS & data are unadjusted



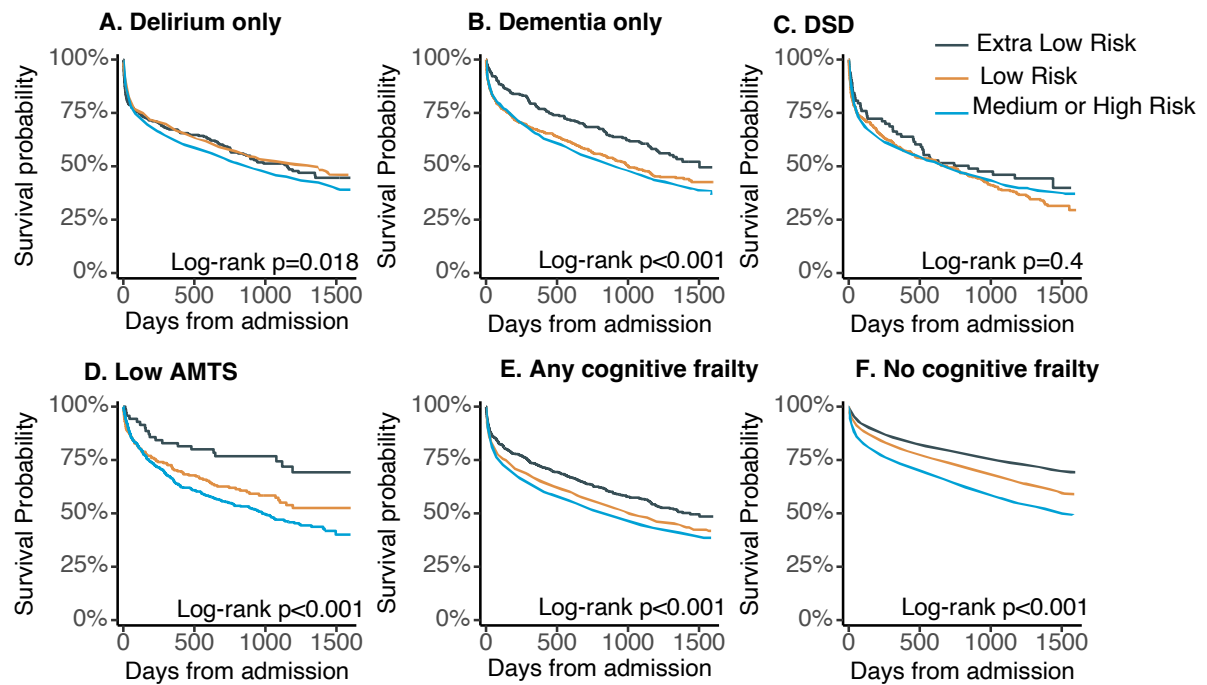
Appendix Figure 8.1 Cognitive diagnosis by physical frailty severity (mHFRS)



Appendix Figure 8.2 Kaplan-Meier plot for survival by cognitive frailty subtype and physical frailty ($\text{HFRS} < 5$, 5-15 and > 15) over the follow-up period



Appendix Figure 8.3 Kaplan-Meier plot for survival by cognitive frailty subtype and physical frailty (mHFRS <1.5, 1.5-5, >5) over the follow-up period



Appendix Table 8.1 Interaction effects between mHFRS and any cognitive frailty. Adjusted for age, sex, mCCI and NEWS category

Multiplicative scale: Evaluates the OR for both exposures (group with cognitive frailty AND mHFRS>5) compared to the product of ORs for both exposures individually (cognitive frailty * mHFRS>5).

RERI: Relative excess risk due to interaction. Evaluates if the OR for both exposures compared to the sum of exposures individually.

In hospital death	mHFRS <5		mHFRS ≥5		Relative effect OR [95% CI]
	n/N (%)	OR [95% CI]	n/N (%)	OR [95% CI]	
No cognitive frailty	417/11,586 (3.6%)	1 [Reference]	657/7,867 (8.4%)	1.93 [1.69, 2.2]	1.93 [1.69, 2.2]
Cognitive frailty	248/2,460 (10%)	2.39 [2.02, 2.84]	875/6,677 (13%)	2.9 [2.55, 3.3]	1.21 [1.04, 1.42]
Multiplicative scale		0.63 [0.51, 0.77]			
RERI		-0.42 [-0.86, 0.03]			
LoS >10 days		OR [95% CI]		OR [95% CI]	OR [95% CI]
No cognitive frailty	1,311/11,586 (11%)	1 [Reference]	2,435/7,867 (31%)	3.32 [3.07, 3.58]	3.32 [3.07, 3.58]
Cognitive frailty	445/2,460 (18%)	1.72 [1.53, 1.94]	2,836/6,677 (42%)	5.49 [5.08, 5.95]	3.19 [2.85, 3.57]
Multiplicative scale		0.96 [0.84, 1.1]			
RERI		1.45 [1.09, 1.82]			
Discharge to usual destination		OR [95% CI]		OR [95% CI]	OR [95% CI]
No cognitive frailty	758/11,040 [6.9%]	1 [Reference]	1,533/6,949 [22%]	3.43 [3.12, 3.77]	3.43 [3.12, 3.77]

Cognitive frailty	389/2,180 [18%]	2.48 [2.17, 2.84]	2,042/5,576 [37%]	6.25 [5.68, 6.88]	2.52 [2.22, 2.85]
Multiplicative scale		0.73 [0.63, 0.86]			
RERI		1.34 [0.85, 1.82]			
Delayed discharge		OR [95% CI]		OR [95% CI]	OR [95% CI]
No cognitive frailty	295/11,169 [2.6%]	1 [Reference]	1181/7210 [16%]	6.53 [5.71, 7.48]	6.53 [5.71, 7.48]
Cognitive frailty	187/2212 [8.5%]	2.85 [2.35, 3.47]	1656/5802 [29%]	11.57 [10.11, 13.25]	4.06 [3.44, 4.78]
Multiplicative scale		0.62 [0.5, 0.77]			
RERI		3.18 [2.23, 4.14]			
Readmissions <30 days		OR [95% CI]		OR [95% CI]	OR [95% CI]
No cognitive frailty	1,372/10,987 [12%]	1 [Reference]	957/7,007 [14%]	1.04 [0.95, 1.14]	6.53 [5.71, 7.48]
Cognitive frailty	321/2,183 [15%]	1.16 [1.01, 1.32]	873/5,638 [15%]	1.19 [1.08, 1.31]	4.06 [3.44, 4.78]
Multiplicative scale		0.99 [0.84, 1.17]			
RERI		-0.01 [-0.19, 0.18]			
1 year death		OR [95% CI]		OR [95% CI]	OR [95% CI]
No cognitive frailty	1,662/11,169 (15%)	1 [Reference]	1,458/7,210 (20%)	1.15 [1.06, 1.25]	1.15 [1.06, 1.25]
Cognitive frailty	559/2,212 (25%)	1.66 [1.48, 1.85]	1,725/5,638 (31%)	1.81 [1.67, 1.97]	1.09 [0.98, 1.23]
Multiplicative scale		0.95 [0.83, 1.09]			
RERI		0 [-0.21, 0.22]			

Appendix Table 8.2 ORs for in hospital death stratified by illness severity

Subgroup	mHFRS <5		mHFRS 5-15			mHFRS >15		
	n/N	OR	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
NEWS<5								
No cognitive frailty	251/9,973 (2.5%)	1	348/6,040 (5.8%)	1.79 (1.51 to 2.13)	<0.001	53/592 (9.0%)	2.05 (1.47 to 2.82)	<0.001
Any cognitive frailty	139/1,941 (7.2%)	1	410/4,346 (9.4%)	1.22 (1.00 to 1.50)	0.053	123/1,052 (12%)	1.30 (0.99 to 1.69)	0.056
Delirium only	69/687 (10%)	1	208/1,840 (11%)	1.03 (0.77 to 1.39)	0.87	66/490 (13%)	1.08 (0.74 to 1.57)	0.7
NEWS≥5								
No cognitive frailty	166/1,613 (10%)	1	225/1,111 (20%)	1.93 (1.54 to 2.41)	<0.001	31/124 (25%)	2.19 (1.38 to 3.40)	<0.001
Any cognitive frailty	109/519 (21%)	1	279/1,024 (28%)	1.33 (1.03 to 1.72)	0.029	63/255 (25%)	1.08 (0.75 to 1.55)	0.69
Delirium only	50/204 (25%)	1	128/483 (27%)	1.03 (0.70 to 1.52)	0.88	37/141 (26%)	0.94 (0.56 to 1.55)	0.8
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 8.3 ORs for select outcomes by cognitive and physical frailty status adjusted for age, sex, comorbidity and illness severity in non-care home residents

Outcome and strata	mHFRS <5		mHFRS 5-15			mHFRS >15		
	n/N	OR	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
DTOC >2 days								
No cognitive frailty	243/10,645 (2.3%)	1	794/5,864 (14%)	5.76 (4.97 to 6.71)	<0.001	161/519 (31%)	15.7 (12.4 to 19.8)	<0.001
Any cognitive frailty	125/1,721 (7.3%)	1	786/3,432 (23%)	3.67 (3.01 to 4.50)	<0.001	322/776 (41%)	8.66 (6.86 to 11.0)	<0.001
Delirium only	52/658 (7.9%)	1	385/1,659 (23%)	3.33 (2.47 to 4.58)	<0.001	170/397 (43%)	8.23 (5.83 to 11.8)	<0.001
Readmitted <30 days								
No cognitive frailty	1,280/10,468 (12%)	1	760/5,700 (13%)	1.02 (0.92 to 1.12)	0.73	62/496 (13%)	0.83 (0.63 to 1.09)	0.2
Any cognitive frailty	254/1,696 (15%)	1	526/3,353 (16%)	1.06 (0.90 to 1.25)	0.51	106/734 (14%)	0.92 (0.71 to 1.18)	0.5
Delirium only	97/652 (15%)	1	261/1,617 (16%)	1.09 (0.85 to 1.42)	0.5	53/371 (14%)	0.91 (0.62 to 1.31)	0.6
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 8.4 ORs for select outcomes by cognitive and physical frailty status adjusted for age, sex, comorbidity and illness severity in care home residents

Outcome and strata	mHFRS <5		mHFRS 5-15			mHFRS >15		
	n/N	OR	n/N	OR (95% CI) ¹	p-value	n/N	OR (95% CI) ¹	p-value
DTOC >2 days								
No cognitive frailty	39/524 (7.4%)	1	157/714 (22%)	3.60 (2.50 to 5.31)	<0.001	41/113 (36%)	7.41 (4.43 to 12.5)	<0.001
Any cognitive frailty	51/491 (10%)	1	321/1,249 (26%)	2.88 (2.11 to 4.00)	<0.001	147/345 (43%)	5.97 (4.16 to 8.68)	<0.001
Delirium only	13/114 (11%)	1	104/328 (32%)	3.48 (1.91 to 6.81)	<0.001	56/131 (43%)	5.35 (2.75 to 11.0)	<0.001
Readmitted <30 days								
No cognitive frailty	92/519 (18%)	1	121/701 (17%)	1.00 (0.74 to 1.36)	>0.99	14/110 (13%)	0.67 (0.35 to 1.22)	0.21
Any cognitive frailty	67/487 (14%)	1	193/1,217 (16%)	1.20 (0.89 to 1.64)	0.24	48/334 (14%)	1.05 (0.70 to 1.59)	0.8
Delirium only	25/110 (23%)	1	52/317 (16%)	0.66 (0.38 to 1.16)	0.14	17/125 (14%)	0.53 (0.25 to 1.06)	0.075
¹ OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 8.5 Characteristics by cognitive and general frailty status, determined by original HFRS

Characteristic	Overall, N = 28,590	Neither, N = 11,586	Cognitive only, N = 1,512	Physical only, N = 7,867	Cognitive and physical, N = 7,625	p-value, all1,3
Age, Mean (SD)	81.8 (7.4)	79.2 (6.7)	83.0 (7.1)	82.1 (7.3)	85.2 (7.0)	<0.001
Female, n (%)	14,813 (52%)	5,523 (48%)	774 (51%)	4,153 (53%)	4,363 (57%)	<0.001
Care home resident, n (%)	3,594 (13%)	531 (4.6%)	266 (18%)	847 (11%)	1,950 (26%)	<0.001
CCI, Mean (SD)	8.9 (9.2)	5.7 (7.0)	9.8 (9.2)	8.3 (8.7)	14.1 (10.4)	<0.001
mCCI, Mean (SD) ²	7.0 (8.0)	5.7 (7.0)	5.8 (7.2)	8.3 (8.7)	7.6 (8.5)	<0.001
Primary diagnosis of infection, n (%)	2,231 (7.8%)	354 (3.1%)	41 (2.7%)	1,021 (13%)	815 (11%)	<0.001
NEWS category, n (%)						<0.001
Low	21,396 (75%)	9,092 (78%)	1,064 (70%)	5,954 (76%)	5,286 (69%)	
Low-Medium	2,548 (8.9%)	881 (7.6%)	146 (9.7%)	678 (8.6%)	843 (11%)	
Medium	2,789 (9.8%)	1,016 (8.8%)	164 (11%)	751 (9.5%)	858 (11%)	
High	1,857 (6.5%)	597 (5.2%)	138 (9.1%)	484 (6.2%)	638 (8.4%)	
Treating specialty, n (%)						<0.001
General Medicine	17,478 (61%)	5,765 (50%)	1,012 (67%)	4,836 (61%)	5,865 (77%)	
General Surgery	2,304 (8.1%)	1,511 (13%)	209 (14%)	352 (4.5%)	232 (3.0%)	
Specialty Medicine	3,065 (11%)	1,743 (15%)	115 (7.6%)	833 (11%)	374 (4.9%)	
Specialty Surgery	3,129 (11%)	1,875 (16%)	126 (8.3%)	801 (10%)	327 (4.3%)	
Trauma and Orthopaedics	2,614 (9.1%)	692 (6.0%)	50 (3.3%)	1,045 (13%)	827 (11%)	
1Kruskal-Wallis rank sum test; Pearson's Chi-squared test						
2The mCCI is the CCI excluding coded dementia						

Appendix Table 8.6 HRs for original HFRS by cognitive frailty and delirium status adjusted for age, sex, mCCI, NEWS

Outcome and strata	HFRS <5		HFRS 5-15			HFRS >15		
	n/N	OR	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value
In hospital death								
No cognitive frailty	417/11,586 (3.6%)	1	573/7,151 (8.0%)	1.83 (1.59 to 2.10)	<0.001	84/716 (12%)	2.10 (1.59 to 2.73)	<0.001
Any cognitive frailty	146/1,512 (9.7%)	1	609/4,983 (12%)	1.22 (1.01 to 1.50)	0.045	368/2,642 (14%)	1.31 (1.06 to 1.63)	0.012
Delirium only	92/696 (13%)	1	322/2,246 (14%)	1.02 (0.79 to 1.32)	0.91	144/903 (16%)	1.05 (0.78 to 1.41)	0.77
Death up to 1 year								
No cognitive frailty	1,662/11,169 (15%)	1	1,302/6,578 (20%)	1.11 (1.02 to 1.21)	0.016	156/632 (25%)	1.12 (0.92 to 1.37)	0.26
Any cognitive frailty	316/1,366 (23%)	1	1,261/4,374 (29%)	1.24 (1.07 to 1.44)	0.004	707/2,274 (31%)	1.30 (1.11 to 1.52)	0.001
Delirium only	132/604 (22%)	1	525/1,924 (27%)	1.18 (0.94 to 1.48)	0.15	208/759 (27%)	1.05 (0.81 to 1.36)	0.73
LoS >10 days								
No cognitive frailty	1,311/11,586 (11%)	1	2,039/7,151 (29%)	2.91 (2.69 to 3.15)	<0.001	396/716 (55%)	8.31 (7.07 to 9.77)	<0.001
Any cognitive frailty	269/1,512 (18%)	1	1,653/4,983 (33%)	2.30 (1.99 to 2.67)	<0.001	1359/2642 (51%)	4.88 (4.18 to 5.70)	<0.001
Delirium only	152/696 (22%)	1	871/2,246 (39%)	2.24 (1.84 to 2.75)	<0.001	523/903 (58%)	4.82 (3.85 to 6.06)	<0.001
DTOC >2 days								
No cognitive frailty	282/11,169 (2.5%)	1	951/6,578 (14%)	5.63 (4.90 to 6.48)	<0.001	202/632 (32%)	14.7 (11.9 to 18.1)	<0.001
Any cognitive frailty	95/1,366 (7.0%)	1	866/4,374 (20%)	3.19 (2.56 to 4.01)	<0.001	791/2,274 (35%)	6.75 (5.40 to 8.53)	<0.001
Delirium only	51/604 (8.4%)	1	427/1,924 (22%)	2.93 (2.18 to 4.03)	<0.001	302/759 (40%)	6.62 (4.82 to 9.25)	<0.001
Discharge destination								
No cognitive frailty	758/11,040 (6.9%)	1	1,309/6,368 (21%)	3.18 (2.56 to 3.99)	<0.001	224/581 (39%)	6.75 (5.40 to 8.52)	<0.001
Any cognitive frailty	210/1,351 (16%)	1	1,249/4,231 (30%)	2.18 (1.86 to 2.58)	<0.001	972/2,174 (45%)	4.20 (3.54 to 5.00)	<0.001
Delirium only	108/595 (18%)	1	559/1,850 (30%)	1.84 (1.46 to 2.33)	<0.001	348/713 (49%)	3.93 (3.04 to 5.11)	<0.001
Readmitted <30 days								
No cognitive frailty	1,372/10,987 (12%)	1	881/6,401 (14%)	1.03 (0.94 to 1.14)	0.49	76/606 (13%)	0.82 (0.63 to 1.05)	0.12

