Frailty in older adults: Findings from longitudinal studies

by

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List of scholarly activity

Awards

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List of publications as secondary author

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Thompson M. Q., Burdon A. (2013) Translating evidence into practice: Supervised physiotherapy exercise programs. Paper presented at Australasian Association of Gerontology (SA Division) Conference; Adelaide, Australia.

Thesis declaration – Statement of originality

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Mark Quinlivan Thompson   Date

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Abstract

Frailty is common among older adults and represents a state of decreased physiological reserve which places individuals at risk of increased vulnerability to adverse outcomes such as falls, hospitalisation, residential care admission, and mortality. Frailty is a dynamic condition where improvement is possible and remaining stable is common. Furthermore, interventions exist that may delay or reverse frailty. There are two main approaches to describing frailty: the frailty phenotype (FP), which is based on a pre-defined set of physical characteristics of frailty, and the accumulation of deficits approach. In the deficits approach, the proportion of deficits, across a wide range of body systems and health conditions, is identified in an individual and represented as a frailty index (FI).

Internationally, there is a large and growing body of research focused on frailty. However, there are a limited number of Australian population-level studies of frailty prevalence, factors associated with frailty, and the diagnostic value of screening instruments for frailty.

Less attention has been focused internationally on a comparison of the two approaches to frailty measurement, the natural course of frailty, its co-presence with sarcopenia (a loss of lean muscle mass and function), and minimally important difference in frailty, which is the smallest change in a treatment outcome which an individual would perceive as being important.

The aims of this thesis were therefore to:

- identify the prevalence of frailty at a population level and determine factors associated with frailty
- examine the transitions between frailty states and to describe the characteristics associated with frailty status improving, remaining stable, or worsening
- identify the diagnostic test accuracy (DTA) of self-reported screening instruments against a frailty reference standard for community dwelling older adults in a systematic review
- determine the predictive ability of frailty classification, and the effect of recency of frailty measurement, on mortality prediction
- also examine the predictive ability of sarcopenia alone and sarcopenia in combination with frailty on mortality
- examine the predictive validity of the FRAIL Scale and the SARC-F, self-reported screening instruments for frailty and sarcopenia respectively
- determine the relationship between frailty status and health-state utility and to determine a minimally important difference for frailty measures.

Research from this doctoral thesis has confirmed that frailty is common among community dwelling older adults in Australia and it is associated with a range of health and socioeconomic determinants. Findings have also demonstrated that improvement in frailty classification is possible and that remaining stable is common. The dynamic nature of frailty was further highlighted in our findings, which demonstrated the importance of repeated frailty measurement for improved mortality prediction. Additionally, frailty and sarcopenia in combination result in worse survival outcomes.

We have also demonstrated the predictive validity of self-reported screening instruments for both frailty and sarcopenia, and that frailty is associated with lower health-state utility. In terms of conducting assessments for frailty, we have identified values for minimally important differences for both methods of frailty measurement.

These findings have important clinical implications for both the identification and management of frail individuals, and for promoting healthy ageing through offering preventative strategies. A key message from this thesis for health practitioners and older adults is that despite frailty being common, it can be either prevented, reversed, or delayed, and that a regular review of frailty status is important for targeting interventions as required, and maximising quality of life.

Frailty in older adults: Findings from longitudinal studies

Introduction

1.1   Frailty

As the Australian and global population ages, there is a responsibility among health practitioners and policy makers to promote opportunities for healthy ageing (World Health Organization, 2015). These strategies should focus beyond merely extending life, to enhancing wellbeing, function and participation, and quality of life. While ageing is a universal and inevitable part of the life course, there is large variability seen in the health and functional status of older adults, which reflects the multifactorial nature of survival into old age (Prince et al., 2015; Steves, Spector, & Jackson, 2012).

Frailty may be a contributor to this variability in the wellbeing of older adults (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Understanding frailty and its course, therefore, is an important component in promoting healthy ageing locally and globally. This is particularly relevant as there are interventions available to potentially prevent or delay the onset and progression of frailty, including strength-based exercise, and promoting adequate dietary intake, especially of protein (Puts et al., 2017). Much of the identification and management of frailty is ideally suited to primary care and community-based services (Lacas & Rockwood, 2012), and strengthening the evidence base for addressing frailty in these settings is critical.

Frailty is a state of decreased physiological reserve and resilience in which individuals are more vulnerable to stressors and at greater risk of adverse health events, such as falls, fractures, hospitalisation and loss of independence (Clegg et al., 2013). This decreased reserve results from a cumulative decline across multiple physiological systems (Mitnitski, Mogilner, & Rockwood, 2001), and a frail individual may be viewed as a complex system on the threshold of breakdown, with higher order functions usually compromised first: balance, mobility, cognitive function (Nowak & Hubbard, 2009). Frailty may also result from severe disease or comorbidity, or from the physiologic changes of ageing that are not related to disease, such as sarcopenia (Fried et al., 2001).

Frailty also shares common features with **sarcopenia**, a syndrome of lean muscle mass and function loss (Cesari, Landi, Vellas, Bernabei, & Marzetti, 2014). Despite their shared characteristics, there has been no study which has examined the association between the combined presence of frailty and sarcopenia with mortality. A better understanding of how these two conditions interact would provide useful information on prognosis and prioritising treatment for individuals with either or both conditions. This is important, as there are interventions available that may delay the development and progression of frailty, such as exercise focused on strength training, increasing nutritional intake, particularly protein, reducing polypharmacy, and increasing vitamin D levels (Clegg et al., 2013; Puts et al., 2017), and which are also likely to be useful in the management of sarcopenia (Yoshimura et al, 2017).

1.1.1 The prevalence of frailty

There are two approaches commonly used to describe frailty: *the frailty phenotype* (FP) and *the cumulative deficits approach*. The former views frailty as a physiologic syndrome which is manifested when three or more of the following deficits are present: unintentional weight loss, self-reported exhaustion, slow walk speed, weakness, and low physical activity (Fried et al., 2001). The deficits approach defines frailty as a multi-dimensional risk state based on the proportion of potential deficits present in the individual, with a higher proportion representing a higher level of frailty (Mitnitski et al., 2001). This proportion of deficits is referred to as a *frailty index* (FI).

Frailty is common among community-dwelling adults and its prevalence has been estimated internationally at 9.9% (weighted mean, range 4% to 17%) based on FP measurement, and at 13.6% (weighted mean, range 4% to 59%) according to the FI (≥65 years) (Collard, Boter, Schoevers, & Oude Voshaar, 2012).

Australia's population is ageing, with the proportion of individuals aged 65 years and older expected to increase from a current 16% to an estimated 19% of the population by 2031, and to a possible 25% in 2061, with the largest proportional growth expected in those aged 85+ years (Australian Bureau of Statistics, 2013). Understanding frailty prevalence in Australia will be important for planning health and social services to promote the healthy ageing and wellbeing of this cohort. To date there have been several Australian population-level studies that have investigated frailty prevalence (Blyth et al., 2008; Dent, Hoon et al., 2016; Widagdo, Pratt, Russell, & Roughead, 2015; Wong, McCaul, Yeap, Hankey, & Flicker, 2013). However, none of these has examined frailty and factors associated with frailty using both forms of measurement in the one cohort. This is necessary to examine whether the FP and FI share common characteristics in terms of prevalence, distribution of scores, association between measures, and actors associated with frailty.

Regardless of the approach used in measurement, it is important to note that frailty is a dynamic process where individuals are capable of improving and transitioning to lesser states of frailty, particularly those who are pre-frail (Fallah et al., 2011; Gill, Gahbauer, Allore, & Han, 2006). Internationally, frailty state transitions and associated factors have been examined from the perspective of the FP and FI separately in different cohorts (Kojima, Taniguchi, Iliffe, Jivraj, & Walters, 2019); however, the performance of both measures longitudinally in the same cohort is yet to be examined. It is important to understand how the different forms of frailty measurement compare in terms of frailty state change over time.

1.1.2 Recognising and managing frailty

The primary care setting has been identified as playing a crucial role in the recognition and management of frailty, as well as the promotion of healthy ageing through integrated and patient centred care (Cesari et al., 2016; Theou & Rockwood, 2012). A range of frailty screening and assessment instruments is available. The instruments are quick to administer and can be self-reported by patients (Dent, Kowal, & Hoogendijk, 2016). However, there has not been a comprehensive review of self-reported tests for frailty identification or an examination of their diagnostic test accuracy (DTA) against the reference standards of either the FP or FI.

While the case is clearly made for assessing frailty status at the beginning of ageing care (Theou & Rockwood, 2012), the review of frailty status requires just as much attention, taking into account the changeable nature of frailty. However, the predictive ability of repeated frailty measurements on mortality is yet to be determined.

Self-reporting instruments and utility. The FRAIL Scale (Morley, Malmstrom, & Miller, 2012) and SARC-F (Malmstrom, Miller, Simonsick, Ferrucci, & Morley, 2016) are two self-reporting instruments for the screening of frailty and sarcopenia respectively, which have been proposed for use in primary care settings (Burgess & Hercus, 2017; Morley & Malmstrom, 2014). The FRAIL Scale has preliminary evidence in favour of its predictive validity for mortality (Kojima, 2018), and there are similar emerging findings for the SARC-F (Malmstrom et al., 2016; Woo, Leung, & Morley, 2014). Further information about the predictive validity and DTA of both instruments is required, particularly for their use in the Australian population.

Understanding the preference-based value (utility) that individuals place on health states is an important component in the evaluation of interventions (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005; Neumann, Goldie, & Weinstein, 2000). While frailty is known to be associated with reduced quality of life (Kojima, Iliffe, Jivraj, & Walters, 2016), the utility of frailty states is less well understood. Minimally important difference (MID) also provides valuable information regarding the smallest change in a treatment outcome which an individual would perceive as being important. Likewise, MID values are unknown for both forms of frailty measurement.

1.2   Aims of the research

The research that resulted in this thesis by publication focused on frailty at a population level in the Australian context. The research aims were to:

- identify the prevalence of frailty at a population level and describe associated factors (Chapters 4 and 5)
- examine the transitions between frailty states and describe the characteristics associated with frailty status improving, remaining stable, or worsening (Chapter 6)

- identify the diagnostic test accuracy (DTA) of self-reported screening instruments against a frailty reference standard for community dwelling older adults in a systematic review (Chapter 7)

- determine the predictive ability of frailty classification, and the effect of recency of frailty measurement, on mortality prediction (Chapter 8)

- also examine the predictive ability of sarcopenia alone and sarcopenia in combination with frailty on mortality (Chapter 9)

- examine the predictive validity of the FRAIL Scale and the SARC-F, self-reported screening instruments for frailty and sarcopenia respectively (Chapter 10)

- determine the relationship between frailty status and health-state utility and to determine a minimally important difference for frailty measures (Chapter 11).

1.3 The context of the research

The distribution of frailty and associated factors were examined using Australian population cohorts in the studies comprising this thesis. The use of randomly selected population data is important in epidemiological research in order to produce a representative sample of the population and to minimise systematic sampling errors (Fletcher, Fletcher, & Fletcher, 2014).

The majority of studies in this thesis (Chapters 5, 6, 8, 9, 10, and 11) were a secondary analysis of data from the North West Adelaide Health Study (NWAHS), a population representative longitudinal study of men and women (Grant et al., 2009). Participants in the study were randomly selected from households in the North West of metropolitan Adelaide. We included participants aged ≥65 years. Stage 2 data (2004-06) were used as baseline for all studies, and Stage 3 (2008-10) for follow-up.

Chapter 4 was a secondary cross-sectional analysis of data from the Dynamic Analyses to Optimise Ageing Project (DYNOPTA), a pooled dataset of nine Australian longitudinal studies of ageing, and the NWAHS (Anstey et al., 2010; Grant et al., 2009). Three cohorts from DYNOPTA with data available from 2004 and 2006 were using in conjunction with NWAHS Stage 2 (2004-06). This combined data set offered a large sample of participants aged ≥65 years (n = 8804) and enabled frailty prevalence findings to be more generalisable across the Australian population.

The characteristics of both NWAHS and DYNOPTA cohorts are discussed in detail in Chapter 3.

1.4 The organisation of the thesis

The remaining chapters of this thesis are ordered as follows:

- **Chapter 2** provides a background to frailty definitions, prevalence, associated factors, associated outcomes, screening and assessment methods, and interventions that might reverse or delay frailty. Additionally, gaps in the scientific literature regarding frailty are discussed. The chapter is an expanded version of a published manuscript designed to raise general practitioner awareness about the public health issues of frailty (Appendix A).

- **Chapter 3** describes the research cohorts used as the data source for studies included in this thesis. The North West Adelaide Health Study (NWAHS) cohort was used for studies discussed in Chapters 5, 6, 8, 9, 10, and 11. However, NWAHS data were also used in combination with Dynamic Analyses to Optimise Ageing Project (DYNOPTA) in Chapter 4.

- **Chapter 4**
  Published work in this chapter: **Frailty prevalence in Australia: Findings from four pooled Australian cohort studies**
  The paper presented in this chapter reports on the prevalence of frailty from an analysis of four pooled Australian cohort studies from the Dynamic Analyses to Optimise Ageing Project (DYNOPTA) and North West Adelaide Health Study (NWAHS). Frailty was measured using a modified frailty phenotype (FP).

- **Chapter 5**
  Published work in this chapter: **Frailty prevalence and factors associated with the frailty phenotype and frailty index.** Findings from the North West Adelaide Health Study (NWAHS)
  The paper presented in this chapter reports on the prevalence of frailty and associated factors in the North West Adelaide Health Study (NWAHS) using both the frailty phenotype (FP) and frailty index (FI). Frailty prevalence was reported, together with agreement between each form of frailty measurement, as well as factors associated with frailty.

- **Chapter 6**
  Published work in this chapter: **Frailty state transitions and associated factors in South Australian older adults**
  The paper presented in this chapter examines frailty state transitions and factors associated with improvement or worsening frailty status as revealed in the data from the North West Adelaide Health Study (NWAHS). Frailty was measured using the FP and FI, with repeated measures at 4.5 years follow-up.

- **Chapter 7**
  Published work in this chapter (as second author): **Diagnostic test accuracy of self-reported screening instruments in identifying frailty in community-dwelling older people: A systematic review**
  This paper is a systematic review examining the diagnostic test accuracy of self-reported and/or self-administered frailty screening instruments against two frailty reference standards, the frailty phenotype (FP) and the frailty index (FI) within community-dwelling older adult populations. (The protocol for this systematic review is also included in Appendix B).

- **Chapter 8**
  Published work in this chapter: **Recurrent measurement of frailty is important for mortality prediction: Findings from the North West Adelaide Health Study**
  The paper presented in this chapter examines the relationship between frailty status (at baseline and follow-up) and mortality using both the frailty phenotype (FP) and frailty index (FI) in the North West Adelaide Health Study (NWAHS). Frailty was measured at baseline for all participants, while a returning sample had frailty measurement at two time points, with a mean 4.5 years between baseline and follow-up. 10 years of survival data were available for all participants.

- **Chapter 9**
  Paper submitted for publication and under review: **The combination of frailty and sarcopenia is an important mortality predictor: North West Adelaide Health Study findings**
  This study examined the predictive ability of frailty and sarcopenia classification on mortality in the North West Adelaide Health Study (NWAHS). Frailty was measured using the frailty phenotype (FP) and frailty index (FI), and sarcopenia using the revised European consensus definition. The relationship between classification as frail and / or sarcopenic with mortality was examined.

- **Chapter 10**
  Paper submitted for publication and under review: **FRAIL Scale: Predictive validity and diagnostic test accuracy**
  is a study that examines the predictive validity of the FRAIL Scale against mortality as well as diagnostic test accuracy (DTA) against reference standards of the FP and FI for frailty, for 668 community-dwelling adults aged ≥ 65 years from the North West Adelaide Health Study (NWAHS). 10 years of survival data were available for all participants.

- **Chapter 11**
  Paper submitted for publication and is under review: **Frailty state utility and minimally important difference: Findings from the North West Adelaide Health Study**
  This study describes Frailty State Utility and Minimally Important Difference (MID) for both the frailty phenotype (FP) and frailty index (FI) in the North West Adelaide Health Study (NWAHS). Utility (which is a preference-based valuation of a health state) was measured using the six-dimensional health survey (SF-6D) Health Survey. Two methods were used to measure MID for frailty, namely anchor-based (against self-reported health status) and distribution-based (using 1/2 SD of mean frailty scores).

- **Chapter 12** presents a summative discussion of the key findings which were identified in research conducted that formed that basis of this thesis as well as recommendations for further research.

1.5 Summary and going forward

This chapter has provided a brief introduction to the concept of frailty and the research aims of this thesis. It is anticipated that the findings reported in this thesis will contribute to the evidence base informing both policy and practice in promoting the health of older adults. In particular, highlighting that frailty is common, that regular review of frailty status is important to take into account the dynamic nature of the condition, that there are simple screening instruments available to support this process, that sarcopenia should be considered in combination with frailty, and that change to frailty status is important to older adults and can improve their quality of life. The following chapter is a literature review which provides a detailed background to frailty, the gaps in the scientific literature, and the rationale for the studies included in this thesis.

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Chapter 2

Background

Australia's population is ageing, with the proportion of individuals aged 65 years and older expected to increase from a current 16% to an estimated 19% of the population by 2031 and to a possible 25% by 2061, with the largest proportional growth expected in those aged 85+ years (Australian Bureau of Statistics, 2013). Understanding physical issues that will affect people in this age group is critical in order to care effectively for this expanding cohort. Therefore, knowledge of frailty, a condition common among older adults, is a priority (Cesari et al., 2016). Furthermore, the primary care setting has been identified as playing a crucial role in the recognition and management of frailty, as well as the promotion of healthy ageing through integrated and patient centred care (Cesari et al., 2016).

This chapter provides an overview of frailty, its trajectory and complications, as well as describing strategies for identification and management. The second half of the chapter describes gaps in the scientific literature around frailty, and the rationale for the projects conducted as part of this thesis. More detailed reviews on frailty have been recently published (Dent et al., 2019; Hoogendijk et al., 2019).

Aspects of this background review were published in *Australian Doctor.* A copy of the published article is provided in the Appendix.

2.1   Frailty

Frailty is due to a decline across a range of physiological systems resulting in decreased physiological reserve that results in vulnerability to a range of adverse health outcomes such as disability, hospitalisation, entry to residential care, and death when faced with stressors such as illness (Andrew Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Morley et al., 2013). Frailty is a useful concept for explaining the diversity in health and function seen in older people, where some individuals of the same age remain robust and active while others experience substantial deterioration in their health with loss of independence. Frailty is distinct from multi-morbidity and disability, but all three may be present concurrently in some older adults (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004).

2.1.1 Frailty measurement

The two main approaches to defining frailty among researchers are the phenotypic model and the cumulative deficit model (Fried et al., 2001; Mitnitski, Mogilner, & Rockwood, 2001).

Frailty phenotype approach. The frailty phenotype approach (FP) defines individuals as frail where three or more deficits are identified from amongst a range of five physical criteria: unintentional weight loss, exhaustion, low physical activity level, slow walk speed, and weak grip strength (Fried et al., 2001). The physical function variables of weakness and slowness are shared characteristics of sarcopenia (Cesari, Landi, Vellas, Bernabei, & Marzetti, 2014), a separate skeletal muscle disorder that can co-exist with frailty and worsen frailty.

Cumulative deficit approach represented as a frailty index (FI). The cumulative deficit approach counts the proportion of deficits present in an individual across a range of physical and psychological variables which can be evaluated through a comprehensive assessment or drawn from pre-existing medical records or databases, to calculate a frailty index (FI) (Mitnitski et al., 2001). The cumulative deficit model is mathematically based, and frailty is the proportion of deficits present in an individual (Mitnitski et al., 2001; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). For example, if an individual is found to have 25 deficits out of 100 variables evaluated, then their FI would be 0.25. A higher FI represents a higher level of frailty, and those with a score of > 0.21 are classified as frail (Hoover, Rotermann, Sanmartin, & Bernier, 2013).