Any cognitive frailty	190/1,347 (14%)	1	689/4,277 (16%)	1.17 (0.98 to 1.39)	0.087	315/2,197 (14%)	1.00 (0.82 to 1.23)	0.97
Delirium only	90/595 (15%)	1	309/1,879 (16%)	1.10 (0.85 to 1.43)	0.48	106/718 (15%)	0.94 (0.69 to 1.28)	0.69
[†] OR = Odds Ratio, CI = Confidence Interval								

Appendix Table 8.7 Characteristics by cognitive and physical frailty status determined using mHFRS categories of <1.5 and ≥1.5

Characteristic	Overall, N = 28,590	Neither, N = 4,821	Cognitive only, N = 632	Physical only, N = 14,632	Cognitive and physical, N = 8,505	p-value, all1,3
Age, Mean (SD)	81.8 (7.4)	78.4 (6.5)	82.5 (7.1)	81.0 (7.2)	85.0 (7.0)	<0.001
Female, n (%)	14,813 (52%)	2,170 (45%)	315 (50%)	7,506 (51%)	4,822 (57%)	<0.001
Care home resident, n (%)	3,594 (13%)	171 (3.5%)	117 (19%)	1,207 (8.2%)	2,099 (25%)	<0.001
CCI, Mean (SD)	8.9 (9.2)	5.0 (6.5)	11.0 (8.7)	7.4 (8.1)	13.6 (10.4)	<0.001
mCCI, Mean (SD) ²	7.0 (8.0)	5.0 (6.5)	5.0 (6.3)	7.4 (8.1)	7.5 (8.4)	<0.001
Primary diagnosis of infection, n (%)	2,231 (7.8%)	68 (1.4%)	11 (1.7%)	1,307 (8.9%)	845 (9.9%)	<0.001
NEWS category, n (%)						<0.001
Low	21,396 (75%)	3,884 (81%)	453 (72%)	11,162 (76%)	5,897 (69%)	
Low-Medium	2,548 (8.9%)	348 (7.2%)	59 (9.3%)	1,211 (8.3%)	930 (11%)	
Medium	2,789 (9.8%)	387 (8.0%)	67 (11%)	1,380 (9.4%)	955 (11%)	
High	1,857 (6.5%)	202 (4.2%)	53 (8.4%)	879 (6.0%)	723 (8.5%)	
Treating specialty, n (%)						<0.001
General Medicine	17,478 (61%)	2,235 (46%)	393 (62%)	8,366 (57%)	6,484 (76%)	
General Surgery	2,304 (8.1%)	741 (15%)	103 (16%)	1,122 (7.7%)	338 (4.0%)	
Specialty Medicine	3,065 (11%)	847 (18%)	55 (8.7%)	1,729 (12%)	434 (5.1%)	
Specialty Surgery	3,129 (11%)	836 (17%)	73 (12%)	1,840 (13%)	380 (4.5%)	
Trauma and Orthopaedics	2,614 (9.1%)	162 (3.4%)	8 (1.3%)	1,575 (11%)	869 (10%)	
1Kruskal-Wallis rank sum test; Pearson's Chi-squared test						
2The mCCI is the CCI excluding coded dementia						

Appendix Table 8.8 HRs using alternate cut-points for the mHFRS (<1.5, 1.5-5, >5) based on cognitive frailty and delirium status adjusted for age, sex, mCCI and NEWS category

Outcome and strata	mHFRS <1.5		mHFRS 1.5-5			mHFRS >5		
	n/N	OR	n/N	OR (95% CI) [†]	p-value	n/N	OR (95% CI) [†]	p-value
In hospital death								
No cognitive frailty	106/4,821 (2.2%)	1	319/6,914 (4.6%)	1.79 (1.43 to 2.26)	<0.001	649/7,718 (8.4%)	2.79 (2.25 to 3.48)	<0.001
Any cognitive frailty	47/632 (7.4%)	1	206/1,889 (11%)	1.39 (1.00 to 1.98)	0.056	870/6,616 (13%)	1.63 (1.20 to 2.27)	0.002
Delirium only	33/238 (14%)	1	88/680 (13%)	0.86 (0.55 to 1.36)	0.51	437/2,927 (15%)	0.93 (0.63 to 1.40)	0.71
Death up to 1 year								
No cognitive frailty	642/4,715 (14%)	1	1,048/6,595 (16%)	1.04 (0.93 to 1.16)	0.46	1,430/7,069 (20%)	1.13 (1.02 to 1.26)	0.023
Any cognitive frailty	127/585 (22%)	1	445/1,683 (26%)	1.20 (0.96 to 1.52)	0.11	1,712/5,746 (30%)	1.32 (1.08 to 1.63)	0.009
Delirium only	45/205 (22%)	1	134/592 (23%)	0.90 (0.61 to 1.34)	0.59	686/2,490 (28%)	1.04 (0.74 to 1.50)	0.82
LoS >10 days								
No cognitive frailty	364/4,821 (7.6%)	1	972/6,914 (14%)	1.92 (1.69 to 2.18)	<0.001	2,410/7,718 (31%)	4.98 (4.43 to 5.62)	<0.001
Any cognitive frailty	85/632 (13%)	1	371/1,889 (20%)	1.58 (1.23 to 2.06)	<0.001	2,825/6,616 (43%)	4.75 (3.78 to 6.05)	<0.001
Delirium only	46/238 (19%)	1	162/680 (24%)	1.31 (0.91 to 1.91)	0.15	1,338/2,927 (46%)	3.46 (2.50 to 4.87)	<0.001
DTOC >2 days								
No cognitive frailty	50/4,715 (1.1%)	1	244/6,595 (3.7%)	3.25 (2.41 to 4.46)	<0.001	1,141/7,069 (16%)	14.4 (10.9 to 19.5)	<0.001
Any cognitive frailty	24/585 (4.1%)	1	155/1,683 (9.2%)	2.30 (1.51 to 3.66)	<0.001	1,573/5,746 (27%)	8.29 (5.61 to 12.9)	<0.001
Delirium only	14/205 (6.8%)	1	52/592 (8.8%)	1.24 (0.69 to 2.38)	0.49	714/2,490 (29%)	4.95 (2.96 to 9.00)	<0.001
Discharge destination								
No cognitive frailty	229/4,683 (4.9%)	1	541/6,496 (8.3%)	1.62 (1.38 to 1.91)	<0.001	1,521/6,810 (22%)	4.59 (3.97 to 5.33)	<0.001
Any cognitive frailty	72/579 (12%)	1	329/1,653 (20%)	1.70 (1.30 to 2.25)	<0.001	2,030/5,524 (37%)	3.89 (3.04 to 5.06)	<0.001
Delirium only	33/203 (16%)	1	108/580 (19%)	1.09 (0.71 to 1.69)	0.7	874/2,375 (37%)	2.64 (1.82 to 3.95)	<0.001
Readmitted <30 days								

No cognitive frailty	531/4,651 (11%)	1	859/6,472 (13%)	1.14 (1.01 to 1.28)	0.03	939/6,871 (14%)	1.10 (0.98 to 1.24)	0.12
Any cognitive frailty	72/580 (12%)	1	258/1,659 (16%)	1.28 (0.97 to 1.71)	0.088	864/5,582 (15%)	1.28 (0.99 to 1.67)	0.067
Delirium only	30/202 (15%)	1	96/585 (16%)	1.10 (0.71 to 1.74)	0.69	379/2,405 (16%)	1.04 (0.70 to 1.59)	0.87
¹ OR = Odds Ratio, CI = Confidence Interval								

Statement of authorship and copy of protocols and publications resulting from thesis work

1. Statement of Authorship

Degree Title: DPhil in Clinical Neurosciences

DECLARATION OF AUTHORSHIP



Name (in capitals): EMILY BOUCHER

Candidate number: 1302853

College (in capitals): GREEN TEMPLETON

[Supervisor/Adviser:] PROF. SARAH
PENDLEBURY

Title of [thesis/extended essay] (in capitals): THE VALUE OF ELECTRONIC PATIENT
RECORDS FOR DETERMINING THE PREVALENCE AND PROGNOSIS OF COGNITIVE AND
PHYSICAL FRAILTY IN A LARGE HOSPITAL-BASED COHORT

Word count: 43,906 *Approx excluding references, tables, figures, supplement*

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2. Boucher E, Gan, J., Shepperd, S., Pendlebury, ST. The prevalence of frailty and its association with mortality, institutionalization, readmission and length of stay among patients acutely admitted to hospital: a systematic review. 2021.
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021235663

The prevalence of frailty and its association with mortality, institutionalization, readmission and length of stay among patients acutely admitted to hospital: a systematic review

Citation

Emily Boucher, Jasmine Gan, Sasha Shepperd, Sarah Pendlebury. The prevalence of frailty and its association with mortality, institutionalization, readmission and length of stay among patients acutely admitted to hospital: a systematic review. PROSPERO 2021 CRD42021235663 Available from:

https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42021235663

Review question

The objective of this review is to estimate the prevalence of frailty and its association with short-term outcomes, including mortality, institutionalization, readmission and length of stay among patients with unplanned admissions to hospital, and to acute general medicine units.

Searches

We will search three electronic databases (MEDLINE, EMBASE and CINAHL) for peer-reviewed studies using a comprehensive search strategy developed in consultation with a health sciences librarian. Reference lists of included studies will be hand searched for relevant studies.

Only English language studies for which the full-text is available will be included.

Types of study to be included

Prospective and retrospective cohort studies will be included.

Only English language studies for which the full-text is available will be included.

All other study designs, including case-control, cross-sectional and control arms of clinical trials will be excluded.

Condition or domain being studied

Frailty that might be assessed and described using:

1. Phenotype models, such as the Fried phenotype model (exhaustion, weight loss, low activity, weak grip strength, and slow walk);
2. Cumulative deficits models, such as the Rockwood frailty index;
3. Tools based on comprehensive geriatric assessment, such as the FI-CGA (cognition, mood, communication, mobility, balance, bowel, bladder, nutrition, activities of daily living, social and comorbidities);
4. Global measures, such as the CSHA Clinical Frailty Scale;
5. Clinical impression.

Participants/population

We will include studies of patients over 18 years of age with unplanned admissions to hospital, and to acute general medicine units.

We will exclude studies primarily selecting patients from outpatient clinics, day hospital programs, emergency departments, surgical departments, critical/intensive care, rehabilitation units, studies selecting patients based on a diagnosis, and studies with a large proportion of elective admissions.

Intervention(s), exposure(s)

Frailty that might be assessed and described using:

1. Phenotype models, such as the Fried phenotype model (exhaustion, weight loss, low activity, weak grip strength, and slow walk);
2. Cumulative deficits models, such as the Rockwood frailty index;
3. Tools based on comprehensive geriatric assessment, such as the FI-CGA (cognition, mood, communication, mobility, balance, bowel, bladder, nutrition, activities of daily living, social and comorbidities);
4. Global measures, such as the CSHA Clinical Frailty Scale;
5. Clinical impression.

We will exclude studies relying on a single physical performance measure, for example, gait speed only.

Comparator(s)/control

Not applicable to the primary outcome.

Main outcome(s)

The prevalence of frailty.

Measures of effect

Proportions.

Additional outcome(s)

The association between frailty and mortality, institutionalization, readmission and length of stay.

Measures of effect

Relative risk, odds ratios or hazard ratios.

Data extraction (selection and coding)

One reviewer will complete initial title and abstract and full-text screening using pre-specified inclusion and exclusion criteria.

Only English language studies for which the full-text is available will be included.

Where there is any uncertainty as to whether a full-text article meets inclusion or exclusion criteria, a second researcher

will review the study independently.

Discrepancies between the first and second reviewer will be resolved through discussion.

The final list of included studies will be reviewed by at least two members of the review team.

Data will then be extracted from the studies selected for inclusion onto an Excel spreadsheet and verified by at least one researcher and will include study characteristics, frailty assessment, participant characteristics (age, sex, ethnicity, comorbidities) as well as outcome data.

Risk of bias (quality) assessment

Risk of bias will be assessed using a modified version of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data.

Strategy for data synthesis

We will provide a narrative synthesis in accordance with the Synthesis without meta-analysis (SWiM) guidelines if a meta-analysis is not possible.

The distribution and magnitude of effects will be summarized in tables and/or plots.

We will conduct a random-effects meta-analysis if two or more estimates from similar studies are available.

Data will be stratified by setting, i.e. general medicine and hospital admissions.

For time-to-event data, hazard rate ratios will be pooled.

For other dichotomous data, odds ratios or relative risk will be pooled separately for different time points. For continuous data, the mean difference between frail and non-frail individuals will be pooled.

Between-study heterogeneity will be assessed qualitatively and quantitatively, with an $I^2 > 50\%$ considered to be indicative of substantial heterogeneity.

Analysis of subgroups or subsets

Descriptive summaries for each method of frailty will be provided, as well as stratified estimates if there is sufficient data for meta-analysis.

Subgroup data based on age, sex, and cognitive status will be presented if available.

Contact details for further information

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Type and method of review

Epidemiologic, Intervention, Narrative synthesis, Systematic review

Anticipated or actual start date

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England

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Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

Boucher EL, Gan JM, Rothwell PM, Shepperd S, Pendlebury ST. Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts. *eClinicalMedicine*. 2023;59:101947. doi:10.1016/j.eclinm.2023.101947

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Adult; Aged; Age Factors; Frail Elderly; Frailty; Health Services for the Aged; Hospitalization; Hospitals; Humans; Institutionalization; Length of Stay; Mortality; Patient Readmission; Prevalence; Risk Factors; Treatment Outcome

Date of registration in PROSPERO

08 February 2021

Date of first submission

06 February 2021

Stage of review at time of this submission [3 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

The review has been completed and published.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

08 February 2021

11 February 2021

01 April 2021

04 May 2023

- 1) Boucher EL, Gan JM, Rothwell PM, Shepperd S, Pendlebury ST. Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts. *EClinicalMedicine* 2023; **59**: 101947. <https://doi.org/10.1016/j.eclinm.2023.101947>.

Prevalence and outcomes of frailty in unplanned hospital admissions: a systematic review and meta-analysis of hospital-wide and general (internal) medicine cohorts

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Summary

Background Guidelines recommend routine frailty screening for all hospitalised older adults to inform care decisions, based mainly on studies in elective or speciality-specific settings. However, most hospital bed days are accounted for by acute non-elective admissions, in which the prevalence and prognostic value of frailty might differ, and uptake of screening is limited. We therefore did a systematic review and meta-analysis of frailty prevalence and outcomes in unplanned hospital admissions.

Methods We searched MEDLINE, EMBASE and CINAHL up to 31/01/2023 and included observational studies using validated frailty measures in adult hospital-wide or general medicine admissions. Summary data on the prevalence of frailty and associated outcomes, measurement tools, study setting (hospital-wide vs general medicine), and design (prospective vs retrospective) were extracted and risk of bias assessed (modified Joanna Briggs Institute checklists). Unadjusted relative risks (RR; moderate/severe frailty vs no/mild) for mortality (within one year), length of stay (LOS), discharge destination and readmission were calculated and pooled, where appropriate, using random-effects models. PROSPERO CRD42021235663.

Findings Among 45 cohorts (median/SD age = 80/5 years; n = 39,041,266 admissions, n = 22 measurement tools) moderate/severe frailty ranged from 14.3% to 79.6% overall (and in the 26 cohorts with low-moderate risk of bias) with considerable heterogeneity between studies ($p_{\text{het}} < 0.001$) preventing pooling of results but with rates <25% in only 3 cohorts. Moderate/severe vs no/mild frailty was associated with increased mortality (n = 19 cohorts; RR range = 1.08–3.70), more consistently among cohorts using clinically administered tools (n = 11; RR range = 1.63–3.70; $p_{\text{het}} = 0.08$; pooled RR = 2.53, 95% CI = 2.15–2.97) vs cohorts using (retrospective) administrative coding data (n = 8; RR range = 1.08–3.02; $p_{\text{het}} < 0.001$). Clinically administered tools also predicted increasing mortality across the full range of frailty severity in each of the six cohorts that allowed ordinal analysis (all $p < 0.05$). Moderate/severe vs no/mild frailty was also associated with a LOS >8 days (RR range = 2.14–3.04; n = 6) and discharge to a location other than home (RR range = 1.97–2.82; n = 4) but was inconsistently related to 30-day readmission (RR range = 0.83–1.94; n = 12). Associations remained clinically significant after adjustment for age, sex and comorbidity where reported.