Despite differences, the FP and FI are moderately correlated (Rockwood, Andrew, & Mitnitski, 2007). Frailty increases non-linearly with age, is predictive of mortality, and is higher for women (Theou, Brothers, Pena, Mitnitski, & Rockwood, 2014). Studies which report on frailty using the FI tend to report a greater prevalence in comparison with the FP (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Collard, Boter, Schoevers, & Oude Voshaar, 2012). Therefore, some individuals classified as non-frail by the FP can be categorised as frail by the FI. While the FP was designed, and is most commonly used as a categorical measure, it has also been used as a continuous measure to examine the association of frailty with adverse outcomes, and for comparison with other frailty measures (Blodgett et al., 2015; Bouillon et al., 2013; Andrew Clegg et al., 2013; Sanders et al., 2011; Theou, Brothers, Mitnitski, & Rockwood, 2013; Theou et al., 2014). Furthermore, using a continuous FP may result in improved predictive validity of the measure (Sanders et al., 2011).

2.1.2 Frailty screening and instruments

The timely identification and management of frailty in the primary care setting is important as this condition is associated with a range of adverse health outcomes, including geriatric syndromes such as falls and delirium, hospitalisation, decreased quality of life, cognitive impairment, disability, admission to residential aged care, and mortality (Cesari et al., 2016; Andrew Clegg et al., 2013). The phenotypic method (FP) has been popular for its brevity but in population groups where frailty is common and where an electronic health record system exists, the FI is being increasingly utilised. Since July 2017 in the English NHS, primary care practices have used an Electronic Frailty Index to identify patients aged 65 years and older who are living with frailty (British Medical Association, 2018; A. Clegg et al., 2016).

The use of frailty screening tools is one potential approach to identifying frailty in the primary care setting, particularly using instruments which can be self-reported; however, there are many from which to choose such as the FRAIL scale, Kihon checklist, Groningen Frailty Indicator, etc. (Dent, Kowal, & Hoogendijk, 2016), with research underway to determine the best tool for Australian general practice (Ambagtsheer et al., 2017; Dent, Kowal, et al., 2016). Figure 2.1 illustrates one quick and easy way to administer a frailty screening tool, the Clinical Frailty Scale (Rockwood et al., 2005), to support the identification of frailty in the clinical setting. **11**

Clinical Frailty Scale*

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

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

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

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

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

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

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

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

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

Scoring frailty in people with dementia

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

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

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

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

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Figure 2.1: Clinical Frailty Scale (CFS) (Rockwood et al., 2005) Administration time: several minutes. The CFS is scored by a health professional by rating a patient's presentation after a usual consultation which also observes mobility and investigates ADL dependence. Reprinted with permission.

Many of these screening tools have proven to be reliable and valid measures of frailty within different contexts (Dent, Kowal, et al., 2016). However, only some of these are suitable for use as self-administered instruments, which must take the form of either a postal survey or a self-completed questionnaire.

Several systematic reviews have examined the utility of frailty screening within community settings, from the perspective of both self-report and test-based measurements (Apostolo et al., 2017; Drubbel et al., 2014; Sutton et al., 2016; Vermeulen, Neyens, van Rossum, Spreeuwenberg, & de Witte, 2011). Two systematic reviews have reported on the diagnostic test accuracy (DTA) of frailty screening instruments against a reference standard (Clegg, Rogers, & Young, 2015; Pialoux, Goyard, & Lesourd, 2012). A complicating factor in these reviews of frailty screening instruments is a lack of consensus on a definition of frailty, which is reflected in two separate reference standards, together with a large number of potential index tests (Apostolo et al., 2017). Furthermore, while some screening instruments are useful when identifying frailty risk, they are perhaps less helpful in guiding intervention to reverse or delay frailty (Walston, Buta, & Xue, 2018).

The FRAIL Scale. The Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight (FRAIL) scale (Table 2.1), was developed by Morley and colleagues (2012) in order to screen for frailty using a self-reported instrument that did not require a face-to-face clinical examination. This scale is a short and easy to administer tool which has been identified as practical for use in screening for frailty in the general practice setting, and has been recommended as a preferred instrument in the Australian primary care setting (Burgess & Hercus, 2017). The FRAIL Scale has demonstrated preliminary evidence in favour of its predictive validity for mortality (Kojima, 2018). Individuals registering three or more FRAIL characteristics are classified as frail, while those with one or two characteristics are pre-frail, and those with no characteristics are non-frail (Morley et al., 2012).

Table 2.1: FRAIL Scale – modified from (Morley et al., 2012, p. 608)

Fatigue: Do you feel tired all or most of the time?

Resistance: Do you have any difficulty walking up 10 steps without resting?

Ambulation: Do you have any difficulty walking several hundred metres?

Illnesses: More than five illnesses from the following: hypertension, diabetes, cancer (not minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease.

Loss of weight: Unintentional weight loss of more than 5% over the last 12 months

Scoring:

For each question: no = 0, yes = 1

       0: Non-frail

       1-2: Pre-frail

       3 or more: Frail

Administration time: several minutes

Two studies have examined the diagnostic test accuracy (DTA) of the FRAIL Scale against the FP, the first by Braun and colleagues (2018) (Sensitivity: 50.0%, Specificity: 92.0%) and the other by Mijnarends et al. (2015) (Sensitivity: 68.4%, Specificity: 96.2%). The studies

indicated that in these contexts the FRAIL Scale performed well at ruling out the presence of frailty because of its high specificity, but failed to correctly identify a substantial number of those who were frail because of its lower sensitivity. The implication of the low FRAIL Scale sensitivity is that a number of true cases of frailty based on FP are likely to be missed.

2.3   Frailty prevalence

Frailty is common among community-dwelling adults and its prevalence has been estimated internationally at 9.9% (weighted mean, range 4% to 17%) based on FP measurement, and at 13.6% (weighted mean, range 4% to 59%) according to the FI (≥65 years) (Collard et al., 2012). Frailty prevalencehas been investigated in four Australian cohort studies (Blyth et al., 2008; Dent, Hoon, et al., 2016; Widagdo, Pratt, Russell, & Roughead, 2015; Wong, McCaul, Yeap, Hankey, & Flicker, 2013).

One South Australian study using 1992 data compared frailty using both the FP and FI, where frailty prevalence was reported at 9% (FP) and 18% (FI) (mean age 78.2 [6.7]) (Widagdo et al., 2015). Two other male studies reported a prevalence of 9% (FP; New South Wales; mean age 76.9 [5.5]) and 16% (FRAIL Scale; Western Australia; mean age 76.9 [3.8]) (Blyth et al., 2008; Wong et al., 2013). One recent rural South Australian study looked at individuals ≥65 years and found a frailty prevalence of 25% (FI; mean age 75.9 [7.9]) (Dent, Hoon, et al., 2016). The true prevalence of frailty is likely to be higher as these studies excluded residents of aged care facilities.

2.4 Factors associated with frailty

In a systematic review by Feng and colleagues (2017), a range of sociodemographic, physical and psychological factors were found to be associated with frailty in older adults across 23 longitudinal studies. Sociodemographic variables associated with frailty included: older age, female sex, lower education and lower income. Physical factors included: being underweight, obese and demonstrating a higher allostatic load (dysregulation across physiological systems). The presence of depression, cognitive impairment and poor self-rated health were other key variables associated with increased frailty. The largest study included in the review, with 40,657 female participants, by Woods and colleagues (2005) identified that older age, the presence of chronic conditions, smoking, depressive symptoms, and being underweight and overweight / obese were significantly associated with incident frailty (FP), while higher income, moderate alcohol use, living alone, and self-reported health were protective factors.

2.5   Trajectory of frailty

Frailty is a dynamic process and there is growing interest in how frailty changes over time, and the factors that are associated with early versus late stage frailty that may be amenable to intervention (Espinoza, Jung, & Hazuda, 2012; Fallah et al., 2011; Gill, Gahbauer, Allore, & Han, 2006; Lee, Auyeung, Leung, Kwok, & Woo, 2014; Trevisan et al., 2016). Improvement is possible, with rates of improvement in frailty status ranging from 6% to 25% (Espinoza et al., 2012; Gill et al., 2006; Lee et al., 2014; Trevisan et al., 2016). Improvement typically is a single-step transition to an adjacent state, such as from pre-frail to non-frail (Espinoza et al., 2012; Gill et al., 2006; Lee et al., 2014; Trevisan et al., 2016).

Even so, transition to a worse frailty level is more common than improvement (Espinoza et al., 2012; Gill et al., 2006; Trevisan et al., 2016), and remaining in a stable frailty state is the most common outcome in longitudinal studies (Gill et al., 2006; Lee et al., 2014). It is important to note that there are interventions currently available to reverse or delay frailty (Puts et al., 2017).

A range of socioeconomic, clinical, and behavioural factors influences frailty transitions. Increased age, cognitive impairment, obesity, the presence of multi-morbidity, lower education level, and hospitalisation are risk factors for worsening frailty status (Espinoza et al., 2012; Gill, Gahbauer, Han, & Allore, 2011; Lee et al., 2014; Peterson et al., 2009; Trevisan et al., 2016), while increased levels of physical activity, female gender, being overweight, low alcohol consumption, higher educational level, living alone and fewer baseline deficits increase the likelihood of improved frailty (Hubbard, Fallah, Searle, Mitnitski, & Rockwood, 2009; Lee et al., 2014; Peterson et al., 2009; Trevisan et al., 2016)

2.6   Frailty outcomes

2.6.1   Mortality

The relationship of frailty with mortality has been examined in a number of systematic reviews of longitudinal studies, which have determined that those classified as frail by either the FP or FI have a greater risk of mortality when compared to non-frail individuals (Chang & Lin, 2015; Kojima, Iliffe, & Walters, 2018; Shamliyan, Talley, Ramakrishnan, & Kane, 2013; Vermeiren et al., 2016). Pooled odds ratios for increased mortality risk range between 2.58 for the FP and 1.85 for the FI (Vermeiren et al., 2016). Frailty has thus been identified as a significant long-term predictor of mortality. However, predictive strength is best over a short period of follow-up (Shamliyan et al., 2013), potentially due to the dynamic nature of frailty where change is likely over time (Kojima et al., 2018). Furthermore, there is a cumulative effect where the presence of an increased number of deficits is associated with greater mortality risk (Kane et al., 2012).