Interpretation Frailty is common in older patients with acute, non-elective hospital admission and remains predictive of mortality, LOS and discharge home with more severe frailty associated with greater risk, justifying more widespread implementation of screening using clinically administered tools.

Funding None.

Abbreviations: LOS, Length of stay; RR, Relative risk; ROM, Ratio of means; CFS, Clinical Frailty Scale; HFRS, Hospital Frailty Risk Score; ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheids Management Systeem; FAM, Frailty Assessment Method; FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight questionnaire; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Index; eFI, Electronic Frailty Index; eFI-AH, eFI Acute Hospital; MFST-HP, Maastricht frailty screening measure for hospitalised patients; Frail-PPS, Frail-Physical, Psychological and Social; DF-GFS, Dr Foster Global Frailty Score; SOF-1, Study of Orthopaedic Fractures Index; FI, Frailty Index; CGA, Comprehensive geriatric assessment; REFS, Reported Edmonton Frail Scale; MPI, Multidimensional Prognostic Index; MAPLe-AC, Method for assigning Priority Levels-Acute Care; BISEP, Burden of Illness Score for Elderly Persons; FCS-1, FADOI-COMPLIMED Score 1

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Keywords: Frailty; Older adults; Hospitals; General (internal) medicine; Mortality; Length of stay; Readmission; Discharge home

Research in context

Evidence before this study

Current guidelines recommend routine assessment for frailty in all hospitalised older adults to inform care. However, evidence is predominantly from specialty-specific or elective services whereas most hospital bed-days are accounted for by acute, unplanned admissions to generalist services in which the prevalence and prognostic value of frailty might differ. We therefore performed a systematic review and meta-analysis of observational studies using validated frailty measures in adult unplanned hospital-wide or general medicine admissions. We searched MEDLINE, EMBASE and CINAHL from inception to 31/01/2023 using terms relevant to [Frailty], [Geriatric Assessment], [Hospitalisation], [Outcomes] and [Observational Study] and included 45 cohorts (median/SD age = 80/5 years; n = 39,041,266 admissions, n = 22 measurement tools).

Added value of this study

We addressed an important evidence gap on frailty in unplanned hospital admissions. The prevalence of moderate/severe frailty ranged from 14.3% to 79.6%, with substantial heterogeneity ($p_{\text{het}} < 0.001$) unrelated to setting or frailty tool. Despite this variation, frailty was consistently

associated with increased mortality, particularly in studies using clinically administered tools (n = 11; pooled RR = 2.53, 95% CI = 2.15–2.97, $p_{\text{het}} = 0.08$) vs studies using retrospective coding data, with evidence of a dose response effect. Frailty was also associated with increased length of stay (LOS) and discharge to a location other than home in all studies, but associations with readmission were conflicting. Associations remained significant after adjustment for age, sex, comorbidity and other confounders where reported.

Implications of all the available evidence

Frailty prevalence is two-to-four -fold higher in the older acute hospital population with unplanned admission than in community studies and about 50% higher than in the acute surgical setting. Frailty remains predictive of mortality, LOS and discharge destination in the unselected acute hospital setting with more severe frailty linearly associated with worse outcomes. Taken together, the available evidence justifies more widespread screening for both the presence and severity of frailty with clinically administered tools, such as the Clinical Frailty Scale, to inform care and target comprehensive geriatric assessment and interventions.

Introduction

A large proportion of hospital inpatients are older persons: those aged ≥ 65 years account for 70% of hospital days in the UK, and 40–50% in the USA and Canada.^{1–3} Frailty, which is defined by a loss of physiologic reserve, is associated with reduced quality of life and poor health outcomes. Frailty is most common in older people although it may also be present in younger adults, for example with long-term health conditions such as multiple sclerosis or cancer.^{4,5} The importance of frailty in the acute care setting has been highlighted in several guidelines, which recommend routine screening for frailty in all older hospital patients using standard tools to inform clinical decisions, personalise care and target comprehensive geriatric assessment (CGA).^{6–8} In the Netherlands, screening has even been made mandatory under national legislation.⁷ The frailty construct, which is distinct from that of multi-morbidity, is commonly operationalised using the phenotype model comprising defined traits (for example, slow gait speed and weakness),⁹ the accumulation of deficits and related models (for example, the Hospital Frailty Risk Score-HFRS),¹⁰ or the pragmatic Clinical Frailty Scale (CFS), and can include cognitive function.¹¹

Despite current guidance, uptake of hospital-wide frailty screening using standardised tools has generally been poor.¹² Barriers to screening include uncertainty about the clinical utility of identifying frailty in acutely unwell patients, limited awareness of frailty tools and insufficient resources, with lack of evidence synthesis on frailty in the acute hospital setting likely a contributing factor.^{13,14} Most admissions to hospital are unplanned, predominantly to non-specialist general (internal) medicine services, where multi-morbidity and complex care needs are common. However, current guidance is based mostly on studies conducted in outpatient and specialty-specific or elective settings where the prevalence and prognostic value of frailty may differ. Reliable estimates of the burden of frailty in the acute hospital setting are needed to inform policy and plan services, including frailty screening programmes and CGA implementation.¹² In addition, understanding the prognostic implications of frailty, and of different degrees of frailty, would help inform patient management particularly in settings where frailty is common. Current recommendations do not distinguish between more vs less severe frailty, even though care needs and prognosis are likely to vary considerably.^{15–8}

Previous evidence synthesis on frailty in the acute hospital setting is limited.¹⁴ A scoping review (published 2018) included studies across a wide variety of acute settings in which the majority identified frail patients using non-validated methods.¹⁵ A systematic review (published 2019) on hospitalised older people included a large proportion of cohorts from geriatric medicine services or unspecified acute settings and was undertaken prior to the development and widespread uptake of measures using administrative data, primarily the HFRS.¹⁶ Other reviews and multi-centre studies have focused on specific settings and populations (e.g., surgery,^{17,18} including elective procedures,^{19–22} acute coronary syndrome²³). We therefore conducted a systematic review to determine i) the prevalence and measurement methods of frailty in adults with acute, unselected, non-elective admissions to hospital and general medicine services and ii) associations with mortality, length of stay (LOS), discharge destination and readmission, including after adjustment for confounding, and by degree of frailty.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted as per the PRISMA guidelines²⁴ and registered on PROSPERO (CRD42021235663).²⁵ Ethical approval was not required for this study since it used only secondary data from existing published studies. MEDLINE, EMBASE and CINAHL were searched from inception to January 31, 2023 without restrictions using a search strategy developed in consultation with a healthcare librarian. Search terms related to frailty, geriatric assessment, hospitalization, outcomes and observational study design were included (Table S1–S3). We reviewed reference lists of included studies for other potentially eligible studies.

We included cross-sectional and cohort studies of adults ≥ 18 years with predominantly unplanned admissions (>70% unplanned as stated by the study authors or inferred from the study description) to hospital-wide or general (internal) medicine services, who received usual care. Unplanned hospital-wide and general medicine admissions were both included because the majority of unplanned admissions are to general medicine. Participants were required to be assessed for frailty using validated tools during their admission (Supplemental methods). We excluded studies conducted in outpatient, emergency department, short-stay, geriatric or rehabilitation and mixed settings or specialty-specific settings (except general medicine). One reviewer (ELB, STP, JMG) completed initial title-abstract and full-text screening and a second reviewer (JMG, STP) assessed studies independently where eligibility was unclear. Articles not in English were translated using Google Translate with help from colleagues fluent in the relevant language where needed. The final list of included studies was approved by

ELB, SS and STP independently. Data were extracted by one researcher (ELB) using a standardised pro-forma including study and participant characteristics, recruitment method, frailty measurement tool and adjusted and unadjusted data stratified by moderate and severe frailty where reported. Data extraction was verified independently by a second researcher (STP). Risk of bias was assessed independently and in duplicate (ELB, STP) for prevalence and cohort outcomes using modified versions of the Joanna Briggs Institute Critical Appraisal Checklists for Prevalence and Cohort Studies (Tables S4 and S5).^{26,27} Discrepancies were resolved through discussion.

Data analysis

Frailty categories (none, mild, moderate, severe frailty—see Box 1) were defined using accepted cut-offs for each tool where possible (Supplemental methods and Tables S6 and S7). For most analyses, we dichotomised frailty as moderate/severe vs no/mild, but also stratified data by the degree of frailty where relevant. For frailty prevalence, we calculated 95% confidence intervals (CI) for prevalence using Wilson's method for binomial proportions. Owing to high levels of heterogeneity across prevalence estimates, we did not undertake pooled analyses and instead reported the range across studies. We did a meta-regression to explore if heterogeneity was explained by differences in mean cohort age and performed pre-specified subgroup analyses i) for each frailty tool, as different tools might capture different aspects of frailty and ii) setting (general medicine vs all admissions). We assessed publication bias by meta-regression of prevalence against study sample size.

Box 1.

Examples of varying degrees of frailty.

No or mild frailty: As defined by the Clinical Frailty Scale (CFS), a person with no frailty is independent with varying levels of activity (CFS of 1–3). A person with mild frailty may experience symptoms that limit activity or need help with high-order instrumental activities of daily living such as transportation and could have mild dementia (CFS 4–5). On the Hospital Frailty Risk Score (HFRS), a person is considered low risk if they have a total of 5 points or fewer from relevant ICD-10 coded conditions, for example chronic renal failure (1.40 points) and pneumonia (1.10 points).

Moderate frailty: As defined by the CFS, a person with moderate frailty needs help with outside activities, most instrumental and some basic activities of daily living (CFS of 6). They could also have moderate dementia. On the HFRS, a person is considered moderate risk if they have ICD-10 codes for conditions with a total of 5–10 points, for example chronic kidney disease (1.40 points), pneumonia (1.10 points) and a tendency to fall (3.60 points) or unspecified dementia (2.10 points).

Severe frailty: As defined by the CFS, a person with severe frailty is completely dependent for personal care (CFS of 7). They could also have severe dementia. A person with very severe frailty (CFS 8) is also completely dependent and probably would not recover from a minor illness. On the HFRS, a person is considered high risk if they have ICD-10 codes for conditions with a total of 15 points or more, for example chronic kidney disease (1.40 points), pneumonia (1.10 points), a tendency to fall (3.60 points), urinary incontinence (3.20 points), and dementia in Alzheimer's disease (7.10 points).

For the main outcomes analyses, we used data on moderate/severe vs no/mild frailty as this was most frequently reported. We assessed the association of moderate/severe frailty vs no/mild frailty with mortality up to one-year, hospital LOS, discharge to a new institution and readmission within 30-days. For dichotomous outcomes, we calculated relative risks (RR) from the data reported by the authors where at least one event was reported per group.

For continuous data (e.g., LOS), we calculated the ratio of means (ROM) for moderate/severe vs no/mild frailty. 95% CIs for dichotomous and continuous outcomes were determined from the normal approximation of the mean. When multiple estimates were reported for the same cohort (e.g., using different frailty measures), we took the estimate judged to have the best validity (i.e., internal, external, construct and conclusion). Adjusted estimates were extracted but were not used in the main outcomes analyses, because of differences in the reference groups used between studies, and we did not have access to individual patient data to calculate adjusted estimates. We did subgroup analyses based on whether frailty measures were designed for real-time administration by healthcare staff ("clinically administered tools") or retrospective application usually to administrative data ("retrospective coding tools"). We assessed publication bias through funnel plots with Egger's test for asymmetry.

For the outcomes of discharge to a new institution and readmission, we endeavoured to restrict analyses to people alive at discharge because the competing risk of in-hospital death would otherwise result in underestimation of risk. Where not reported by the authors, we subtracted in-hospital deaths from the denominator. In cases where these data were not reported, we estimated in-hospital deaths based on data provided by the study authors (e.g., 30-day mortality including in-hospital deaths) or excluded the study from analysis. Sensitivity analyses were done using denominators as reported by the authors (e.g., including deaths during admission).

Data were pooled using a random-effects (DerSimonian and Laird) model with inverse-variance weights. Data were not pooled where important unexplained heterogeneity was present, which was evaluated based on differences between populations, measurement tools, setting, and study design; and by assessing differences in the direction of effects, and testing for statistical significance with the Chi² test.²⁸ Where it was not possible to perform meta-analysis, we narratively synthesised results.²⁹

To assess for a trend in effect size (dose response effect) with increasingly severe frailty, we plotted outcomes stratified by degree of frailty in individual studies on forest plots and performed the Cochran-Armitage test for trend for each cohort. We also assessed the discriminative performance of categorical

vs dichotomous frailty scores by calculating the apparent c-statistic to evaluate the prognostic value of differentiating between varying degrees of frailty.

Given differences in the likely sensitivity of different frailty measures and their operationalisation between studies (e.g., accuracy of administrative coding), variation in prevalence beyond that attributable to differences in case-mix and population was expected. Therefore, we explored the relationship between measured prevalence and the predictive value of frailty for mortality (log RR of death) in a meta-regression. The analysis was repeated with the addition of mean cohort age as a covariate in the model.

The certainty of evidence on outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach adapted for prognostic questions by ELB with input from SS and STP.³⁰ Studies were downgraded from high-certainty evidence due to bias, imprecision, indirectness, unexplained inconsistency in the direction and magnitude of effects.^{31,32}

Statistical analyses were performed in R version 3.6.3 (R Project for Statistical Computing),³³ using the packages *meta*, *DescTools* and *pROC*.^{34–36}

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors (ELB, JMG, PM, SS, STP) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We screened 14,006 abstracts and 2287 full texts, from which 45 cohorts (n = 39,041,266 admissions, 49 publications)^{37–85} were eligible for inclusion (Fig. 1). Most studies (30/45) aimed to investigate outcomes associated with frailty. All except one were published after 2010.⁷² The mean/SD age was 80/5 years (range = 64–87 years; 39 cohorts) and minimum age for inclusion was ≥65 years in 35/45 cohorts (Tables 1 and 2).

Forty cohorts in 17 high-income countries with universal healthcare, three in the USA, one each in India and Indonesia were included, largely from urban tertiary care or teaching hospitals. Seventeen cohorts included hospital-wide unplanned admissions (n = 39,002,111) and 28 included general medicine admissions only (n = 39,155). Prior to admission, 68–97% of participants lived at home (12 cohorts) and four studies limited eligibility to community-dwelling adults. The prevalence of any-cause cognitive impairment ranged from 1 to 68% (24 cohorts) and Charlson comorbidity scores ranged from 2 to 8 (14 cohorts). In general medicine cohorts, the most frequent (rank-sum) admission diagnoses were infection, circulatory or respiratory problems (Tables S8–S10).

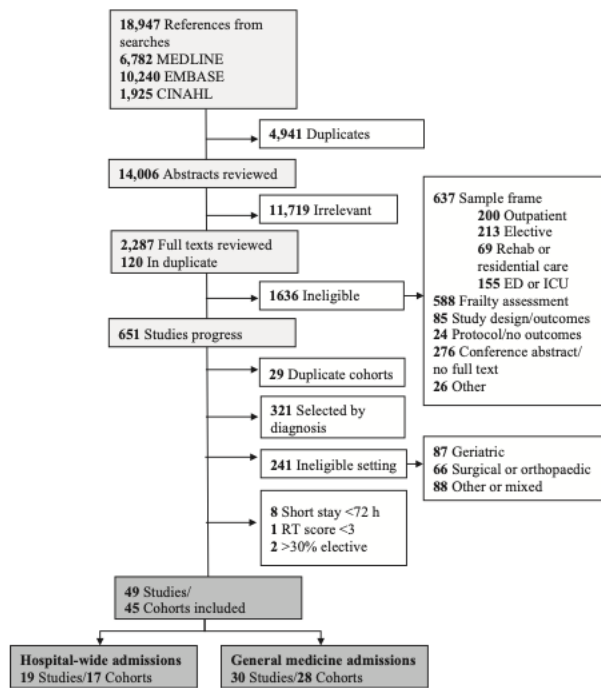


Fig. 1: PRISMA diagram. PRISMA diagram showing the search results and process of study selection. ED = emergency department, ICU = intensive care unit, RT = reverse triage score.

Twenty-two frailty tools were identified (Tables S3–S11), including 12 developed for the hospital setting (eight clinically administered, three retrospective coding tools, one other). Deficit-accumulation methods were the most common (18/54 prevalence estimates from the 45 cohorts), followed by the CFS (10/54), and phenotype (9/54), multi-dimensional (7/54), brief (5/54) or other (5/54), but there were differences in the operationalisation of tools. For example, some studies calculated the HFRS using the index admission alone ($n = 5$), whereas others ($n = 6$) used the index and any other admissions in the previous two years. Three studies used the CFS to assess frailty status pre-admission (i.e., prior to the acute illness), but in the other seven, it was unclear how the CFS was operationalised.

The most common domains covered (Table 3) were mobility, balance or falls ($n = 16$), function ($n = 14$) and cognition ($n = 14$ overall, $n = 7$ delirium). Twelve assessed psychosocial factors. Data sources included administrative data, questionnaires, physical/functional assessments and chart review (Table S12).^{66,72} Cognition was assessed using self/proxy report in two

measures,^{55,86} chart review or diagnostic coding in seven^{40,42,48,49,66,72,79} and objective testing in five.^{10,38,43,87,88} The number of items included ranged from 4 to 6 for brief, 3–9 for phenotype, 8–18 for multidimensional and 31–109 for deficit accumulation tools. All clinically administered tools required additional assessments by staff or questionnaires, but only three studies reported the time required and none evaluated feasibility further.

Risk of bias was low-moderate for 26/45 studies of prevalence (Fig. S1), with common sources of bias related to sample frame and coverage, for example due to restrictive eligibility criteria (Table S13). Risk of bias was low/moderate for 27/37 studies of outcomes (Fig. S2) and the most common source of bias was confounding by comorbidity and illness severity (Table S13). There was no evidence of publication bias in frailty prevalence (Fig. S3) or mortality outcomes (Fig. S4). Certainty of the evidence (GRADE) is reported in Table S14.

The prevalence of moderate/severe frailty ranged from 14.3 to 79.6 in all cohorts ($N = 40$ cohorts; $n = 4,994,931$ admissions), and in the 26 cohorts with low-moderate risk of bias, with rates <25% in only 3/45

Study	Location	N	Age	% Female	Exclusion criteria (summary)	Frailty tool	Type of tool
Asmus-Szepesi (2013) ³⁷	Netherlands	460	76	56%	Age <65 years, refused, terminally ill, unable to follow instructions, LOS <48 h	ISAR-HP	CA
Fujita (2022) ³⁸	Australia	6771	84	52%	Age <75 years, <30 eFI-AH deficits assessed	eFI-AH, HFRS	CR/RC, RC
GMRC (2019) ³⁹	England	1507	80	53%	Age <65 years, CCU, end-of-life, logistics, missing 4AT or delirium status	9-point CFS	CA
Gilbert—local cohort (2018) ⁴⁰	England	569	80	56%	Age <75 years	HFRS	RC
Gilbert—national cohort (2018) ⁴⁰	England	1,013,590	84	57%	Age <75, non-emergency admission	HFRS	RC
Gilbert (2022) ⁴¹	France	1,042,234	85	60%	Age <75 years, non-emergency admission, missing socioeconomic data	HFRS	RC*
Hollinghurst (2021) ⁴²	Wales	126,600	79	53%	Age <65 years, non-emergency admission, no GP registration	HFRS, eFI	RC*, OC
Lim (2023) ⁴³	Singapore	366	74	56%	Age <65 years, ICU, transferred from other hospital, terminally ill, cognitive impairment/dementia, admitted for stroke or LOS <48 h	Frail-PPS, FAM, ISAR-HP	CA, CA, CA
Lujic (2022) ⁴⁴	Australia	257,535	83	57%	Age <75 years	HFRS	RC*
McAlister (2018) ⁴⁵	Canada	452,785	83	60%	Age <75 years, psychiatric or non-urgent admission	HFRS	RC*
Romero-Ortuno (2016a, 2016b) ^{46,47}	England	5899	84	56%	Age <75 years, elective admission	9-point CFS	CA*
Soong (2015) ¹⁸	England	50,540,141 ^a	NR	50%	Age <65 years	Author	RC
Soong (2019) ^{49,50}	Multinational	1,366,187	NR	54%	Age <75 years, missing data, LOS <2 days	DF-GFS	RC
Street (2021) ⁵¹	England	282,091 ^b	NR	NR	Age <75 years, non-emergency admission	HFRS	RC*
Timmons (2015) ⁵²	Ireland	598	80	51%	Age <70 years, refused, moribund on admission	SHARE-FI	CA
Wallis (2015) ⁵³	England	5764	85	56%	Age <75 years, non-emergency admission	9-point CFS	CA*
Warnier (2017, 2019) ^{54,55}	Netherlands	2581 ^c	79	51%	Age <70 years, not community-dwelling, not admitted to a regular ward, LOS <48 h, in hospital deaths (for outcomes data)	VMS, MFST-HP	CA, CA

Age = mean or median age in years. Author = Developed by author (Soong et al., 2015). CA = Clinically administered. CA* = Clinically administered, pre-morbid. CFS = Clinical Frailty Scale. CR = Clinical data from chart review. DF-GFS = Dr Foster Global Frailty Score. eFI = Electronic Frailty Index. eFI-AH = eFI Acute Hospital. FAM = Frailty Assessment Method. FRAIL = FRAIL questionnaire. Frail-PPS = Frail-Physical, Psychological and Social. HFRS = Hospital Frailty Risk Score. ISAR-HP = Identification of Seniors at Risk-Hospitalized Patients. MFST-HP = Maastricht frailty screening measure for hospitalised patients. N = Number of patients or admissions. NR = Not reported. OC = Other coded administrative data. RC = Retrospective coding data from the index admission acquired after discharge. RC* = Retrospective coding data from the index admission and previous admissions. SHARE-FI = Survey of Health, Ageing and Retirement in Europe-Frailty index. VMS (Veiligheids Management System) = Dutch National Safety Management Program. ^aA count of frailty syndromes was only reported for ~34,044,050 hospital admissions. ^bn = 282,091 patients with 674,615 hospital admissions. ^cn = 2691, but outcomes data were only reported for 2581 people who did not die in hospital so this number was used in analyses.

Table 1: Summary of included cohorts from studies of hospital-wide unplanned admissions (n = 17 cohorts).

cohorts. Moderate frailty was more common (range 10.0–50.7%) than severe frailty (range 2.2–39.6%; Fig. S5) in 18/22 cohorts reporting both ($p < 0.01$). Data were not pooled due to heterogeneity, which remained after stratification by study setting, frailty tool, and risk of bias ($p_{\text{het}} < 0.001$) and was not explained by average cohort age in meta-regression (y -intercept = -1.5402 , $\beta = 0.0174$; $R^2 = 2.02\%$; $p = 0.36$). The prevalence of moderate/severe frailty appeared similar between hospital-wide (range 16.1–66.9%; $N = 15$ cohorts; $n = 4,956,548$ admissions) and general medicine cohorts (range 14.3–79.6%; $N = 25$ cohorts; $n = 38,383$ admissions) (Fig. 2) and for most tools except for brief measures for which prevalence ranged from 52.2 to 72.6% ($N = 5$ cohorts; $n = 4530$) (Fig. S6).

Consistent associations with mortality, LOS and discharge to a location other than home were found across all levels of frailty. Moderate/severe frailty was associated with an increased risk of death up to one year

after hospital admission in 20/21 cohorts for which data were available ($n = 3,486,819$) but study estimates were not pooled due to heterogeneity in the absolute size of the effect ($p_{\text{het}} < 0.001$) (Fig. S7). However, when restricted to studies using clinically administered measures, heterogeneity was reduced ($p_{\text{het}} = 0.08$), with a pooled RR of 2.53 (95% CI 2.15–2.97; $n = 17,337$; $N = 11$; Fig. 3 and Fig. S8).

Increasing severity of frailty was associated with a stepwise increase in the risk of death up to one year after hospital admission for all six studies using clinically administered (CFS, brief and multidimensional) tools and four of six using retrospective frailty coding tools for which data were available (p for test of binomial proportions = 0.039) suggesting a dose response effect (Fig. 4, Figs. S9 and S10). Discrimination (c -statistic) also improved when ordinal instead of dichotomous frailty groups were used for both clinically administered and retrospective coding tools (Table S17).

Study	Location	N	Age	% Female	Exclusion criteria (summary)	Frailty tool	Type of tool
Anani (2020) ⁵⁶	Israel	980	72	43%	Age <55 or >85 years, no consent, advanced illness, bedridden, hospitalized <30 days prior, not admitted via ED	FRAIL	CA
Belga (2016) ⁵⁷⁻⁵⁹	Canada	495	64	51%	Age <18 years, life expectancy <3 months, admitted from long-term care/other hospital, out-of-province, poor English, moderate-severe CI	9-point CFS, Fried, HFRS	CA*, CA, RC*
Bonjour (2021) ⁶⁰	Switzerland	22,323	80	52%	Age <65 years	HFRS	RC
Buurman (2021) ⁶¹	Netherlands	639	78	54%	Age <65 years, no consent, too ill to participate, transferred from other ward, LOS or ward transfer <48 h, poor Dutch	ISAR-HP	CA
Dani (2017) ⁶²	England	710	83	59%	Age <70 years, LOS <48 h, poor English	FI	U
Eckart (2019) ⁶³	Switzerland	4957	82	51%	Age <75 years, non-urgent admission	HFRS	RC*
Eeles (2012) ⁶⁴	Wales	273	82	NR	Age <75 years, no consent, readmission	FI	U
El-Sharkaway (2005) ⁶⁵	England	200	82	47%	Age <65 years, terminal illness, life expectancy <3 months	CFS	CA
Evans (2014) ⁶⁶	USA	751	84	64%	Age <75 years	FI-CGA	CR
Fitriana (2021) ⁶⁷	Indonesia	266	NR	NR	Age <60 years, died in-hospital, transferred to other hospital	FRAIL	CA
Forti (2014) ⁶⁸	Italy	470	81	53%	Age <65 years, died, terminal illness, coma, LOS or transfer <48 h, refused, incomplete data	SOF-I	CA
Gregoravic (2016) ⁶⁹	Australia	170	82	49%	Age <65 years, transferred to specialty unit	9-point CFS	CA
Hernandez-Luis (2018) ⁷⁰	Spain	298	77	53%	Age <61 years, life expectancy <6 months, delirium or impaired consciousness persisting on day two of admission, not admitted via ED	7-point CFS, Fried	CA, CA
Hoogerduijn (2012) ⁷¹	Netherlands	492	78	56%	Age <65 years, too ill to participate	ISAR-HP	CA
Inouye (2003) ⁷²	USA	535	78	56%	Age <70 years, terminal condition, severe dementia, aphasia, coma, intubation, LOS <48 h, refused	BISEP	CA
Irina (2018) ⁷³	Israel	179	72	46%	Age <18 years, dementia/CI, ALT >40 IU/L, no follow-up, unable to complete FRAIL	FRAIL	CA
Juma (2016) ⁷⁴	Canada	75	81	64%	Age <65 years, palliative or life expectancy <7 days, <1 chronic health conditions and independent ambulation at baseline	9-point CFS	CA
Khandelwel (2012) ⁷⁵	India	250	66	38%	Age <60 years, mechanical ventilation/life support, comatose, neurologic deficits	Fried	CA
Laura (2022) ⁷⁶	Singapore	1507	76	51%	Age <65 years, live in shelter/nursing home, admitted via HDU, ICU or non-medical unit, no consent, died in hospital, transferred, discharged against medical advice	9-point CFS	CA
McCrow (2016) ⁷⁷	Australia	44	81	55%	Age <60 years, unstable CHF, severe CKD, nil by mouth on admission, expected LOS <24 h, poor English	7-point CFS	CA
Nardi (2019) ⁷⁸	Italy	541	80	51%	Age <40 years, <2 chronic diseases	FCS-1, MPI	CA, U
Noro (2011) ⁷⁹	Nordic countries	763	NR	65%	Age <75 years, CCU	MAPLe-AC	CA
Polidoro (2013) ⁸⁰	Italy	140	79	60%	NR	FI	U
Ramdass (2018) ⁸¹	USA	503	80	54%	Age <65 years, refused, died in-hospital, advanced dementia, transferred from other facility, admitted under observation, not living in community	REFS	CA
Rizza (2021) ⁸²	Italy	80	82	46%	Age <75 years, unable to complete CGA, no consent, end-stage cancer or CKD, connective tissue or inflammatory bowel diseases, sepsis	MPI	U
Rose (2014) ⁸³	Australia	133	87	61%	Age <70 years, unable to complete REFS, refused	REFS	CA
Sharma (2022) ⁸⁴	Australia	263	84	52%	Age <65 years, no consent, terminally ill	REFS	CA
Subramanian (2020) ⁸⁵	Australia	1118	NR	NR	Age <80 years, LOS <24 h	HFRS	RC

Age = mean or median age in years. ALT = Alanine transaminase. BISEP = Burden of Illness Score for Elderly Persons. CA = Clinically administered. CA* = Clinically administered, pre-morbid. CCU = Coronary Care Unit. CFS = Clinical Frailty Scale. CHF = Congestive heart failure. CI = Cognitive impairment. CKD = Chronic kidney disease. CR = Clinical data from chart review. ED = Emergency Department. FCS-1 = FADOI-COMPLIMED Score 1. FI = Frailty Index. FI-CGA = Frailty index-CGA. FRAIL = Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight questionnaire. Fried = Fried phenotype. HDU = High Dependency Unit. HFRS = Hospital Frailty Risk Score. ICU = Intensive Care Unit. N = Number of patients or admissions. ISAR-HP = Identification of Seniors at Risk-Hospitalized Patients. MAPLe-AC = Method for assigning Priority Levels-Acute Care. MPI = Multidimensional Prognostic Index. NR = Not reported. OC = Other coded administrative data. RC = Retrospective coding data from the index admission acquired after discharge. RC* = Retrospective coding data from the index admission and previous admissions. REFS = Reported Edmonton Frail Scale. SOF-1 = Study of Orthopaedic Fractures Index. U = Uncertain.

Table 2: Summary of included cohorts from studies of general medicine admissions (n = 28 cohorts).

Category	Domain	CFS		Brief				Fried				Deficit/ related				Multi-dimensional				Other				
		CSHA CFS	ISAR-HP ^a	VMS ^c	Fried	FAM ^b	FRAIL	SHARE-FI	SOF-1	HFRS ^d	eFI	eFI-AH ^e	FI	FI-CGA ^g	REFS ^h	MFST-HP ⁱ	MPI ^j	MAPLe-AC ^k	BISEP ^l	FCS-1 ^m	Frail-PPS ⁿ	DF-GFS ^o	Soong 2015 ^p	
Cognitive and sensory	Cognitive								x	x	x	x	x	x	x	x	x	x	x		x	x	x	x
	Delirium			x					x		x		x		x								x	x
	Vision/hearing								x	x	x	x	x		x									
	Communication								x		x		x											
Physical function	Function			x	x			x		x	x		x	x	x	x	x	x		x		x	x	x
	Balance or falls			x			x		x	x	x		x		x		x						x	x
	Mobility			x			x	x		x	x	x	x		x	x			x			x	x	x
	Slow walk					x																		
	Low activity					x		x																
	Weakness					x	x	x	x					x									x	
Weight and nutrition	Weight					x	x	x	x					x	x	x							x	x
	Nutrition or appetite			x				x		x				x	x		x							
Skin and excretory	Pressure sores									x	x	x	x			x	x	x			x		x	x
	Incontinence									x	x	x	x	x	x									x
Comorbidity and medications	Polypharmacy/medications									x	x	x	x	x	x	x	x	x						
	Comorbidity					x	x			x	x	x	x	x		x			x			x	x	
Psycho-social	Mood									x		x	x	x	x	x							x	x
	Social supports					x				x	x					x	x						x	
Other	Socio-demographic			x			x	x		x		x											x	x
	Clinical frailty scale	x																						

Legend

Cognitive or sensory

Physical function

Other physical

Psycho-social or other

CSHA CFS = CSHA Clinical Frailty Scale; ISAR-HP = Identification of Seniors at Risk-Hospitalized Patients; VMS (Veiligheids Management Systeem) = Dutch National Safety Management Program; FAM = Frailty Assessment Method; FRAIL = FRAIL questionnaire; SHARE-FI = SHARE-Frailty index; SOF-1 = Study of Orthopaedic Fractures Index; HFRS = Hospital Frailty Risk Score; eFI = Electronic Frailty Index; eFI-AH = eFI Acute Hospital; FI = Searle et al., 2008 Frailty Index; FI-CGA = Frailty Index-CGA; REFS = Reported Edmonton Frail Scale; MFST-HP = Maastricht frailty screening measure for hospitalised patients; MPI = Multidimensional Prognostic Index; MAPLe-AC = Method for assigning Priority Levels-Acute Care; BISEP = Burden of Illness Score for Elderly Persons; FCS-1 = FADOI-COMPLIMED Score 1; Frail-PPS = Frail-Physical, Psychological and Social; DF-GFS = Dr Foster Global Frailty Score; Soong et al., 2015 = Developed by author (Soong et al., 2015). ^aOriginally developed for use in hospital settings. ^bComplete information on these frailty tools was not available. ^cMultiple variations of the FI were included in this review.

Table 3: Summary of domains included in frailty measures.