2.6.2   Other outcomes

Frailty has also been associated with a range of other adverse outcomes. Frail individuals have a greater likelihood for incident disability in activities of daily living (Kojima, 2017; Vermeiren et al., 2016), increased rates of hospitalisation and nursing home admission (Vermeiren et al., 2016; Wang, Shamliyan, Talley, Ramakrishnan, & Kane, 2013), a greater risk of future falls (Kojima, 2015), and an inverse association with quality of life (QOL) (Crocker et al., 2019; Kojima, Iliffe, Jivraj, & Walters, 2016).

2.7   Frailty and sarcopenia

Sarcopenia is a skeletal muscle disorder characterized by loss of muscle mass and function (Cruz-Jentoft & Sayer, 2019). Increasingly, frailty and sarcopenia are being examined together, as these conditions share features in common, in particular in relation to lower lean mass and physical function (Cesari et al., 2014). Internationally, sarcopenia prevalence has been estimated at 10% in adults aged ≥60 years (Shafiee et al., 2017), and individuals with sarcopenia have significantly higher mortality risk compared with their healthy counterparts (Liu et al., 2017). The prevalence of sarcopenia has been previously reported at 6.2% for men and 9% for women aged ≥ 65 years in a community-dwelling cohort of older adults (Yu et al., 2014).

While there are various approaches to the measurement and definition of frailty, the European consensus definition is most commonly used (Cruz-Jentoft & Sayer, 2019). Using this approach, individuals are classified as sarcopenic if both of the following criteria are present: weakness and low skeletal muscle mass (SMI). Weakness is defined by either gripstrength measured using a hand-held dynamometer and stratified by sex and BMI, or through chair rise testing. Low SMI may be calculated using appendicular skeletal muscle mass (ASM) measured using dual energy x-ray absorptiometry (DXA), or whole body skeletal muscle mass using bioelectrical impedance analysis (BIA) (Cruz-Jentoft et al., 2019).

The prevalence of frailty and sarcopenia in combination has been explored in a small number of studies. Mori et al (2019) identified 3.6% of participants in a population of Japanese community-dwelling adults (n=331; mean age 71.5 [SD 5.1] years; 72% female) as being both frail (using FP approach) and sarcopenic, while Yoshimura and colleagues (2019) identified 2.1% as being both frail (FP) and sarcopenic in a Japanese community-dwelling cohort (n=963; mean age 72.2 [SD 7.6] years; 67% female). This proportion was higher (18%, FP) for a Spanish sample of older adults either hospitalised or attending a geriatric outpatient clinic (n=444; mean age 77.3 [SD 8.4] years; 45% female) (Bernabeu-Wittel et al., 2019), and for a sample of participants attending a Dutch geriatric outpatient clinic (n = 299; mean age 82.4; [SD 7.1] years; 65% female) at 42% FP and 25% FI (Reijnierse et al., 2016).

2.8   Comprehensive assessment and management of frailty

A comprehensive assessment should be used to confirm an individual's frailty level, identify remediable factors, undertake investigations and then institute an appropriate management plan (e.g., chronic disease or mental health plan) in collaboration with both the individual and their carers. It is possible for some components to be assessed through self-report or via other healthcare professionals (e.g., practice nurse) and, as previously mentioned, aspects of these assessments can be computed to produce a frailty index score (Theou et al., 2015).

Domains that could be regularly assessed in a comprehensive assessment include:
- Medications
- Continence
- Falls, osteoporosis and fractures
- Syncope or dizziness
- Gait, walk speed, and balance
- Activities of daily living
- Cognition
- Mood
- Oral health
- Body mass index (BMI), anorexia and nutritional status
- Sensory ability (vision and hearing)
- Presence of pain
- Physical activity level
- Presence of chronic diseases (e.g., arthritis, cerebrovascular disease, cardiovascular disease, diabetes, respiratory disease, renal disease, anaemia)
- Blood pressure (i.e., postural hypotension or hypertension), heart rate and rhythm (i.e., atrial fibrillation)
- Immunisation status
- Social support and transport
- Advance care directives

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2.8.1 Comprehensive geriatric assessment (CGA)

The comprehensive geriatric assessment (CGA) is a multidimensional holistic assessment of the health and wellbeing of the older person, which results in a management plan to address issues that have been identified (British Geriatrics Society, 2019). Typically, this covers the assessment domains of physical function, social and physical environment, psychological components, and medication review. In addition, the goals and preferences of the individual are taken into account to ensure that the management plan is personalised and person-centred. CGA has been found to benefit older adults in terms of minimising adverse outcomes when applied across both community and acute care settings (Ellis, Whitehead, Robinson, O'Neill, & Langhorne, 2011; Garrard, Cox, Dodds, Roberts, & Sayer, 2019).

2.8.2 75+ Health Assessment

In the Australian context, the Medicare Benefits Schedule (MBS)-funded 75+ Health Assessment is an ideal framework in which to comprehensively assess an individual's frailty status in the primary care setting (Department of Health, 2019b). A range of MBS item numbers can be used to comprehensively assess an individual, confirm their frailty level, identify remediable factors, undertake investigations, and then institute an appropriate management plan (e.g., chronic disease or mental health plan) in collaboration with patients and carers. These items include:

- 75+ health assessment (MBS items: 705 / 707)
- GP management plan and review (MBS item: 721)
- coordination of team care arrangements (MBS item: 721)
- medication review (MBS item: 900)
- referral for geriatrician assessment (MBS item: 141)

Another source of comprehensive assessment of older adults in Australia is through the Aged Care Assessment Program (Department of Health, 2019a). One of the aims of this program is to assess older adults' support needs and eligibility for access to subsidised aged care services, as well as to locate and access these services. The assessments are designed to be holistic, and incorporate physical, medical, psychological, cultural, social, environmental and wellness dimensions of ageing.

2.9 Frailty intervention

Two systematic reviews which examined interventions aimed at reversing frailty, by Puts et al (2017) (12 RCTs and 2 cohort studies) and Apostolo et al (2018) (21 RCTs) respectively, identified the strongest evidence in favour of exercise and nutrition interventions. While findings for comprehensive geriatric assessment (CGA) have been mixed, the landmark Australian Frailty Intervention Trial (FIT) of Cameron and colleagues (2013), which used CGA principles to underpin assessment and intervention, demonstrated a 14.7% lower prevalence in the intervention group. The intervention, delivered over 12 months, was both multidisciplinary and multifactorial (nutrition, exercise, psychological treatment, social linkage, and equipment) and was tailored to frailty (FP) characteristics identified at baseline. A tailored approach to monitoring and intervention is recommended depending on the stage of frailty progression (Sternberg, Wershof Schwartz, Karunananthan, Bergman, & Mark Clarfield, 2011). Robust individuals would benefit from prevention strategies

focused on minimising risk factors such as hypertension, smoking, cholesterol, and ensuring vaccinations are up-to-date; while pre-frail individuals may require prevention strategies, such as chronic disease management, geriatric assessment, falls prevention; and for frail individuals, rehabilitation, geriatric management, symptom management, and strategies to maintain function and quality of life, including rehabilitation (Sternberg et al., 2011). Some of these strategies will involve linking patients to relevant allied health and support services, local gyms, pharmacy, geriatricians, and geriatric outpatient services. For frail patients who are approaching end of life, a discussion on the goals of care is also required, considering advanced care directives, supportive and palliative care, and a transition from active treatment to comfort care (Cardona-Morrell et al., 2017).

When planning frailty interventions, older adults should be engaged in setting goals based on the needs that are most important to them (Theou & Rockwood, 2012). As most frailty interventions require some form of behaviour change, using the principles of motivational interviewing and working collaboratively with patients is critical for success (Rollnick, Miller, & Butler, 2008).

It is important to note that a number of the interventions described to treat frailty are likely to have a complementary benefit for sarcopenia, particularly exercise in combination with other strategies, such as protein supplementation (Dent et al., 2018; Puts et al., 2017).

2.9.1 Physical activity and nutritional status

Exercise and nutritional strategies (especially increasing protein intake) are critical in the prevention and treatment of frailty (Puts et al., 2017). Older people are keen to know more about exercise, but, importantly, have expressed a desire to be kept informed and encouraged by their GP (Jadczak, Dollard, Mahajan, & Visvanathan, 2017). Exercise interventions, in addition to improving frailty status, also have positive effects on falls reduction, balance, mobility, mood, and functional ability (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millan-Calenti, 2015).

Group exercise programs can provide opportunities for socialisation, which has its own beneficial effects, as well as contributing to exercise adherence (Farrance, Tsofliou, & Clark, 2016). Exercise programs for addressing frailty should ideally be multi-component, involving a combination of resistance, balance, and flexibility (Jadczak, Makwana, Luscombe-Marsh, Visvanathan, & Schultz, 2018). Strength training is emphasised as a key component of exercise (Puts et al., 2017). Online exercise prescribing resources are available to aid decision making (Exercise is Medicine Australia, 2018).

As nutrition is an important factor in the pathophysiology of frailty, it also has a role in its treatment (Cruz-Jentoft, Kiesswetter, Drey, & Sieber, 2017). It is recommended that the optimal daily protein intake for older people should be at least 1.0-1.2 g/kg/day (Baum, Kim, & Wolfe, 2016), with an increase to 1.2-1.5g/kg/day in those who are unwell or have a chronic disease (including dialysis) (Bauer et al., 2013). Protein intake should be <0.8g/kg/day and for those with moderate kidney disease, however, protein intake can be > 0.8 g/kg/day with regular monitoring of glomerular filtration rate (GFR) required for those with GFR >30 but <60 mL/min/1.73m^2 (Bauer et al., 2013). There is evidence to recommend protein supplementation in combination with exercise to reduce the progression of frailty (Kim & Lee, 2013), and to improve frailty status, muscle strength and mobility in older adults (Liao et al., 2018). The Asia Pacific clinical practice guidelines for the management of frailty support protein supplementation, particularly in combination with physical activity, for frail individuals demonstrating unintentional weight loss (Dent et al., 2017).

2.9.2 Medication regime

Strategies to minimise polypharmacy are an important component of the medical management of older adults who are both frail or at risk of becoming frail, and medications with an anticholinergic effect (e.g., antihistamines, tricyclic antidepressants, major tranquilisers, old and atypical antipsychotics, and antimuscarinics for urinary incontinence) have been specifically highlighted as being associated with frailty after adjusting for polypharmacy in general (Gnjidic et al., 2012, Page et al., 2016).

The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty (Dent et al., 2017) strongly recommend that polypharmacy be addressed by reducing or de-prescribing any inappropriate and / or superfluous medications. Guidelines for depresribing, such as the Screening Tool of Older Person's Prescriptions (STOPP) criteria (Hamilton et al., 2011), and the 2015 updated Beers Criteria can be used to support this strategy.

2.10 Gaps in scientific knowledge on frailty and rationale for this thesis

This section describes gaps in the scientific literature on frailty and the rationale for each of the studies included as chapters in this thesis. Internationally, there is a large and growing body of research focused on frailty prevalence and outcomes (Collard et al., 2012; Shamliyan et al., 2013; Vermeulen et al., 2011). However, at the time of commencement of this PhD, there were a limited number of population-level studies that had investigated frailty in the Australian context (Blyth et al., 2008; Dent, Hoon, et al., 2016; Widagdo et al., 2015; Wong et al., 2013). Frailty prevalence was the focus of the research reported in Chapters 4 and 5.

2.10.1 Frailty measurement

While there has been some comparison of the two dominant approaches to frailty measurement internationally (Blodgett et al., 2015), to date there has been no examination of the FP and FI together in an Australian cohort. Likewise, the dynamic nature of frailty has been examined in several international and Australian cohorts, which used single measures to examine frailty state transitions (Kojima, Taniguchi, Iliffe, Jivraj, & Walters, 2019). However, no study has compared frailty state transitions and factors associated with transition for both the FP and FI in the same cohort. Given the lack of consensus as to which assessment method is the gold standard, the research in this PhD describes findings according to both forms of measurement. These topics are the focus of research reported in Chapters 5 and 6. Understanding which factors pose different risks for frailty transition at different stages of the frailty process, for each model of frailty measurement, can support a tailored approach in targeting intervention to vulnerable individuals.

Repeated assessment. Clinicians and policy makers increasingly recognise the need for assessing the frailty status of their older patients (Theou & Rockwood, 2012), while balancing this against the burden to clinicians and consumers of repeated assessment. The dynamic nature of frailty means that a single assessment of frailty status may not reflect the changing frailty risk profile of individuals over time, and that regular review would be of benefit in order to offer appropriate interventions. While both approaches to frailty measurement have strong predictive validity for mortality, disability and other adverse health outcomes (Shamliyan et al., 2013; Vermeulen et al., 2011), the predictive ability of

repeated frailty measurement on mortality is yet to be determined and therefore, the benefit of a regular review of frailty status over time is yet to be established. This observation has been addressed through the research described in Chapter 8.

2.10.2 Screening for frailty

Primary care is a key setting for frailty identification as it is typically the first point of contact for older adults with the health system (Cesari et al., 2016; Dent, Kowal, et al., 2016; Morley et al., 2013). In the time-poor environment of clinic and general practice, there is a need for screening tools that are accurate and quick to administer. Screening for frailty using self-report instruments is a potential strategy for reducing the clinical resources required to screen for this condition (Pialoux et al., 2012). There is a wide range of potential screening instruments (Dent, Kowal, et al., 2016), a number of which have diagnostic test accuracy (DTA) estimates reported. However, at the beginning of the research reported here, there was yet to be a systematic review to examine the DTA of self-reported screening instruments for frailty against the FP or FI reference standard. Chapter 7 presents the results of such a review conducted for this study.

In light of a call for the use of the FRAIL Scale as a screening instrument in Australia (Burgess & Hercus, 2017), it must be remembered that no study has yet reported on this instrument's predictive validity for mortality in an Australian cohort of both men and women. A recent systematic review of the FRAIL Scale reported that while there is preliminary evidence for the predictive validity for mortality of the instrument, more studies are warranted to examine the properties of this tool (Kojima, 2018). Further research is required into the applicability of this instrument in the Australian context, which is why this topic was addressed in this research, as reported in Chapter 10.

2.10.3 Sarcopenia

Frailty may also be occur with sarcopenia (Cesari et al., 2014). The two conditions share similar features and both are associated with increased mortality risk (Liu et al., 2017; Shamliyan et al., 2013). The relationship between the two conditions has been examined in a limited number of studies internationally, particularly at population level (Mori & Tokuda, 2019; Yoshimura et al., 2019). Despite their shared characteristics, and individually each being associated with increased mortality, there has been no study which has examined the combined presence of frailty and sarcopenia and association with mortality.

A better understanding of how these two conditions interact would provide useful information on prognosis and prioritising treatment for individuals with either or both conditions. This is important as there are interventions available that may delay the development and progression of frailty, such as exercise focused on strength training, increasing nutritional intake, particularly protein, reducing polypharmacy, and increasing vitamin D levels (Andrew Clegg et al., 2013; Puts et al., 2017). The relationship between frailty and sarcopenia is examined in Chapter 9.

2.10.4 Health-state utility of frailty

Frailty is associated with lower quality of life (QOL) (Crocker et al., 2019; Kojima et al., 2016). QOL can be represented in terms of preference-based health-state utilities, which reflect preferences that individuals or groups place on a set of health outcomes (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). Health-state utilities range between 1 (perfect health) and 0 (death) and are used in evaluating the comparative effectiveness of health interventions (Drummond et al., 2005). Despite a range of studies describing the association between frailty and QOL at a population level (Crocker et al., 2019; Kojima et al., 2016), there have been no population level estimates using preference-based measures of health-state utility, which can be used in health economic evaluation of frailty interventions (Neumann, Goldie, & Weinstein, 2000). Drawing utility data from a range of sources, particularly cohort surveys, is an important component of economic evaluation, particularly when coupled with health-state transition data as it improves the reliability and generalisability of estimates (Drummond et al., 2005; Neumann et al., 2000). Chapter 11 addresses the topic of frailty health-state utility.

2.10.5 Frailty: Minimally important difference

A challenge remains for clinicians and researchers in interpreting statistically significant improvement in frailty status when examining frailty interventions; namely, what level of incremental change in condition is sufficient to be considered clinically meaningful? Minimally important difference (MID) is the smallest change in a treatment outcome which an individual would perceive as being important, and can assist with the understanding of how much change associated with an intervention is important to health consumers (Wyrwich et al., 2005). At the beginning of this research, no studies had yet published frailty MID findings for either the frailty phenotype (FP) or frailty index (FI). MID may be useful in providing a patient perspective that informs clinical decision making regarding the effectiveness of frailty interventions (Sloan, Cella, & Hays, 2005). Frailty MID estimates are the focus of Chapter 11.

2.11 Summary

In summary, frailty is common among older adults, and despite being associated with adverse health outcomes, is a dynamic condition where interventions are available to prevent, delay or slow its progression. The primary care setting is ideally suited to the identification and management of frailty, and a range of quick and easy to administer screening instruments is available as the starting point in a stepwise process of more detailed assessment which may result in comprehensive management. However, a challenge facing clinicians is the differing approaches to frailty measurement (the FP and FI), and the wide variety of frailty screening instruments available. When assessing for frailty, it is important to also consider the presence of sarcopenia which has shared features with frailty, particularly weakness and slowness. Efforts to improve frailty status or maintain healthy ageing are likely to result in improved quality of life.

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Research cohort profile

This chapter provides background information on the research cohorts used in the studies that are described in the chapters that follow.

3.1   North West Adelaide Health Study (NWAHS)

The studies comprising each chapter of this thesis (with the exception of Chapters 1, 2 and 12, and Chapter 4, which included additional population cohorts) were a secondary analysis of data from the North West Adelaide Health Study (NWAHS), a population representative longitudinal study of 4060 men and women aged≥18 years (Grant et al., 2009).

All households in the North West of metropolitan Adelaide (see Figure 3.1, reproduced from Melaku et al [2019]) with a listing in the *Electronic White Pages* telephone directory were eligible for study selection. Households were randomly selected, and within each household the person who had the most recent birthday and was aged ≥18 years was invited to participate. Participants were interviewed by phone, attended a clinic for a biomedical examination, and completed a written questionnaire. Individuals unable to answer questions in English at the initial recruitment stage were excluded from the study, as were individuals living in residential institutions, such as nursing homes. For Stage 1 4060 males and females aged ≥18 years were recruited to the study (51% female).
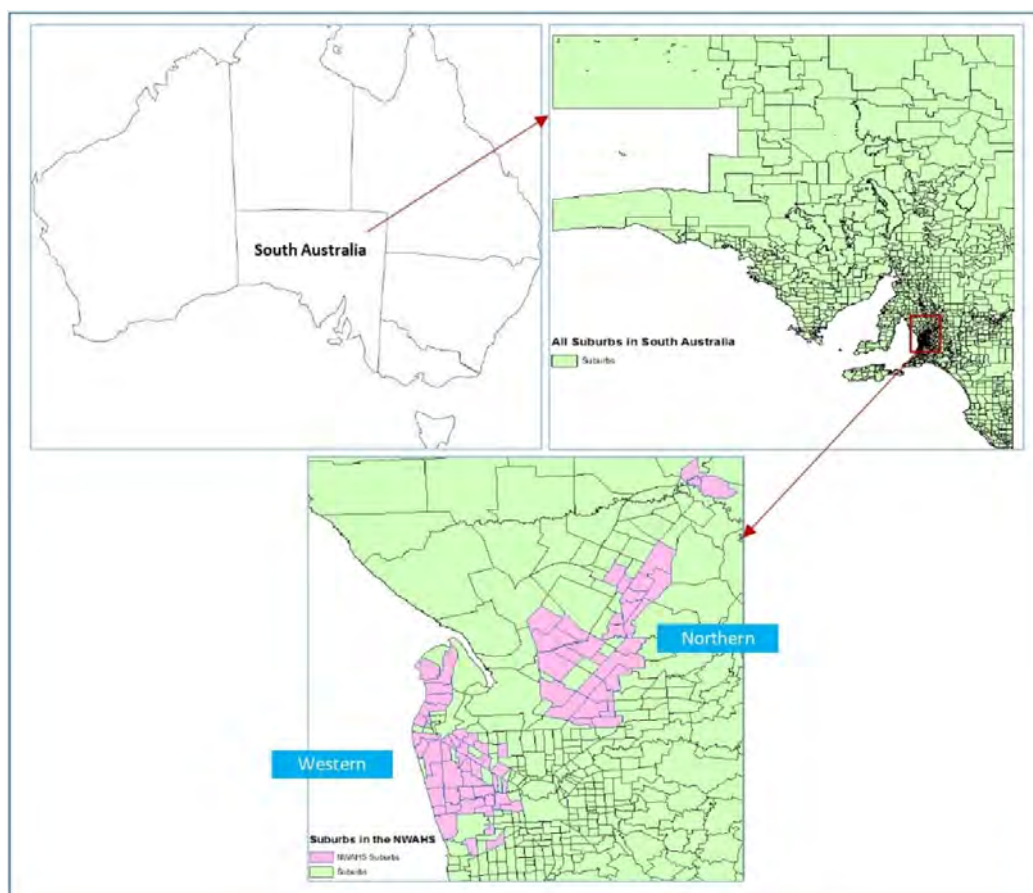
Figure 3.1   Map of the NWAHS study area (Reproduced from Melaku et al. 2019, p.2)