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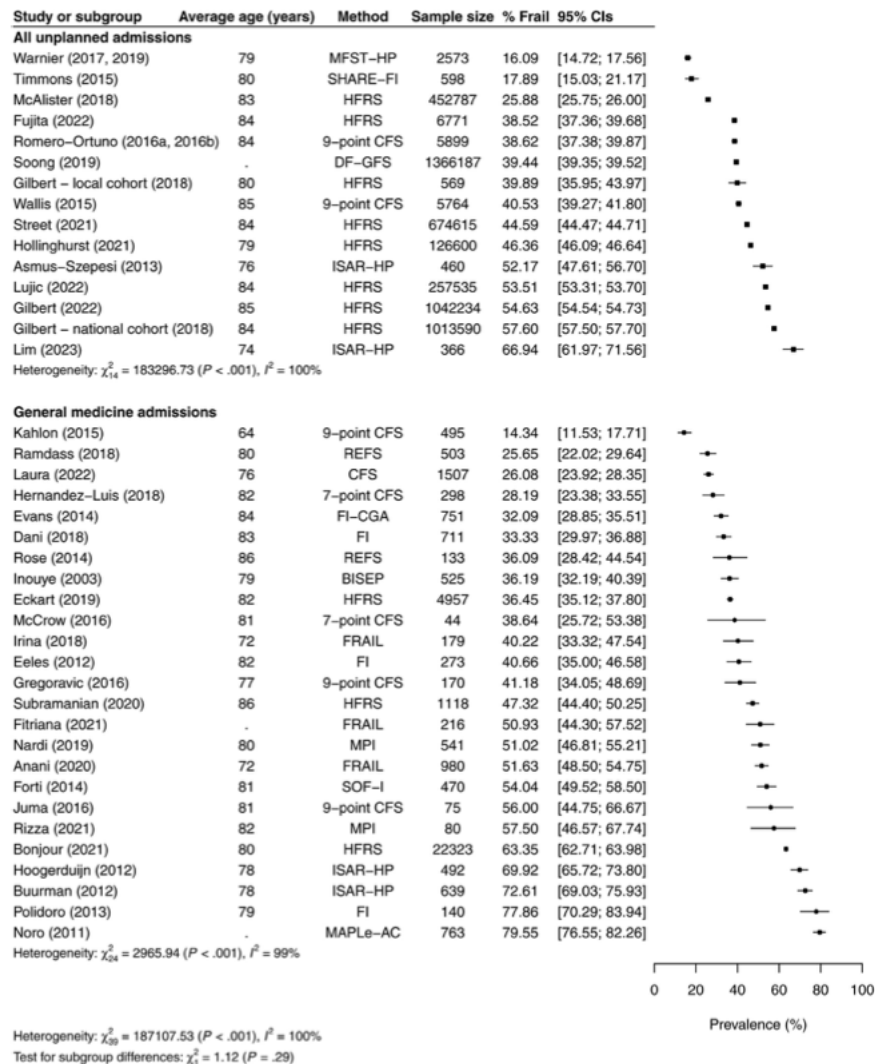


Fig. 2: Prevalence of moderate/severe frailty stratified by study setting. Forest plots of % prevalence with 95% CI of moderate/severe frailty stratified by hospital-wide unplanned vs general medicine admissions.

Meta-regression of frailty prevalence vs the log RR of death showed that frailty prevalence accounted for half of the variation in mortality risk (y-intercept = 1.0022; beta = -0.0069; $R^2 = 60.38\%$; $p = 0.04$) (Fig. S10). The addition of average cohort age to the model did not

account for additional heterogeneity (y-intercept = -1.099, $\beta_{\text{frailty}} = -0.0070$; $\beta_{\text{age}} = 0.0255$; $R^2 = 53.42\%$; $p_{\text{frailty}} = 0.05$; $p_{\text{age}} = 0.16$).

All ten studies examining the risk of a longer LOS by frailty status showed an increase in LOS for moderate/

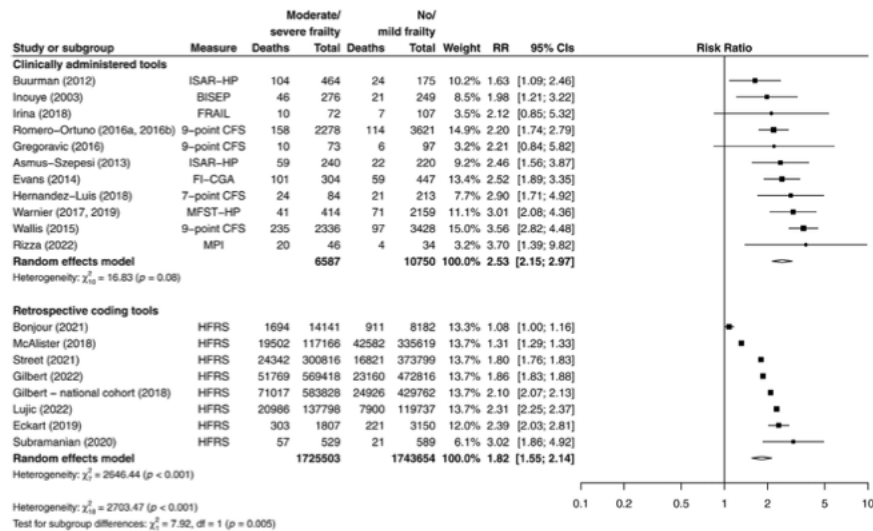


Fig. 3: Unadjusted relative risks of mortality for moderate/severe versus no/mild frailty by type of measure. Unadjusted relative risks of death with 95% CI for moderate/severe vs no/mild frailty in studies using clinically administered tools versus retrospectively applied tools using administrative diagnostic coding. To avoid artificially reducing the standard error, when multiple estimates were reported for the same cohort (i.e., using different frailty measures), the estimate judged to have the best validity (e.g., validated in a similar setting previously or based on included constructs) was included in the pooled estimate. Estimates not included in the pooled estimate included Warnier et al. (2017, 2019), which reported a RR for 30-day mortality of 8.97 (95% CI 4.71–17.10). Studies with no events in either group are not shown (i.e., Juma 2016 and Khandelwel 2012), but are included in Fig. 58.

severe frailty ($n = 3,454,879$ admissions). Relative risk for a LOS of >8 –10 days ranged from 2.14 to 3.04 for six cohorts ($n = 3,445,716$) inclusive of inpatient deaths (Fig. 5A), with increasing severity of frailty associated with greater risks in all studies (Fig. 6A). The ratio of means for LOS in days ranged from 1.19 to 2.14 for moderate/severe frailty ($n = 1,051,397$ admissions; $N = 5$ cohorts; Fig. 5A). Sensitivity analyses where inpatient deaths were censored showed similar results (Fig. S11A).

All four studies examining discharge to a destination other than home in participants alive at discharge ($n = 27,986$) also reported increased risks for participants with moderate/severe frailty. The relative risk for discharge to a destination other than home ranged from 1.97 to 2.82 (Fig. 5B), with increasing severity of frailty associated with greater risks in 3/3 studies (Fig. 6B). Similar results were obtained using the denominators reported by the authors (e.g., including patients who died during admission, Fig. S11B).

The risk of 30-day readmissions in moderate/severe frailty showed conflicting findings with variation in the direction of effect in participants alive at discharge ($n = 3,055,748$; $N = 12$ cohorts). RRs ranged from 0.83 to 1.94 with 4/12 cohorts showing a reduced or unchanged risk of readmission, not explained by stratification by study setting (Fig. S12) or clinically administered vs retrospective coding tools (Fig. 5C). Similar results were obtained using the denominators reported by the authors (e.g., including patients who died during admission, Fig. S11C).

Regarding adjusted analyses for outcomes, five individual studies adjusted for a minimum of age, sex and comorbidity and also reported unadjusted estimates (Table S15). Odds ratios (adjusted relative risks were not available) were a mean of 15% lower than crude estimates for moderate frailty and 20% lower for severe frailty (Table S16). Eleven studies variably adjusted for multiple covariates including multimorbidity (and did not report unadjusted estimates),

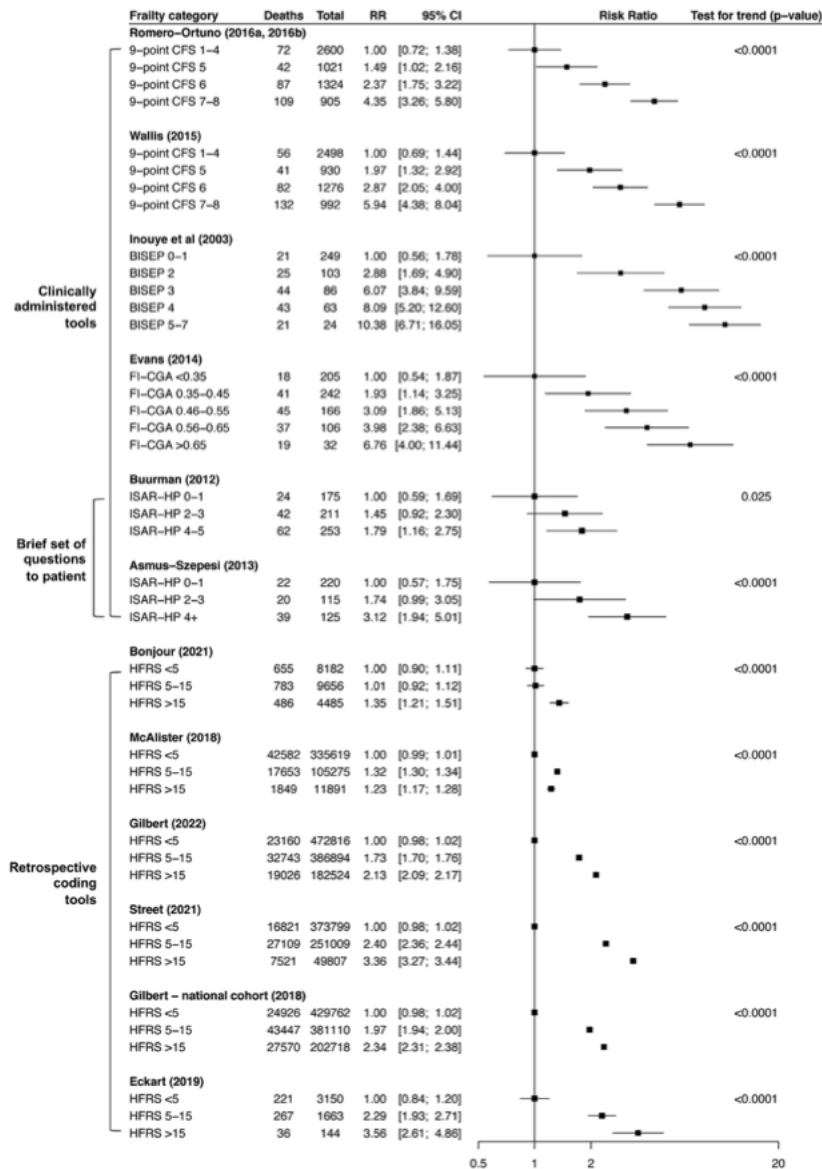


Fig. 4: Unadjusted relative risks for mortality up to one year after discharge across ordinal categories of degree of frailty and two-sided Cochran-Armitage test for trend. Unadjusted relative risks with 95% CI for death up to one year after discharge by degree of frailty. Studies with >5 events per cell were included. Romero-Ortuno et al. (2016a, 2016b) only reported data for people with CFS 1-8. Dani et al. (2018) (not shown) reported data on mortality up to 3 years and found 48% mortality among people in the first FI tertile, 51% in the second and 60% in the third ($n = \sim 237$ per group). P-values for the two-sided Cochran Armitage test for trend are shown.

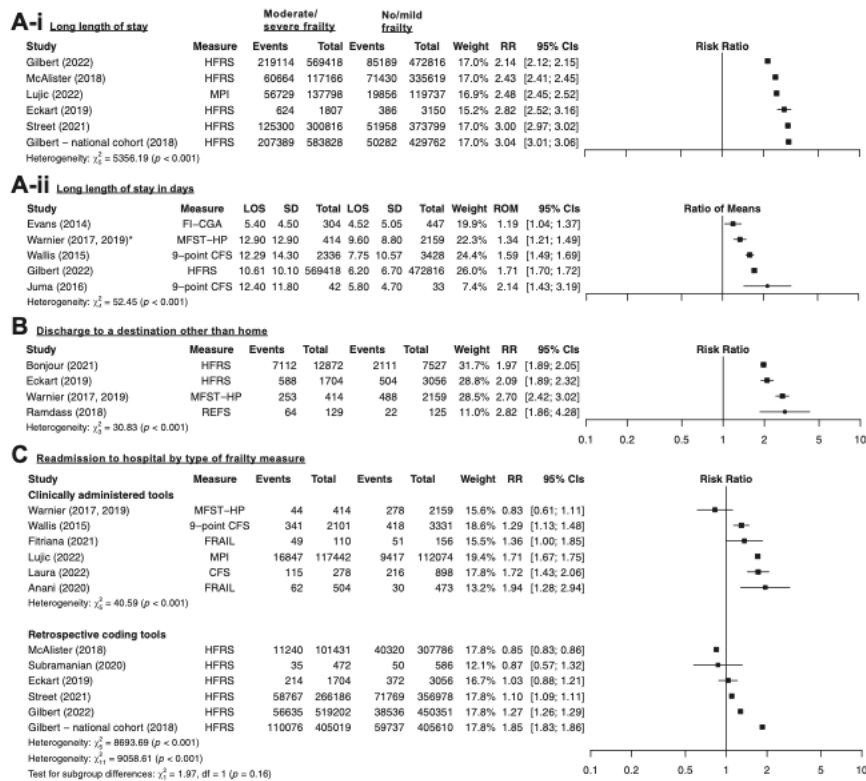


Fig. 5: Unadjusted relative risks of moderate/severe vs no/mild frailty for (A) LOS >8–10 days and ratio of means for LOS in days, (B) discharge to location other than home in survivors and (C) 30-day readmissions stratified by type of frailty measure in survivors. Unadjusted relative risks with 95% CI of moderate/severe vs no/mild frailty for (A-i) LOS >8–10 days with (A-ii) ratio of means for LOS in days, (B) discharge to location other than home (i.e., nursing home or post-acute care facility) in survivors and (C) 30-day readmissions stratified by type of frailty. For LOS, Forti (2014) was not shown because it excluded in-hospital deaths (relative risk of 1.35, 95% CI 1.11–1.64). In-hospital deaths were estimated for Gilbert (2018) by multiplying the number of 30-day deaths after the date of admission (including in-hospital deaths) for each frailty category by the % of overall deaths that occurred in hospital and McAlister (2018) by using the n and % of survivors with readmissions and may be subject to rounding errors. In-hospital deaths were assumed to be absent from Anani (2020).

but nevertheless found clinically important associations of frailty with death. Risk of death remained significant after adjustment/stratification for illness severity on admission (i.e., NEWS, MEWS) in two studies.^{47,43} Additional adjusted estimates are reported in the supplementary material (Table S15), but the majority could not be pooled due to differences in reporting and statistical heterogeneity (Figs. S13 and S14).

Discussion

Frailty was common in the older acute unselected hospital population with a median prevalence of around 40%, although estimates varied. Despite the wide variation in prevalence, moderate to severe frailty remained an independent predictor of mortality up to one-year, longer LOS and discharge to a care home, although the evidence on readmission risk was conflicting. More severe frailty associated with worse outcomes,

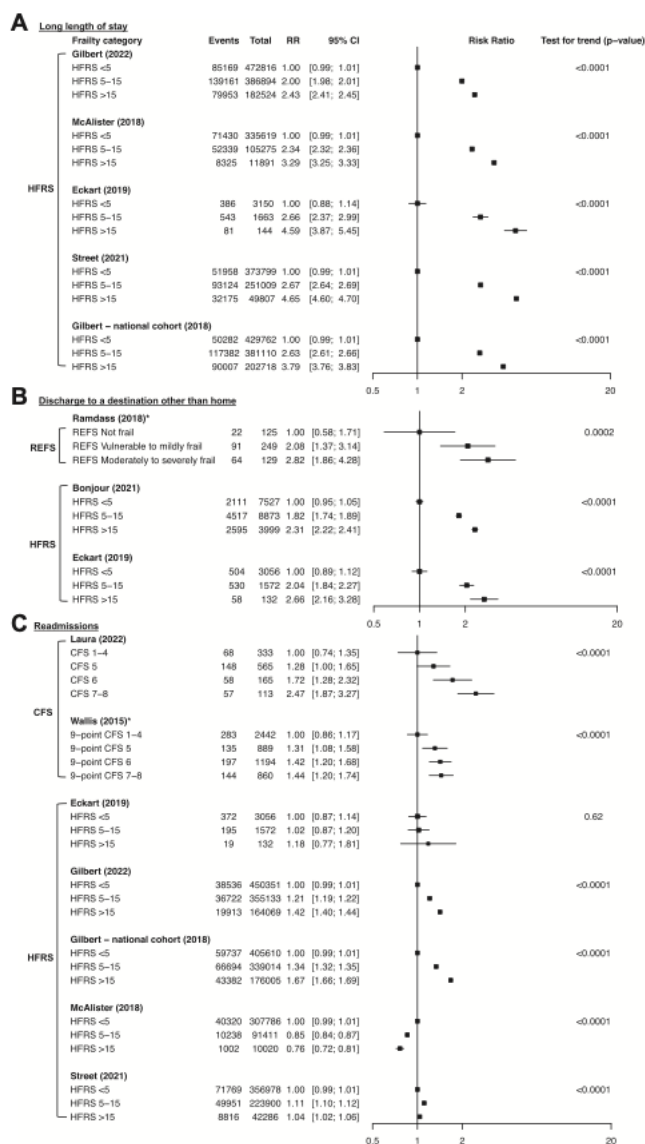


Fig. 6: Unadjusted relative risks across ordinal categories of degree of frailty and two-sided Cochran-Armitage test for trend for (A) long LOS, (B) discharge destination other than home in survivors and (C) readmissions in survivors. Unadjusted relative risks with 95% CI by degree of frailty for (A) long LOS, (B) discharge destination other than home in survivors and (C) readmissions in survivors. Studies with >5 events per cell were included. P-values for the two-sided Cochran-Armitage for trend (increasing or decreasing) are shown.

suggesting a dose response effect. Associations were strongest and most consistent across studies using clinically administered tools, but variation in measured frailty prevalence also accounted for a large proportion of statistical heterogeneity in mortality risk ratios.