The data collection for Stage 1 occurred between 1999-2003. For Stage 2 data were collected between 2004-2006, and for Stage 3 between 2008 and 2010. A phone interview, clinic examination, and written questionnaire were repeated for each stage. The probability of selection was known, which allowed for weighting of data to the area population. For each stage of the study, participants were contacted in approximately the same order to maintain a four year follow up time.

Stage 2 data were used as baseline for all studies included in this thesis to construct both frailty measures: the frailty phenotype (FP) and frailty index (FI). Stage 1 weight was used to calculate weight loss over four years preceding Stage 2, and likewise Stage 2 weight for weight loss over four years preceding Stage 3. Detailed discussion on the method of frailty measurement occurs in subsequent chapters.

Stage 3 data were used to construct both the FP and FI in order to measure the change in frailty at follow up. The mean time between baseline and follow up was 4.5 (SD 0.45) years. Information on participant mortality was drawn from data matching to official death records. The follow-up window for mortality was to a censoring date of 30/9/2016. (There was a minimum of 10 years of mortality data for all participants.)

In summary, the NWAHS data collected during **Stage 2** (baseline for studies in this thesis) included:

- *phone interview*:
  demographic information; health conditions; health care utilisation; joint pain; falls and injury; and Centre for Epidemiological Studies Depression Scale (CES-D)

- *written questionnaire:*
  36-Item Short Form Survey (SF-36); exercise; family history of health conditions; osteoporosis and sequelae; sunlight exposure; diabetes and sequelae; respiratory function and sequelae; alcohol consumption; smoking; mental health and wellbeing – General Health Questionnaire-12 (GHQ-12); and demographics.

- *clinic measurement:*
  height and weight; blood pressure; spirometry; grip strength; dual-energy X-ray absorptiometry (DEXA); and blood and urine analysis.

Data collected during **Stage 3** (follow-up for studies in this thesis) included:

- *phone interview:*
  demographics; health conditions; falls and injury; joint pain; health care utilisation; exercise; Assessment of Quality of Life (AQOL) instrument; cardiovascular disease and health literacy; self-reported body measurements; household food habits; household environment; other members of the household; and early learning

- *written questionnaire:*
  36-Item Short Form Survey (SF-36); carers; family history; diabetes and sequelae; respiratory function and sequelae; Asthma Control Questionnaire (ACQ); Chronic Lung Disease (CLD) severity index; alcohol consumption; smoking; sleep quality; Centre for

Epidemiological Studies Depression Scale (CES-D); Pearlin Mastery Scale; joint pain; and cardiovascular disease questionnaire

- *clinic measurement:*
    height and weight; blood pressure; spirometry; grip strength; and blood and urine analysis.

Frailty was examined in the NWAHS cohort as it was a local population study that included a comprehensive range of assessments that allowed both frailty measures to be quantified together with other outcomes of interest such as sarcopenia, quality of life, and mortality. Stage 2 was used as baseline rather than Stage 1 as weight loss between these stages was used as a FP variable.

3.2 DYNOPTA

The study described in Chapter 4 of this thesis was a secondary cross-sectional analysis of data from the Dynamic Analyses to Optimise Ageing Project (DYNOPTA) and the NWAHS.

DYNOPTA is a pooled dataset of nine Australian longitudinal studies of ageing consisting of: the Australian Longitudinal Study of Ageing (ALSA); Australian Longitudinal Study on Women's Health (ALSWH); Australian Diabetes and Obesity Survey (AusDiab); Blue Mountains Eye Study (BMES); Canberra Longitudinal Study (CLS); Household, Income and Labour Dynamics of Australia (HILDA); Melbourne Longitudinal Study Healthy Ageing (MELSHA); Personality and Total Health through life (PATH); and the Sydney Older Person's study (SOPS) (Anstey et al., 2010) (Figure 2).

DYNOPTA included 50,652 baseline participants (wave 1 of each study between 1990 and 2001). Of these, 39 085 (77.2%) were female. The pooled DYNOPTA dataset consisted of :

- demographic information
- outcome variables for four key domains of
    - cognition
    - mental health
    - physical disability
    - sensory function
- medical conditions
- health behaviours
- psychosocial measures.

For DYNOPTA studies to be included in the Chapter 4 analysis, the single phases of each study had to have been conducted between 2004 and 2006, with variables available to construct the FP. There were three studies in DYNOPTA which met the criteria for inclusion–the Australian Longitudinal Study of Women's Health Old Cohort (ALSHW-old) (Lee et al., 2005); Australian Diabetes and Obesity Lifestyle Study (AusDiab) (Dunstan et al., 2002); and the Blue Mountains Eye Study (BMES) (Attebo, Mitchell, & Smith, 1996; Mitchell et al., 1998).
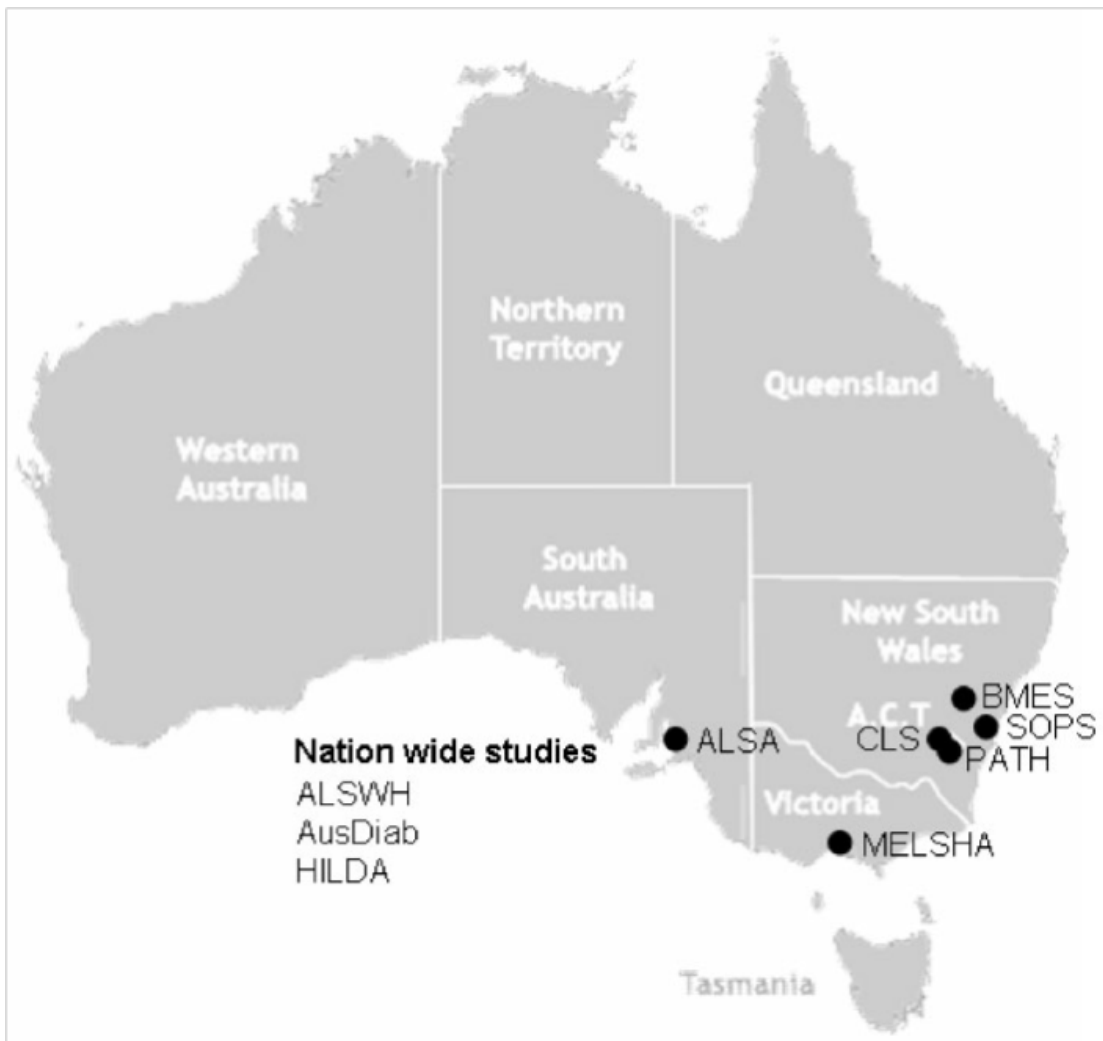
Figure 3.2 **Locations of contributing Australian Longitudinal Ageing Studies,**
Reproduced from Anstey et al (2009) p4.

Participants included in our secondary analysis were community-dwelling, aged ≥65 years, and had at least three valid responses to the five potential frailty variables. Participants from DYNOPTA studies living in residential care facilities and those with missing information regarding community or residential status were excluded from this study. Frailty was not measured directly in any of the cohorts; however, it was operationalised using a modification of the FP and is described in detail in chapter 4. All data was collected regardless of age.

We decided to examine frailty in DYNOPTA as the combination of population level studies from across Australia was useful for reporting frailty prevalence in Australia. The cohort profiles included DYNOPTA studies are discussed below.

3.2.1 Australian Longitudinal Study of Women's Health Old Cohort (ALSHW-old)

The ALSHW-old is a national population-based sample of women aged 70-75 years living in both the community and residential care (Lee et al., 2005). Participants were randomly selected from the database of the Health Insurance Commission (HIC) that runs Medicare, the national health insurance scheme. Sampling from the population was random; however,

women living in rural and remote areas were sampled at twice the rate of those living in urban areas. Surveys were posted to potential participants with information packs inviting participation. The postal survey measured:

- 36-Item Short Form Survey (SF-36)
- Center for Epidemiologic Studies Depression Scale (CES-D)
- measures of social support and neighbourhood satisfaction
- demographics
- health behaviours
- diagnoses and symptoms
- health service utilisation
- stress
- life events.

3.2.2 Australian Diabetes and Obesity Lifestyle Study (AusDiab)

The AusDiab is a national population-based sample of community-dwelling men and women aged ≥25 years; (Dunstan et al., 2002). A cluster sampling method was used based on a random selection of six census collector districts, which are the smallest geographic units defined by the Australian Bureau of Statistics at each census, consisting of an average of 225 dwellings each. All private dwellings within the cluster received a letter inviting participation. An interviewer visited each household and conducted an interview with every resident who met the eligibility requirements. The interviewer collected information on demographics and any history of diabetes.

Participants then attended a local testing site for a biomedical examination of individuals' physical features, including height, weight, blood pressure, ECG; fasting blood measurements; and urine measurement. Participants also completed a self-administered questionnaire, consisting of a 36-Item Short Form Survey (SF-36) and questions about general health and wellbeing. For the purposes of this study, we only included participants aged ≥65 years.

3.2.3 Blue Mountains Eye Study (BMES)

The BMES is a population-based sample of community-dwelling men and women in New South Wales aged ≥49 years (Attebo et al., 1996; Mitchell et al., 1998). Participants living in two postcode areas to the west of Sydney (Katoomba, Leura, Medlow Bath (postcode 2780) and Wentworth Falls (postcode 2782) were recruited through a door-to-door census. All permanent residents who were not living in residential care were invited to attend a clinic examination. The examination consisted of an assessment of eye conditions, and general health status, diet, family history, fasting blood tests, hearing assessment, tests of memory and cognition (mini mental state examination), and quality of life (the 36-Item Short Form Survey [SF-36]).

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Frailty prevalence in Australia:
Findings from four pooled Australian cohort studies

Frailty prevalence in Australia: Findings from four pooled Australian cohort studies was published in the *Australasian Journal of Gerontology*. The statement of authorship and paper (.pdf) follow over the page.

This article, together with the article in Chapter 5, were the subject of an invited commentary on frailty in the same journal issue by Vasikaran Naganathan (2018). The results from this study were used as the basis for analysis in a publication by Taylor and colleagues (2019) which examined geospatial modelling of the prevalence and changing distribution of frailty in Australia.

4.1 Summary of the study

Objectives: To examine the prevalence of frailty in Australian older adults.

Methods: Frailty was measured using a modified Fried frailty phenotype (FFP) in a combined cohort of 8804 Australian adults aged $\geq$65 years (female 85.6%, median age 80 [79-82] years) from the Dynamic Analyses to Optimise Ageing Project (DYNOPTA) and the North West Adelaide Health Study (NWAHS).

Results: Using the FFP, 20.5% of participants were identified as frail, while a further 47.9% were pre-frail. Chi square testing of frailty among four age groups (65-69, 70-74, 75-79, and 80-84 years) for sex and marital status revealed that frailty was significantly higher for females (approximately double that of men), increased significantly with advancing age for both sexes, and was significantly higher for women who were widowed, divorced or never married.

Conclusions: If frailty could be prevented or reversed it would have an impact on a larger number of older people.

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Principal Author

Name of Principal Author (Candidate)	Mark Q Thompson	
Contribution to the Paper	Performed analysis on data from both cohorts, interpreted data, wrote manuscript.	
Overall percentage (%)	80%	
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper	
Signature		Date 12/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that.

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Olga Theou	
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation	
Signature		Date 20/12/16

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Contribution to the Paper	Helped in data interpretation, and to evaluate and edit the manuscript	
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Name of Co-Author	Robert J Adams
Contribution to the Paper	Representative of the North West Adelaide Health Study – source of data. Helped to evaluate and edit the manuscript
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Name of Co-Author	Renuka Visvanathan
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation
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Brief Report
Frailty prevalence in Australia: Findings from four pooled Australian cohort studies

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Objective: *To examine frailty prevalence in Australian older adults.*

Methods: *Frailty was measured using a modified Fried Frailty Phenotype (FFP) in a combined cohort of 8804 Australian adults aged ≥65 years (female 86%, median age 80 (79–82) years) from the Dynamic Analyses to Optimise Ageing Project and the North West Adelaide Health Study.*

Results: *Using the FFP, 21% of participants were frail while a further 48% were prefrail. Chi-squared testing of frailty among four age groups (65–69, 70–74, 75–79 and 80–84 years) for sex, and marital status revealed that frailty was significantly higher for women (approximately double that of men), increased significantly with advancing age for both sexes, and was significantly higher for women who were widowed, divorced or never married.*

Conclusion: *If frailty could be prevented or reversed, it would have an impact on a larger number of older people.*

Policy Impact: Population studies show a high prevalence of frailty. The challenge for researchers in this field is to find effective and practical interventions that can reverse and/or prevent frailty.

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Key words: *Australia, cohort studies, epidemiologic measurements, frail older adults, prevalence.*

Introduction

Frailty is a state of decreased physiological reserve in which individuals are more vulnerable to stressors and at greater risk of adverse health outcomes such as falls, fracture, hospitalisation and loss of independence [1]. There are two approaches commonly used to describe frailty: The Fried Frailty Phenotype (FFP) and the cumulative deficits approach. The former views frailty as a physiologic syndrome which is present when three or more of the following deficits are present: Unintentional weight loss, self-reported exhaustion, slow walk speed and low physical activity [2]. The latter approach defines frailty as a multidimensional risk state based on the proportion of potential deficits present in the individual, with a higher proportion representing a higher level of frailty [3]. Both approaches have been shown to have strong predictive validity for mortality, disability and other adverse health outcomes [4,5]. Individuals classified as prefrail also have an elevated but intermediate risk of adverse outcomes [2]. Regardless of the approach used in measurement, it is important to note that frailty is a dynamic process where individuals are capable of transitioning to lesser states of frailty, particularly those who are prefrail [6,7]. Furthermore, interventions such as exercise in combination with other strategies may delay the development and progression of frailty; however, there is not yet consensus among researchers on the ideal approach [1,8].

Internationally, pooled measurements of frailty prevalence for both men and women have been identified at between 10 and 14% using the FFP [4,9]. Frailty prevalence is known to increase with age, is higher among women, and is associated with social vulnerability [4,10]. Frailty has been examined in Australia using various frailty methods [11,12]; however, the FFP is the most commonly used frailty scale internationally [13]. No Australian study has pooled data from Australian cohort study data sets to determine frailty prevalence in men and women.

The aim of this study was to examine frailty point prevalence using the FFP in Australian adults aged ≥65 years from the Dynamic Analyses to Optimise Ageing Project (DYNOPTA) and the North West Adelaide Health Study (NWAHS).

Methods

This study was a secondary cross-sectional analysis of data from the DYNOPTA, a pooled data set of nine Australian longitudinal studies of ageing (data from three studies used), and the NWAHS, a population-based sample of community-dwelling adults aged ≥18 years living in the north-western metropolitan area of Adelaide [14,15]. The studies contributing to the DYNOPTA data set for this study included the following: The Australian Longitudinal Study of Women's Health Old Cohort (ALSWH-old), a national population-based sample of women aged 70–75 years living in both the community and residential care; the Australian Diabetes and Obesity Lifestyle Study (Aus-Diab), a national population-based sample of community-dwelling men and women aged ≥25 years; and the Blue Mountains Eye Study (BMES), a population-based sample of community-dwelling men and women in New South Wales aged ≥49 years [14].

Data were drawn from single phases of each study conducted between 2004 and 2006. In this secondary analysis, participants included in the study were community-dwelling, aged ≥65 years and had at least three valid responses to the five potential frailty variables. Data from six DYNOPTA studies were not able to be included in our analysis as variables were not measured to construct the FFP or data collection was out of the date range. Frailty was not measured directly in any of the cohorts; however, it was operationalised using a modification of the FFP (Table 1) [2]. The recruitment and follow-up of participants are described elsewhere [14,15]. Participants from DYNOPTA studies living in residential care facilities (*n* = 99) and those with missing information regarding community or residential status (*n* = 67) were excluded from this study.

Individuals with three or more criteria were classified as frail, those with one and two criteria as prefrail, while those with no deficits were considered not frail [2]. It is common for studies to make more than one modification to the FFP, particularly when using existing data to operationalise frailty and to use only self-reported items [16]. Approximately 88% of studies which use the FFP modify at least one criterion [16]. The modified frailty criteria used in this study were developed according to the availability of variables across the multiple data sets and that the modifications had been used previously in other published studies [16].

Data were analysed using IBM SPSS Statistics 23 software. Descriptive characteristics were reported as percentages. Subgroup analysis of frailty prevalence was determined for sex, age groups (65–69, 70–74, 75–79 and 80–84 years) and marital status, due to the known association between these factors and frailty [4,10]. Chi-squared testing of statistical significance between subgroups was measured using an alpha value of 0.05. Weighting of results was not performed due to the combination of multiple cohorts.