Variation in frailty prevalence could not be attributed to average age, setting or frailty measure. Differences in eligibility criteria, such as the need to be able to complete questionnaires or give consent will have impacted case-mix and probably frailty prevalence. The proportion of participants who were care home residents or had cognitive impairment varied widely, although definitions differed. Not all frailty measures included cognition (or delirium, a marker of cognitive frailty), potentially resulting in underestimation of prevalence.⁸⁹ Further, regional differences in demographics, health and social services may have had an impact including number of hospital beds, and access to ambulatory emergency care which may reduce inpatient admissions preferentially amongst younger, fitter people.^{90,91}

Differences in the administration/operationalisation of frailty measures might also contribute to heterogeneity in measured prevalence. For example, retrospective, administrative data-based tools depend on the accuracy of diagnostic coding, which is variable and known to be poor for frailty syndromes.⁹² However, associations between frailty and poor outcomes held irrespective of the frailty tool administered, indicating that all measures identified a group at risk with different tools probably capturing different but overlapping groups.³⁷ Studies with higher frailty prevalence generally reported weaker associations with mortality possibly because these studies operationalised frailty in a more inclusive way, identifying some individuals as frail who would have been classed as fit in other studies.

Mortality risk ratios for clinically administered frailty tools appeared quantitatively similar. However, mortality risk ratios for retrospective coding tools varied widely and accuracy of administrative coded data was again, likely a contributing factor. More severe frailty was consistently associated with worse outcomes, supporting the construct of 'frailty' as a spectrum rather than a dichotomous state. Future studies may therefore reasonably assume a linear relationship between frailty and mortality as recently described specifically for frailty indices.⁹³ Associations between frailty and mortality remained significant after adjustment for multimorbidity and also for severe illness where reported, both factors being prevalent in acute hospital settings.⁹⁴ We also observed a consistent direction of relationship between frailty and LOS and discharge destination, again with a stepwise increase in effect size although the size of the effect varied, possibly because these outcomes are dependent on healthcare system factors.^{95,96}

Comparing our findings with previous studies, frailty prevalence was two-to-four fold higher in the acute hospital setting than in population-based studies

(consistent with frailty being a risk factor for hospitalization)^{91,97} and about 50% higher than in the acute surgical setting.^{98,99} The median prevalence in our study was lower (~40% vs 51%) than in general medicine studies using non-validated as well as validated frailty tools¹⁵ but similar to findings in geriatric medicine/unspecified acute hospital settings (25–97%).¹³ Our findings on mortality are broadly consistent with the greater risk reported in specialist hospital services (2–4 fold increase) and in population-based samples (2-fold increase).^{15,17–19,21,23,100,101} Specialty-specific studies also found associations with LOS and discharge destination.^{21,23,100} Stepwise increases in risk of death have been reported for 'pre-frailty' (two-fold increase compared no frailty) and frailty (3.5-fold increase).¹⁶

Strengths of our review include a comprehensive literature search with detailed synthesis of evidence from a large number of unselected cohorts enhancing generalizability and filling an important evidence gap. We compared clinically administered and retrospective coding frailty tools, examined degrees of frailty and accounted for a proportion of statistical variation. Our review has limitations. First, associations between frailty and readmission risk were inconsistent, and not explained by setting, tool used or the competing risk of death where reported.⁴⁵ This finding was not unexpected, however, because a broad range of healthcare system factors are known to impact readmission risk.^{102–104} Second, we could not account for case-mix factors in prevalence estimates using meta-regression or subgroup analysis because of limitations in reporting. Data on cognition were limited, so its impact on outcomes could not be evaluated despite the implications for patient care.^{42,64} Third, categorisations of moderate and severe frailty were based on accepted cut-offs and author's judgement, but were approximations. Fourth, the applicability of our results to people <65 years is uncertain since they were excluded from the majority of studies.

Our findings provide evidence to support robust implementation of frailty screening in acute hospitals to inform decision making and the targeting of interventions/CGA (see Box 2).¹² Frailty should inform clinical care through an understanding of likely outcomes but should not be used in isolation to direct clinical decisions. Importantly, future guidelines, policy documents and health economic analyses should also differentiate between varying degrees of frailty. More specifically, our findings support current guidance recommending the CFS as a first line screening tool since it is pragmatic but nevertheless identifies a group at-risk as reliably as more lengthy/complex tools.⁶ However, we found variations in CFS operationalisation in the acute setting, supporting the need for training.¹³ Also, because the CFS is a global frailty score only, further assessment is required to identify frailty domains and fully individualise care. Other clinically administered tools

Box 2.

How data on the prevalence, measurement tools used, and outcomes of frailty in the acute setting can inform policy, planning and care.

Policy

- Staffing levels and skill mix calculations
- Frailty training requirements
- Resourcing and service design

Service planning

- Development of frailty care pathways
- Need for Comprehensive Geriatric Assessment and multidisciplinary team care
- Case-mix evaluation

Clinical care

- Frailty measures as communication tools for handover and transfers
- Individualisation of acute treatment according to frailty status
- Risk-stratification for further needs assessment or specialised frailty care
- Enhanced discharge planning and strengthening of post-discharge care
- Improved patient and caregiver experience including counselling about prognosis
 - Advanced care planning and power of attorney
 - Readmission avoidance strategies

appeared impractical for first line routine use and despite their length, most did not include valid measures of cognition or social risk factors, which are both important drivers of admission.^{91,92,105–108}

Several retrospective tools based on administrative data (primarily the HFRS) were identified, which are useful for policy or research purposes. Importantly, retrospective coding frailty tools may incorporate frailty syndromes occurring as complications of admission (e.g., falls, pressure sores) in contrast to prospective clinical tools. In case-mix adjustment for mortality and other acute hospital outcomes, retrospectively acquired frailty measures may therefore conceal preventable safety and quality issues.^{109–111}

In conclusion, frailty is prevalent in older people with acute, non-elective hospital admissions and is an important independent prognostic factor, with a dose response effect. Our findings support robust implementation of hospital-wide frailty screening in line with current guidance.^{6,8} Challenges remain around the large scale implementation of CGA which is time consuming and requires multi-disciplinary input. Future studies may explore the use of real-time rich clinical information in hospital electronic health records (i.e., beyond just retrospective diagnostic codes) to identify and monitor frailty and patients' domain-specific needs, prior to discussions with patients and their families, to reduce the burden to patients and staff. Such a "streamlined CGA" could also be used by (virtual) frailty teams to provide individualised recommendations, goal-setting and decision-making in partnership with patients and carers. These methods should also

differentiate between varying degrees of frailty and could enhance the quality of routinely acquired frailty data available for policy and research.

Contributors

ELB was responsible for the protocol, data acquisition (i.e., running searches, screening articles, extracting data, risk of bias assessment), analysis, interpretation and drafting the manuscript. JMG contributed to the protocol, screened articles and reviewed the final list of studies for inclusion. PMR contributed to the interpretation of data and drafting of the manuscript. SS provided supervision and contributed to study design, development of the protocol, approval of the final list of studies for inclusion, the interpretation of data, and drafting of the manuscript. STP provided supervision and was responsible for study conception, design, development of the protocol, approval of the final list of studies for inclusion, data acquisition (i.e., risk of bias assessment) and interpretation, and drafting of the manuscript. The underlying data was accessed and verified by ELB and STP. All authors (ELB, JMG, PM, SS, STP) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data extracted from studies will be made available upon reasonable request by email to sarah.pendlebury@ndcn.ox.ac.uk.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2023.101947>.

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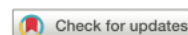
BMJ Open Protocol for the Development and Analysis of the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records (ORCHARD-EPR)

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ABSTRACT

Background Hospital electronic patient records (EPRs) offer the opportunity to exploit large-scale routinely acquired data at relatively low cost and without selection. EPRs provide considerably richer data, and in real-time, than retrospective administrative data sets in which clinical complexity is often poorly captured. With population ageing, a wide range of hospital specialities now manage older people with multimorbidity, frailty and associated poor outcomes. We, therefore, set-up the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records (ORCHARD-EPR) to facilitate clinically meaningful research in older hospital patients, including algorithm development, and to aid medical decision-making, implementation of guidelines, and inform policy.

Methods and analysis ORCHARD-EPR uses routinely acquired individual patient data on all patients aged ≥65 years with unplanned admission or Same Day Emergency Care unit attendance at four acute general hospitals serving a population of >800 000 (Oxfordshire, UK) with planned extension to the neighbouring Berkshire regional hospitals (>1 000 000). Data fields include diagnosis, comorbidities, nursing risk assessments, frailty, observations, illness acuity, laboratory tests and brain scan images. Importantly, ORCHARD-EPR contains the results from mandatory hospital-wide cognitive screening (≥70 years) comprising the 10-point Abbreviated-Mental-Test and dementia and delirium diagnosis (Confusion Assessment Method—CAM). Outcomes include length of stay, delayed transfers of care, discharge destination, readmissions and death. The rich multimodal data are further enhanced by linkage to secondary care electronic mental health records. Selection of appropriate subgroups or linkage to existing cohorts allows disease-specific studies. Over 200 000 patient episodes are included to date with data collection ongoing of which 129 248 are admissions with a length of stay ≥1 day in 64 641 unique patients.

Ethics and dissemination ORCHARD-EPR is approved by the South Central Oxford C Research Ethics Committee (ref: 23/SC/0258). Results will be widely disseminated

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ ORCHARD-EPR overcomes the limitations of prospective cohorts, which are subjected to resource constraints, recruitment challenges and selection bias (eg, from the requirement for research consent) through providing multimodal rich clinical data at scale.
- ⇒ ORCHARD-EPR has complete coverage of the target population without selection and electronic follow-up, including through linkage to mental health records and brain imaging (CT, MRI, other) not routinely available in existing administrative data sets.
- ⇒ ORCHARD-EPR exploits the successful regional implementation of routine on-admission cognitive screening, which is often poorly captured adding further value to the rich phenotypic data collected as part of routine clinical care.
- ⇒ ORCHARD-EPR is a two-centre UK study and may not be generalisable to other populations, but the combined Oxfordshire and Berkshire populations are representative of England as a whole.
- ⇒ Free text entries including medical clerking and allied health assessments are currently unavailable for analysis, although information from these entries could eventually be extracted using artificial intelligence tools.

through peer-reviewed publications and presentations at conferences, and regional meetings to improve hospital data quality and clinical services.

INTRODUCTION

The advent of hospital electronic patient records (EPRs) offers the opportunity to exploit large-scale routinely acquired clinical data to improve patient care. Such data offer several advantages. First, they can be obtained at scale without additional burden to patients or staff and at relatively low cost.

Second, the use of EPR data (with the appropriate governance and ethical approvals) allows the entire hospital population to be studied without the unavoidable selection bias incurred in requiring individual consent for research assessments.¹ This is particularly advantageous in studies on older, frail and cognitively impaired patients in whom capacity to consent to research may be lacking, or ability to tolerate research assessments may be limited.^{2 3} Third, obtaining data from the EPRs provides a considerably richer source of data than is currently available from hospital administrative data sets that are comprised largely of ICD-10-coded diagnoses, which have limitations especially in capturing complexity including frailty syndromes.^{2 4 5} Fourth, EPRs provide real-time information allowing implementation of algorithms to identify those at high risk (eg, of delirium).⁶

The case-mix of general hospitals is changing across high-income countries in line with population ageing with implications for a wide range of hospital specialties.⁷⁻⁹ Older people aged ≥65 years occupy the majority of hospital bed-days and many have complex conditions.¹⁰ Up to a half have a cognitive disorder (eg, delirium, dementia) and around 40% are physically frail with an increased vulnerability to stressors such as a sudden decline in health.^{2 11-16} Both cognitive and physical frailty are associated with a broad range of adverse health and social outcomes^{2 11 13 15 16} and improving acute hospital care for older patients is a priority as reflected in policy documents and guidelines internationally.¹⁷⁻²² Therefore, hospital data systems need to be established to identify frail patients across the hospital and across specialties, discriminate cognitive from physical frailty and ideally, the frailty domains affected given the implications for care.^{2 11 17-22} In addition, collection of detailed clinical data including on diagnosis, comorbidities and illness acuity will aid understanding of the prognostic value of frailty across a range of acute hospital specialties and settings, improve risk stratification, inform secondary and tertiary prevention measures and provide data for research.^{2 11 20}

In this protocol, we describe the methods underpinning the Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database—Electronic Patient Records (ORCHARD-EPR), which uses routinely acquired rich multimodal electronic individual patient data including routine cognitive/delirium screening, nursing risk assessments (falls risk, nutrition, pressure sore risk), observations, laboratory tests and brain imaging. ORCHARD-EPR will facilitate healthcare innovation and medical decision-making including the development/validation of risk prediction algorithms including for delirium and future dementia. ORCHARD-EPR will also enable key evidence gaps to be addressed around cognitive and physical frailty in the hospital setting as summarised in **box 1** overcoming the limitations in existing studies from small selected samples (prospective studies) or reliance on hospital diagnostic ICD-10 coding (large retrospective studies).^{4 5}

Box 1 Knowledge gaps to be addressed using ORCHARD-EPR

Cognitive frailty

Prevalence of all-cause and subtypes of cognitive frailty in the acute hospital population overall and by age, sex and specialty.

Accuracy of ICD-10 coding for cognitive diagnoses.

Outcomes of all-cause cognitive frailty and by subtype (adjusted for confounding).

Overall frailty

Prevalence in the acute hospital population overall and by age, sex and specialty including same day emergency care (SDEC) as measured by different frailty tools (eg, Clinical Frailty Scale, Hospital Frailty Risk Score, Dr Foster score, frailty aggregate score).

Prevalence of frailty markers identified from nursing assessments (eg, at risk of falls, pressure sores and malnutrition).

Time trends in frailty prevalence in in-patient vs SDEC populations.

Outcomes of frailty (adjusted for comorbidity burden, illness severity, comorbid dementia, care home residence).

Prevalence and prognosis in key subgroups, that is, care home residents, comorbid dementia/delirium, severe illness.

Healthcare innovation

Development of predictive algorithms for delirium, and for dementia on follow-up.

Use of routinely acquired brain imaging for the development of AI tools to quantify 'brain frailty' including atrophy and small-vessel disease and old stroke lesions to aid dementia subtyping and risk stratification.

Real-time tracking of frail individuals through the hospital system to inform service delivery and design.

Development of a real-time, 'streamlined Comprehensive Geriatric Assessment' to identify care needs using routinely acquired electronic patient record data.

Aims and objectives

The primary aim of ORCHARD-EPR is to use individual patient EPRs to study the prevalence, complications and outcomes of cognitive and physical frailty in a large unselected, consecutive cohort of adults with unplanned hospital admission or emergency ambulatory care assessment.

The main objectives are to:

1. Estimate the hospital-wide prevalence of cognitive frailty (ie, delirium, dementia, delirium superimposed on dementia, low cognitive test score) by age, sex and specialty.
2. Estimate the prevalence of physical/global frailty using a variety of measures, including global scores (Clinical Frailty Scale-CFS),²³ and administrative diagnostic coding (ICD-10) data (Hospital Frailty Risk Score (HFRS),¹⁶ coded frailty syndromes)²⁴ by age, sex and specialty.
3. Determine the associations of cognitive and physical frailty with outcomes (death, length of stay, readmission, increased care needs at discharge) adjusted for demographics, deprivation, multimorbidity, illness severity and other putative effect modifiers.^{2 11}
4. Develop and integrate within the EPR a pragmatic tool (EPR-Comprehensive Geriatric Assessment (eCGA)) to identify frailty domains using routinely acquired

- clinical EPR hospital data to target frailty interventions in real time.
5. Provide a rich research resource for further studies, including disease-specific studies (eg, on stroke), time trends in frailty prevalence and outcomes, investigation of risk factors for cognitive frailty (eg, neuroimaging markers and vascular disease), the development and validation of diagnostic and risk prediction tools (eg, for delirium and for dementia on follow-up) and health economics studies.

METHODS AND ANALYSIS

Study design and setting

The ORCHARD-EPR database was established by collecting pseudo-anonymised routinely acquired data extracted from the Oxford University Hospitals National Health Service (NHS) Foundation Trust (OUHFT) Cerner Millennium EPR (2015 onwards). Adult patients with unplanned admission or same day emergency care (SDEC) are included. The OUHFT is a large teaching and research trust consisting of four hospitals (John Radcliffe Hospital, Nuffield Orthopaedic Centre and Churchill Hospital in Oxford, and the Horton General Hospital in Banbury) providing all acute hospital care in Oxfordshire, UK with a catchment area of >800 000 people. There are short-stay nursing home beds for those requiring further assessment prior to discharge back to the community, and some specialty services to neighbouring counties.²⁵ The Oxfordshire population is older than the England average, all levels of deprivation are represented but with a lower average deprivation, and the urban/rural mix is in line with England as a whole.²⁶ ORCHARD-EPR is approved by the South Central Oxford C Research Ethics Committee (REC reference: 23/SC/0258). From 2024 onwards, we plan to extend ORCHARD-EPR to include the Royal Berkshire NHS Foundation Trust, with a larger catchment population (~1 million), subject to the necessary agreements. The combined Oxfordshire and Berkshire population is well matched to the overall English population demographic characteristics.

Regulatory approvals

Extensive work (by SP, 2017-current) to meet regulatory requirements and overcome logistical barriers was required to set up ORCHARD-EPR. This has included:

- ▶ Initial OUHFT audit approval and registration to obtain the EPR data from the OUHFT Information team (AJ).
- ▶ Assigning of a unique study number (ORCHARD-EPR studyID) generated using an algorithm by the Information team (AJ) to enable deidentification of ORCHARD-EPR data.
- ▶ Extensive iterative checking of ORCHARD-EPR data accuracy in collaboration with the OUHFT Information team (SP, AJ).

- ▶ Working with the OUHFT clinical coding team (SP) to improve ICD-10 coding for cognitive frailty including delirium.⁴
- ▶ Data Protection Impact Assessment and Caldicott guardian sign-off for use of OUHFT EPR and brain imaging data and transfer of deidentified data to the University of Oxford servers.
- ▶ Ethics approval to use ORCHARD-EPR for research purposes with opt-out publicised on the OUHFT website and via posters.
- ▶ Approval from the Clinical Records Interactive Search (CRIS) oversight group for use of Oxford Health NHS Foundation Trust CRIS, Powered by Akrivia Health, mental health data in linkage to ORCHARD-EPR OUHFT data.²⁷
- ▶ Data transfer agreement between Oxford Health NHS Foundation Trust and OUHFT for transfer of pseudonymised mental health CRIS data.
- ▶ Collaboration agreement between University of Oxford and OUHFT to cover use of OUHFT data in research that might generate intellectual property.
- ▶ Development of a pipeline to automatically deidentify, link to study ID and transfer brain scan images from the OUHFT Picture Archiving and Communication System to the University of Oxford servers (JD).
- ▶ Currently, the ethics approval for this study does not allow access to data to researchers outside the University of Oxford/OUHFT but widening access to researchers from other institutions is currently being explored.

Participants and eligibility

The EPR was introduced to OUHFT in 2015, but complete coverage of all clinical areas and for all functionalities was not achieved until 2017. ORCHARD-EPR contains data on eligible patients from January 2015 with data added every 6 months and includes data covering the period of the COVID-19 pandemic and beyond.

Inclusion

OUHFT in-patients and acute ambulatory care (SDEC) patients ≥65 years as well as patients <65 years with a completed cognitive screen (see later), and adult out patients with conditions increasing the risk of cognitive or physical frailty in which data have been collected as part of OUHFT-approved audits (see online supplemental file 1). Individual consent is not obtained for inclusion of pseudonymised data in the database although patients may opt out as stated earlier.

Exclusion

Adult patients <65 years without a completed cognitive screen or test or otherwise at risk of cognitive or physical frailty.

Study size

Over 200 000 unplanned hospital admission episodes and ambulatory care assessments are included in ORCHARD-EPR (2015-to date, with data collection

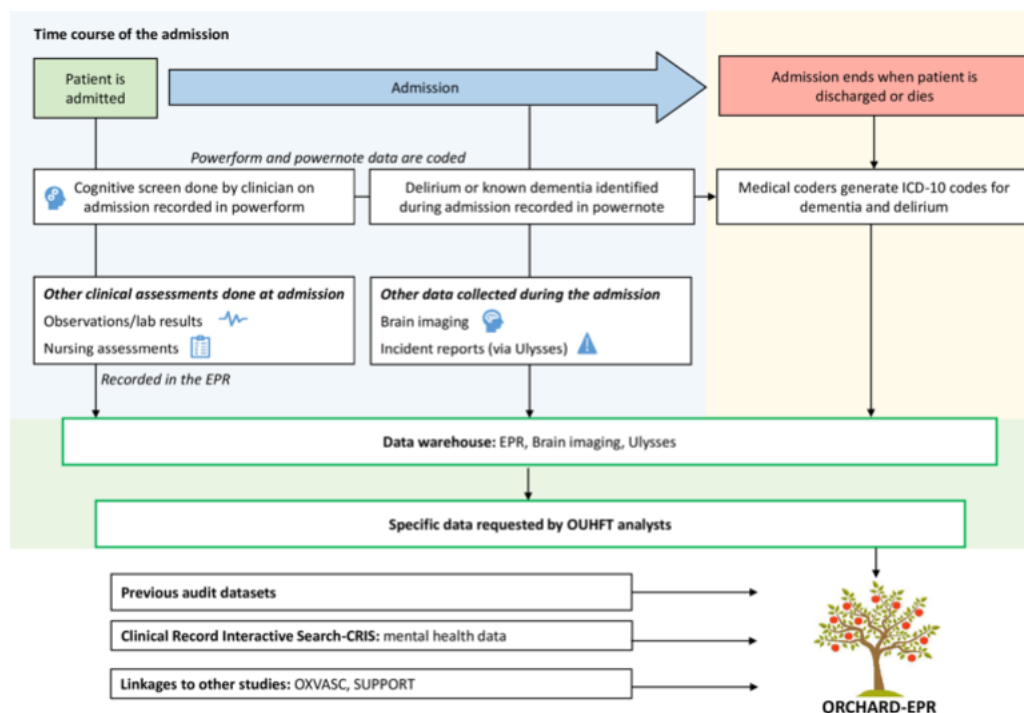


Figure 1 ORCHARD-EPR—origin of data and creation of the database showing inclusion of clinical EPR data, observations and laboratory tests, brain imaging, secondary mental health diagnoses and relevant audits. Additionally, shows how cognitive data are ascertained in ORCHARD-EPR using the cognitive screening results together with administrative diagnostic (ICD-10) coding. CRIS, Clinical Records Interactive Search; ORCHARD-EPR, Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database—Electronic Patient Records; OUHFT, Oxford University Hospitals NHS Foundation Trust; OXVASC, Oxford Vascular Study; SUPPORT, Prospective Cohort Study of Proactive Supportive Care for Hospitalised Adults with Life-limiting Conditions: Evaluation of Patient Outcomes and Hospital Costs.

ongoing). Of these, 129 248 are inpatient admissions with a length of stay ≥ 1 day in 64 641 unique patients.

Study procedures

All ORCHARD-EPR data are obtained from assessments completed by medical, nursing and allied health professional or administrative staff as part of routine patient care. Data are obtained from the EPR via the OUHFT information team or manually (>100 data fields in total, figure 1). The database contains data from EPR powerforms (ie, electronic proformas from which structured data can be extracted) but not powernotes (ie, free-text entries by clinicians, see online supplemental file 1). Individual patient records are assigned an ORCHARD-EPR study number by the Information Team and patient identifiers (eg, name, date of birth, hospital MRN, NHS number, etc) are removed before transfer to the database.

Table 1 summarises the data items collected in ORCHARD-EPR and whether they are available at multiple time points over an admission, and how these compare with the data available from UK-wide Hospital

Episode Statistics-HES, which are similar to most international hospital administrative data sets. Key data fields extracted include demographics, postcodes, treating specialty, diagnoses, cognition, nutrition, falls and pressure sore risk, observations, illness severity, laboratory analyses and outcomes including length of stay. Importantly, ORCHARD-EPR contains extensive cognitive phenotyping data obtained through embedded hospital routine cognitive screening and linkage to mental health data as well as brain imaging.

Cognitive screen

ORCHARD-EPR exploits previous extensive work (2010 onwards) led by SP to develop, validate and implement routine cognitive screening including for delirium for at-risk OUHFT patients (figure 2 and see below).^{4 5 15 28–33} Since 2013, OUHFT has mandated that all patients with unplanned admission ≥ 70 years of age or younger patients at high-risk (eg, alcohol excess, multiple sclerosis, stroke history) are administered the validated cognitive screen on admission.^{4 15} This was initially delivered as part of

Table 1 Data items available in ORCHARD-EPR, including at multiple time-points during admission, with comparison of availability in UK Hospital Episode Statistics (HES) administrative data predominantly composed of ICD-10 diagnostic codes

Category	ORCHARD-EPR variable	Available at multiple time-points in ORCHARD-EPR	Availability in administrative datasets (eg, HES)
Demographic	Age, gender, ethnicity, postcode, deprivation	-	✓
Admission	Presenting complaint‡	-	x
	Method (ie, GP, ED), source	-	✓
Vitals	HR, BP, RR, SpO ₂ , tympanic temp, AVPU	✓	x
Illness severity	NEWS, SIRS	✓	x
Cognitive screen	AMTS, MMSE, MoCA, ACE	✓	x
	Reason for cognitive untestability	✓	x
	Delirium diagnosis	✓	Limited*
	Delirium on admission (prevalent) and arising de novo during admission (incident)‡	✓	x
	Pre-admission dementia diagnosis	-	Limited*
Multimorbidity	Charlson, Elixhauser indices	-	✓
Frailty	HFRS	-	✓
	Clinician's impression of frailty‡	-	x
	Dr Foster Global Frailty Score	-	✓
	Frailty Markers, including vision and hearing	-	Limited
	Long-term catheter (medical/nursing notes)‡	✓	x
	Catheter insertion during admission (medical/nursing notes)‡	✓	x
Functional status	Nursing risk assessments	✓	x
Nutrition	Malnutrition universal screening tool (MUST)	✓	x
Pressure sore risk	Braden scale (pressure sore risk), including sensory perception, moisture, activity, mobility, nutrition, friction and shear	✓	x
Falls risk factors (based on NICE)	Orthostatic hypotension, appropriate footwear, safe walking unaided/with an aid, urinary incontinence or urgency, vision problems, fall history, fear of falling, environment (hazards, lighting, call bell), confusion/agitation/cognitive impairment	✓	x
Mental capacity	Documented mental capacity assessment yes/no, decision assessed,‡ outcome of decision‡	✓	x
Course in hospital	Ward	✓	x
	Specialty (ie, treatment function, main specialty)	-	✓
	Procedures, including radiologic imaging	✓	✓
	Incidents in hospital	✓	x
Diagnoses	ICD-10 codes	-	✓
	Clinician working diagnosis and final diagnosis‡	-	x
Disposition	Residence‡	-	x
	Care needs/care package‡	-	x
	Increased care needs at discharge: new care home, rehabilitation bed, intermediate care, increased care package‡	✓	x
	LOS in hospital, critical care, palliative care, rehabilitation,	-	✓

Continued

Table 1 Continued

Category	ORCHARD-EPR variable	Available at multiple time-points in ORCHARD-EPR	Availability in administrative datasets (eg, HES)
	Delayed transfer of care, reasons for delayed transfer	✓	x
	Discharge destination	–	✓
	Death (via National Office of Statistics)	–	✓
Labs	Haemoglobin, white cell, neutrophil and lymphocyte counts, albumin, C reactive protein, creatinine, eGFR, glucose, HbA1c, lactate, pH, sodium, thyroid stimulating hormone, urea	✓	x
Brain imaging	Brain imaging reports, raw brain scan images	✓	x
Mortality	During admission and on follow-up	–	✓
Long-term cognitive/mental health outcomes	Dementia and mild cognitive impairment from mental health services assessment	✓	Limited†
	Cognitive test scores	✓	x
	Depression and mental illness	✓	Limited†

CRIS uses artificial intelligence to extract data from free text.

*Only available via clinical coding that is known to be insensitive.

†Only available for patients readmitted to hospital in whom a corresponding ICD-10 diagnosis was recorded by the coders.

‡Only available in manual audits.

ACE, Addenbrooke's Cognitive Examination; AMTS, Abbreviated Mental Test Score; AVPU, Alert, Voice, Pain, Unresponsive Scale; CRIS, Clinical Record Interactive Search; eGFR, Estimated glomerular filtration rate; HbA1c, Hemoglobin A1C; LOS, Length of stay; MMSE, mini-mental-state examination; MoCA, Montreal Cognitive Assessment; MUST, Malnutrition Universal Screening Tool; NEWS, National Early Warning Score; NICE, National Institute for Health and Care Excellence; ORCHARD-EPR, Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records; SIRS, Systemic Inflammatory Response Syndrome.

a paper clerking proforma (2013–2015) designed by SP and SSI but since 2015, this has been integrated as a powerform into the EPR (28 466/40 439 (70%) eligible patients staying ≥1 day screened for period 2017–2019).³⁴ Ongoing performance feedback and governance reviews are in place to ensure that screening rates are maintained.

The OUHFT cognitive screening EPR powerform (online supplemental figure 1) includes:

- ▶ The 10-point Abbreviated Mental Test Score,³⁵ a brief screen for cognitive problems or drop-down list for reason for lack of completion (eg, patient too unwell, aphasia).
- ▶ Recording of formal dementia diagnosis (recorded as yes/no/uncertain).
- ▶ Recording of delirium diagnosis (recorded as yes/no/uncertain) informed by the CAM.³⁶ Since screening is mandated on admission, prevalent (on-admission) delirium is more likely to be recorded via the powerform than incident delirium (arising during admission).⁴ Incident delirium may be recorded via launching another cognitive screening powerform or may be documented in a free text powernote form, which is then assigned an ICD-10 delirium code by coding staff (figure 1).

Training in delirium diagnosis, using the CAM, and according to the Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV, now DSM-5) criteria, is provided to

junior medical staff during foundation and middle grade training and this together with trust-wide delirium education and awareness raising was implemented as part of a multicomponent intervention:⁴ staff education/training including of the coding team, implementation of mandatory cognitive screening via the clerking proforma and then the EPR powerform, and introduction of regular performance feedback on rates of screening at hospital governance meetings, figure 2. Other cognitive screening tests built as powerforms in EPR including the mini-mental-state examination (MMSE),³⁷ Montreal Cognitive Assessment (MoCA),³⁸ Addenbrooke's Cognitive Examination (ACE-III)³⁹ and Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)⁴⁰ are also included in ORCHARD-EPR where available.

Nursing risk assessments

ORCHARD-EPR includes data from relevant nursing risk assessments, including the Malnutrition Universal Screening Tool,⁴¹ Braden Scale for pressure sore risk⁴² and a multifactorial falls risk assessment based on National Institute for Health and Care Excellence guidance.⁴³ These include data on functional status, vision and continence.

Derived variables

Laboratory test results and physiologic measures, including heart rate, blood pressure and temperature,

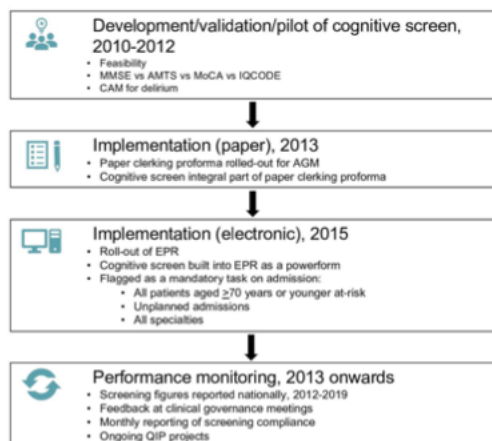


Figure 2 Development, validation and implementation of the cognitive screen. In two audit cycles undertaken in acute general medicine (AGM) in 2010 and 2012, the CAM was piloted in conjunction with first the MMSE and then the AMTS. The AMTS was then compared with the MoCA and the IQCODE to determine its sensitivity and specificity for mild and moderate/severe cognitive impairment.^{28 31} The cognitive screen comprising the AMTS+CAM was subsequently implemented in AGM for all those aged ≥70 years via a paper clerking proforma, and from 2015, hospital-wide via an EPR powerform. AMTS, Abbreviated Mental Test Score; CAM, Confusion Assessment Method; EPR, electronic patient record; IQCODE, Informant Questionnaire for Cognitive Decline in the Elderly; QIP, Quality Improvement Project; MMSE, mini-mental-state examination; MoCA, Montreal Cognitive Assessment.

from routine patient observations on admission are included allowing for the calculation of derived variables. These data are used to calculate measures of illness severity, including the:

- ▶ National Early Warning Score.⁴⁴
- ▶ Systemic Inflammatory Response Syndrome criteria⁴⁵ (white cell count, blood pressure, respiratory rate, temperature).
- ▶ Acute Physiology and Chronic Health Evaluation II (APACHE II).^{46 47}
- ▶ Quick Sequential Organ Failure Assessment (qSOFA) score.⁴⁸

Since such data are available throughout admission, they can be used to generate dynamic data on intra-admission trajectories. ICD-10 codes are allocated by OUHFT coding administrators and are used to calculate the Charlson comorbidity index with updated weights,⁴⁹ and the HFRS.¹⁶ Postcodes are collected as part of admission demographics and to allow calculation of the English Index of Multiple Deprivation (2019) to obtain percentiles of deprivation.⁵⁰ Postcodes are also used to cross-check against social services lists of care homes to assign care home residence pre-admission.⁵¹

Data linkage

ORCHARD-EPR linkage to the Oxford Vascular Study (OXVASC) transient ischemic attack (TIA)/stroke cohorts has already provided long-term follow-up data on hospital admission after TIA and stroke to inform delirium, infection and future dementia risk associations.^{29 30 52}

ORCHARD-EPR is also linked to:

- ▶ local mental health trust data (Oxford-Health-CRIS);
- ▶ the OUHFT incident reporting database (Ulysses);
- ▶ Criteria for Screening and Triaging to Appropriate Alternative care scores collected by the OUHFT Palliative care team.⁵³
- ▶ routinely acquired CT and MRI brain imaging.

Oxford-Health CRIS contains deidentified, pseudonymised data on mental health diagnoses including dementia, mild cognitive impairment, cognitive test scores, depression and other psychiatric diagnoses including extracted from free text inpatient and outpatient clinical records using artificial intelligence methods.²⁷ Linkage to CRIS will allow reliable identification of dementia preadmission and on follow-up. Brain scan images (n>1300 linked CT-brain and MRI-brain scans to date) will allow incorporation of brain ageing/neuropathology markers. Linkage to the OUHFT incident reporting database (Ulysses) will provide data on adverse events in hospital, including falls (severity, associated harm), pressure ulcers and challenging patient behaviours. Linkage of ORCHARD-EPR to other OUHFT and University of Oxford-approved studies will provide data on acute hospital illness and cognitive and physical frailty, where participants have given consent for access to their medical records.

Outcome measures

Data are collected for the following outcomes:^{2 20}

- ▶ Mortality obtained from the Office of National Statistics, which registers all deaths in the UK.
- ▶ Length of stay calculated from the time of admission to the time of discharge or transfer.
- ▶ Delayed transfers in care where a patient is determined to be ready to go home by their clinician and multidisciplinary team, but remains in a hospital bed, for example, because their care package is not ready;
- ▶ Discharge destination to public or private care homes or other hospitals (eg, for rehabilitation);
- ▶ Readmissions identified from ORCHARD-EPR including within 30 days of discharge;
- ▶ Cognitive decline and dementia from ORCHARD-EPR readmissions and Oxford Health (CRIS) data.

Inclusion of previous audits

Additional pseudonymised data from OUHFT-approved audits around frailty and outcomes are transferred to ORCHARD-EPR. Such audit data include comparisons of the OUHFT cognitive screen with additional objective cognitive testing (eg, MMSE, IQCODE)^{28 31} and rates of delirium occurrence in acute general medicine (n=6

cycles to date) with delirium diagnosis made by a consultant physician according to the DSM-IV criteria.^{4 15} These audit data will act as the reference standard in evaluating the accuracy of the ORCHARD-EPR routinely acquired real-world EPR data (see below).

Data accuracy

ORCHARD-EPR accuracy is carefully verified using the following:

- ▶ Selection and identification of data fields for extraction is done by SP, a clinician working in acute and complex medicine who uses the EPR interface on a daily basis, and has led implementation of changes to EPR;
- ▶ Extracted data is checked for accuracy by SP in collaboration with the information team analysts (AJ, ie, for missing data, and sense-checking of extracted values);
- ▶ Extracted data are verified against prospective audit data (eg, for rates of delirium and diagnosed dementia)¹⁵ and against data extracted independently by the Information team for other purposes (eg, monthly cognitive screening rates).

Statistical analyses

Demographic and patient characteristics will be presented using descriptive statistics (χ^2 for categorical data and t-test/Analysis of Variance-ANOVA for continuous data as appropriate). Prevalence of cognitive frailty syndromes (ie, any cognitive syndrome/deficit, dementia, delirium, delirium superimposed on dementia, low objective test score) will be calculated overall and stratified by age, sex and specialty with 95% CIs. To determine the association between frailty syndromes (independent variables) and the outcomes listed above (dependent variables), risk ratios will be modelled using logistic, Poisson and Cox regression. Effect modification and confounding by age, sex, deprivation, comorbidity, residence at the time of admission and illness severity will be evaluated. Statistical analysis methods will be updated over time, as new data are added and research questions identified.

Adherence to reporting guidelines

All research will be reported in accordance with relevant guidelines including Strengthening The Reporting of OBservational Studies in Epidemiology⁵⁴ and Transparent Reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines.⁵⁵

Patient and public involvement

ORCHARD-EPR has been informed since its inception by a patient and public involvement (PPI) group, set up in 2015 by SP, to help develop studies on cognitive and physical frailty. PPI members provided input into the ORCHARD-EPR proposal and objectives. The PPI group comprises patients with cognitive and physical frailty with lived experience of hospitalisation and their carers, a retired general practitioner, Alzheimer's society representatives and a PPI lead with experience in frailty and dementia studies. Discussions with the PPI group

highlighted that a key concern for patients and families is the need for better information about prognosis in relation to frailty and confusion in hospital. The PPI group has also facilitated several projects that have impacted the richness and depth of ORCHARD-EPR data including the system-wide multicomponent intervention to improve the recognition, recording and diagnostic coding of delirium and other cognitive frailty syndromes, implementation of cognitive screening in acutely unwell patients and development of the delirium susceptibility score, now implemented as an EPR digital algorithm to flag patients at risk in real time.^{4 6 15}

DISCUSSION

Summary

ORCHARD-EPR is unique in terms of its size, inclusiveness and scope (>200 000 unselected unplanned patient episodes, 2015–2021) with extensive real-world multimodal routinely acquired EPR data largely unavailable in administrative data sets based on ICD-10 diagnostic coding (table 1). ORCHARD-EPR combines detailed phenotyping for cognitive and physical frailty and other clinical characteristics with physiologic and laboratory measures, illness severity, care home residence, brain scan images and outcomes including mental health diagnoses from linkage to mental health secondary care data. ORCHARD-EPR will enable large-scale studies on the prevalence and outcomes of cognitive and physical frailty including delirium, with robust adjustment for confounding thereby filling existing knowledge gaps. ORCHARD will also enable the development of risk prediction algorithms (eg, for dementia) and disease-specific studies through selection of appropriate subgroups or through linkage to existing cohorts.

Cognitive frailty

Cognitive frailty has multiple direct implications for patient care, service planning and policy including capacity to consent for procedures, medication use, discharge planning, communication and advanced directives/proactive palliative care.^{2 13 15 20} Despite its importance, however, reliable estimates in unselected cohorts of its prevalence (and of relevant subtypes, particularly delirium) including by specialty are scarce.² Existing prospective studies of highly phenotyped cohorts tend to have small sample sizes and restrictive eligibility criteria, resulting in exclusion of high risk groups such as those unable to give informed consent.^{1–3} Retrospective administrative data sets (eg, UK HES data) are large and inclusive but are usually unreliable for ascertainment of cognitive frailty because of the insensitivity of ICD-10 diagnostic coding or reliance on non-specific free text terms (eg, 'disturbed behaviour').^{2 4 5}

ORCHARD-EPR addresses the limitations of previous data sets through combining the detailed cognitive phenotyping data usually only available in small, labour-intensive prospective studies with the large sample size,

inclusivity and efficiency of retrospective administrative 'Big Data' studies. Specifically, the value of the electronic cognitive data in ORCHARD-EPR is greatly enhanced by several factors. First, ORCHARD-EPR exploits routine hospital-wide cognitive screening including for delirium embedded via an electronic powerform, implemented using a multicomponent intervention ensuring better recognition and documentation of cognitive frailty. Second, ORCHARD-EPR ascertains cognitive frailty using both the results of the EPR cognitive screen powerform and the ICD-10 diagnostic coding applied by the hospital coding team who have been trained by SP ensuring that free text powerform entries documenting cognitive frailty are translated into the appropriate ICD-10 code. Third, the accuracy of ORCHARD-EPR cognitive frailty data is assessed against reference standard data provided by prospective audit (using analogous methodology to that used in the development and validation of the HFRS).^{15 16} Fourth, linkage to secondary care mental health data provides enhanced information on dementia and other mental health conditions enhancing the sensitivity of cognitive outcomes.

Physical frailty/frailty domains

In comparison to cognitive frailty, established methods are available to identify (global) frailty in large unselected retrospective administrative datasets. The widely used HFRS uses a combination of a broad range of administrative diagnostic (ICD-10) codes known to be present in those with frailty but is dependent on coding accuracy, resulting in heterogeneity across studies.^{2 16} In addition, the HFRS provides a single numeric measure of frailty (which can be stratified as mild/moderate/severe) rather than providing information on specific frailty domains and, therefore, cannot inform care in real time during admission. In contrast, the rich routinely acquired clinical data in ORCHARD-EPR could be used to derive an eCGA,⁵⁶ in which frailty is identified across a range of domains (cognition, continence, mobility, vision, nutrition, falls risk etc) without further burden to patients or staff. Such an eCGA could be implemented into EPR to identify domains of need in real time to better target frailty interventions in collaboration with patients and families.

Frailty trajectories, time trends and prognosis

Reliable capture of cognitive frailty in ORCHARD-EPR will allow evaluation of the extent of overlap with physical frailty, individual frailty trajectories across multiple admissions, and time trends in frailty prevalence in which there are few studies. Hospital frailty prevalence is likely to be increasing given the ageing population, and the introduction of ambulatory care, SDEC and Hospital-at-Home/virtual ward services which tend to be accessed by younger, fitter people.³² ORCHARD-EPR will also provide a better understanding of the prognostic value of cognitive and physical frailty and their interactions with the potential for improved risk stratification.^{2 11} Inclusion of

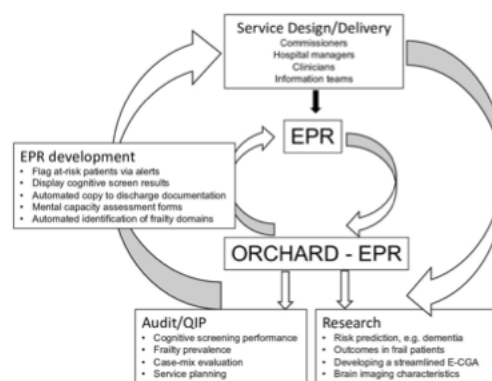


Figure 3 Virtuous circle—the uses of ORCHARD-EPR. ORCHARD-EPR data can drive audit and research and the findings used to inform policy, commissioning and service planning/development as well as EPR developments to improve documentation and care. CGA, Comprehensive Geriatric Assessment; ORCHARD-EPR, Oxford and Reading Cognitive Comorbidity, Frailty and Ageing Research Database-Electronic Patient Records; QIP, Quality Improvement Projects.

more than 100 covariates allows robust adjustment for confounders and exploration of potential effect modifiers impacting outcomes such as care home residence and illness severity.² Linkage to other local hospital datasets (eg, incident reporting for in-patient falls, challenging behaviour) will provide reliable information on the impact of cognitive and physical frailty on healthcare safety and quality to inform care bundles and policy.

Data accuracy and creating a virtuous circle

Reliable data are key to NHS management, service evaluation, planning and development, audit and research and the advent of hospital EPRs enables rich routinely acquired data to be exploited. However, healthcare staff entering data will tend to prioritise immediate patient care which may impact data accuracy.⁵⁷ ORCHARD-EPR data accuracy is checked through close working between SP, a clinician on the ground using the EPR user interface on a daily basis, and the hospital Information Team (AJ). This enables selection of data fields of interest and the necessary iterative work to be undertaken to ensure data fields are correctly identified and populated. Accuracy can be further checked against the reference standard of local prospective audit data.¹⁵ ORCHARD-EPR aims to create a virtuous circle whereby audit and research informs EPR developments, improves data quality and ultimately improves patient care (figure 3). Further, since the EPR is a dynamic entity, ORCHARD-EPR can be used to drive future EPR developments to improve data capture as evidenced by the implementation of the EPR cognitive screen to improve recognition, documentation and administrative diagnostic coding of cognitive frailty. Delirium recognition has also been enhanced by the

development, validation and EPR implementation of the delirium susceptibility score algorithm to identify those at risk in real time.⁶

Additional research questions

ORCHARD-EPR will enable researchers to explore a large number of additional research questions in the acute secondary care setting in a large, representative and inclusive population of older adults. Examples include outcomes in disease-specific studies (eg, COVID-19) and validation and recalibration of commonly used prognostic tools, (eg, the CURB-65 tool for mortality risk in pneumonia).⁵⁸ The availability of routinely acquired unselected brain imaging will allow development of artificial intelligence (AI) tools to extract markers of brain pathology (or “brain frailty”) such as cerebral small vessel disease, brain atrophy and stroke lesions in representative older patient cohorts. The resultant imaging AI tools could be integrated into clinical imaging systems at source to provide quantitative data to aid neuroradiologists/clinicians without the need for human input. Inclusion of brain imaging data with linked clinical data will enhance the development of risk prediction tools (eg, for delirium and dementia) to improve care and selection for trials and understand mechanisms. ORCHARD-EPR will facilitate development of algorithms for in-hospital falls risk prediction/prevention and an eCGA to identify frail patients and their needs in real time without the need for additional assessments to target individualised interventions.⁵⁶ Finally, ORCHARD-EPR could act as an exemplar for the Subnational Secure Data Environments currently being setup across England to harness the power of NHS data for the benefit of patients.⁵⁹

Strengths and limitations

This paper has outlined the strengths of ORCHARD-EPR in detail. However, there are some limitations. Not all patients have cognitive screening because of service pressures, or lack of clinician engagement, and screening might be less likely in certain patient groups including the severely ill, resulting in non-random missingness and bias. However, screening rates have been high (~75% of those aged ≥75 years staying ≥72 hours) as documented by NHS England (2017–2019)³⁵ and ICD-10 coding for cognitive frailty has been substantially improved by a multicomponent intervention.⁴ Second, the CFS²³ was only introduced during the COVID pandemic (2020 onwards) and is only now becoming routinely administered. Third, patients aged <70 years do not get routine cognitive screening and cognitive data are, therefore, limited to those deemed as at risk by clinicians. However, the age cut-off has now been lowered to 65 years and over (2024 onwards), so cognitive data will be routinely available on those aged 65–69 years going forward. Fourth, medications are not currently captured in ORCHARD-EPR, but there are plans to include these data in the future. Finally, free-text entries including the medical clerking and entries from allied health and specialist personnel

are currently unavailable, although AI methods could eventually be used to extract analysable data as is done for mental health (CRIS) data.²⁷

ETHICS AND DISSEMINATION

See ‘regulatory approvals’ heading above—ORCHARD-EPR is approved by the South Central Oxford C Research Ethics Committee (REC reference: 23/SC/0258). Results from this study will be disseminated through peer-reviewed publications, presentations at national and international conferences as well as regional meetings to improve hospital data quality and clinical services.

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Contributors EB assembled and cleaned the ORCHARD-EPR data and drafted the manuscript. AJ identified data variables within the OUHFT data warehouse and extracted and pseudonymised individual patient EPR data prior to transfer to ORCHARD-EPR. SSI provided OUHFT management support to embedding OUHFT-wide cognitive screening and ensuring compliance and in the set-up of ORCHARD-EPR. JD located, de-identified, pseudonymised with studyID and securely transferred brain images from the hospital PACS system to the University of Oxford servers. TS (Head of Research Informatics) and AP (Informatics Analyst) led the linkage to Oxford Health mental health data and secure transfer of pseudonymised mental health data using data systems from the NIHR Oxford Biomedical Research Centre. KV, KW, DW provided support with obtaining OUHFT EPR data, AM provided support with the planned Royal Berkshire Hospitals data linkage. SSH provided critical input to the manuscript. SP developed and implemented OUHFT-wide routine cognitive screening, led the multicomponent intervention to improve compliance and ICD-10 coding of delirium and other cognitive frailty, conceived and set-up ORCHARD-EPR, obtained funding, worked with AJ to ensure data accuracy and drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Currently, the ethics approval for this study does not allow access to data to researchers outside the University of Oxford/OUHT but widening access to researchers from other institutions is currently being explored.

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