Results

This study included 8804 participants aged ≥65 years (median age 80 (79–82) years, female = 86%). The breakdown of participants by individual studies was as follows: NWAHS (*n* = 944, mean age 74.0 (6.4), female 51%); ALSWH-old (*n* = 6131, mean age 80.8 (1.4), female 100%); AusDiab (*n* = 1634, mean age 73.0 (6.0), female 52%), and BMES (*n* = 95, mean age 76.3 (7.1), female 68%).

Frailty prevalence is reported in Table 2. Using the FFP, 21% of participants were classified as frail while a further 48% were prefrail. Frailty prevalence ranged from 6% in AusDiab to 26% in ALSWH–old. Frailty was significantly higher for women (*P* < 0.001), increased significantly with

Table 1: Fried Frailty Phenotype: Comparison of original and modified version used in Dynamic Analyses to Optimise Ageing Project and North West Adelaide Health Study

Item	Original phenotype	Modified phenotype
Weight loss	Unintentional weight loss of ≥10 pounds in prior year or at follow-up, of ≥5% of body weight in prior year (by direct measurement of weight)	BMI <21 kg/m^2. Clinic measurement
Weakness	Grip strength (kg) measured using dynamometer in the lowest 20% at baseline adjusted for sex and BMI. Cut points stratified by sex and BMI	Reporting health limits lifting or carrying groceries 'a lot' from the SF36
Exhaustion	Two questions used from the CES–D Scale. How often in the last week did you feel: (i) I felt that everything I did was an effort; and (ii) I could not get going Scoring: Rarely or none (0), some or a little (1), moderate (2), most (3). Deficit present when answering '2' or '3' to either question	Responding to the question 'during the past four weeks did you feel worn out?' with 'good bit, most or all'
Slowness	The slowest 20% of the population based on time to walk 15 feet, adjusting for sex and height	Reporting that health limits walking 100 m either 'a little' or 'a lot' from the SF36
Low activity	Minnesota Leisure Time Activity Questionnaire. Kilocalories per week stratified by sex. Men <383 kcal per week, women <270 kcal per week	Reporting no walking for sport, recreation or fitness in the last two weeks

BMI, body mass index; CES-D, Centre for Epidemiologic Studies Depression; SF36, 36-item Short Form Survey.

Table 2: Frailty prevalence using the Fried Frailty Phenotype (FFP) and association with demographic variables

	Total, n (%)	Phenotype categories			P-value
		Not frail, n (%)	Prefrail, n (%)	Frail, n (%)	
Whole sample	8804	2780 (32)	4217 (48)	1807 (21)	—
Study					
NWAHS	944 (11)	402 (43)	418 (44)	124 (13)	—
ALSWH-old	6131 (70)	1492 (24)	3074 (50)	1565 (26)	—
AusDiab	1634 (19)	856 (52)	674 (41)	104 (6)	—
BMES	95 (1)	30 (32)	51 (54)	14 (15)	—
Sex					
Male	1272 (14)	666 (52)	527 (41)	79 (6)	<0.001*
Female	7532 (86)	2114 (28)	3690 (49)	1728 (23)	—
Age, mean (SD)	78.6 (5)	76.7 (6)	79.0 (5)	80.4 (3)	—
Age, median (IQR)	80 (79–82)	79 (72–81)	80 (79–82)	81 (79–82)	—
Age groups, years†					
65–69	905 (10)	521 (58)	343 (38)	41 (5)	<0.001*
70–74	696 (8)	362 (52)	286 (41)	48 (7)	—
75–79	2076 (24)	659 (32)	1044 (50)	373 (18)	—
80–84	4990 (57)	1205 (24)	2468 (50)	1317 (26)	—
Marital status‡					
Married/De facto	4042 (46)	1436 (36)	1895 (47)	711 (18)	<0.001*
Divorced/Widowed/Never married	4702 (53)	1329 (28)	2287 (49)	1086 (23)	—
Stratified by sex					
Age groups (male), years†					
65–69	427 (34)	256 (60)	159 (37)	12 (3)	<0.001*
70–74	331 (26)	188 (57)	130 (39)	13 (4)	—
75–79	274 (22)	123 (45)	129 (47)	22 (8)	—
80–84	172 (14)	76 (44)	72 (42)	24 (14)	—
Age groups (female), years†					
65–69	478 (6)	265 (55)	184 (39)	29 (6)	<0.001*
70–74	365 (5)	174 (48)	156 (43)	35 (10)	—
75–79	1802 (24)	536 (30)	915 (51)	351 (20)	—
80–84	4818 (64)	1129 (23)	2396 (50)	1293 (27)	—
Marital status (male)‡					
Married/De facto	990 (78)	528 (53)	408 (41)	54 (6)	0.174
Divorced/Widowed/Never married	259 (20)	130 (50)	107 (41)	22 (9)	—
Marital status (female)‡					
Married/De facto	3052 (41)	908 (30)	1487 (49)	657 (22)	0.008*
Divorced/Widowed/Never married	4443 (59)	1199 (27)	2180 (49)	1064 (24)	—

*P < 0.05 (chi-squared test; main effects only reported). †Participants aged ≥85 years excluded from age group analysis due to small sample size (males n = 70, females n = 75). ‡Not stated or missing not included. Fried Frailty Phenotype cut points for number of deficits: 0 = not frail, −, Not reported; 1–2 = prefrail, ≥3 = frail. —, Not reported; ALSWH-old, Australian Longitudinal Study of Women's Health Old Cohort; AusDiab, Australian Diabetes and Obesity Lifestyle Study; BMES, Blue Mountains Eye Study; IQR, interquartile range; NWAHS, North West Adelaide Health Study; SD, standard deviation.

older age groups (P < 0.001), and was significantly higher for those widowed, divorced or never married (P < 0.001). When stratified by sex, frailty was significantly associated with older age groups for both men (P < 0.001) and women (P < 0.001); however, being widowed, divorced or never married was associated with higher frailty prevalence for women only (P = 0.008). For those classified as frail (n = 1807), the most common deficits present were slowness (n = 1693, 94%), followed by low physical activity (n = 1645, 91%), weakness (n = 1120, 62%), exhaustion (n = 661, 37%) and weight loss (n = 351, 19%).

Discussion

Based on our study of pooled data from four Australian longitudinal studies on ageing, 21% of participants were identified as frail, with a further 48% as prefrail. The prevalence of frailty in women was approximately double that seen in men across all age groups, and as expected, the prevalence of frailty increased significantly with

increasing age. The prevalence of frailty in this sample is substantially higher than has been reported previously in Australian studies [17,18]. Frailty was significantly higher in our study for women who were divorced, widowed or never married compared to their married or de facto counterparts. A range of social vulnerability variables, including being divorced or widowed, have been previously identified with increased frailty [10].

The higher prevalence in this study is most likely due to the large proportion of female participants, who are known to have higher rates of frailty than men [9]. Also, using a modified FFP consisting of self-report items may have contributed to a prediction of frailty prevalence 4% higher than using original criteria [16]. Frailty prevalence in our study was similar to a systematic review of 24 international studies where frailty prevalence was 7% for men and 13% for women, with frailty by age group in women ranging from 3% for those aged 65–70 years to 31% for those aged 85–90 [4].

Modifications to the FFP are common across studies in order to make use of available variables, but can result in substantial differences to frailty prevalence [16]. The modification of the five phenotype variables was a limitation of this study, and the findings should be considered in this light. These specific five criteria used in combination have not been validated. The prevalence reported here is likely an underestimate of frailty in the total population as older adults living in residential aged care or those unable to participate in clinic assessments were not included. The use of the phenotypic method rather than the deficit accumulation method is also likely to have resulted in a lower prevalence [1]. As our study was a secondary analysis of four pooled studies, we were unable to report on other descriptive characteristics of the sample due to differences in measurement of these variables between each study. Despite the limitations outlined above, this is the largest study to examine frailty prevalence in Australia to date.

Conclusion

Currently, with more than 3 million Australian adults aged 65 and over, at least 700 000 may be frail and a further 1.6 million prefrail. By 2031, 5.7 million Australians will be aged 65 years and older [19]. By then, the number of frail older adults may be 1.2 million with a further 2.7 million prefrail if the prevalence is unchanged. If an intervention was to reduce the onset of frailty by just 5% [8], there could be 370 000 less frail older people in our society by 2031, thus potentially reducing the health and aged care cost burden [20].

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Frailty prevalence and factors associated with the frailty phenotype and frailty index. Findings from the North West Adelaide Health Study

Frailty prevalence and factors associated with the frailty phenotype and frailty index. Findings from the North West Adelaide Health Study was published in the *Australasian Journal of Gerontology*. This article, together with the article which comprises Chapter 4, were the subject of an invited commentary on frailty in the same journal issue by Vasikaran Naganathan (2018). The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 5.

5.1   Summary

Objectives: To determine the prevalence of frailty and associated factors in the North West Adelaide Health Study (2004-06) using the frailty phenotype (FP) and frailty index (FI).

Methods: Frailty was measured in 909 community dwelling participants aged ≥65 using the FP and FI.

Results: The FP classified 18% of participants as frail, and the FI 48%. The measures were strongly correlated (r = 0.76, p < 0.001) and had a kappa agreement of 0.38 for frailty classification, with 37% of participants classified as non-frail by the FP being classified as frail by the FI. Being older, a current smoker, and having multimorbidity and polypharmacy were associated with higher frailty levels by both tools. Female, low income, obesity, and living alone were associated with the FI.

Conclusions: Frailty prevalence was higher when assessed using the FI. Socioeconomic factors and other health determinants contribute to higher frailty levels.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 12/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Research

Frailty prevalence and factors associated with the Frailty Phenotype and Frailty Index: Findings from the North West Adelaide Health Study

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Objective: *To determine the prevalence of frailty and associated factors in the North West Adelaide Health Study (2004–2006) using the Frailty Phenotype (FP) and Frailty Index (FI).*
Methods: *Frailty was measured in 909 community-dwelling participants aged ≥65 years using the FP and FI.*
Results: *The FP classified 18% of participants as frail and the FI 48%. The measures were strongly correlated (r =*

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0.76, P < 0.001) and had a kappa agreement of 0.38 for frailty classification, with 37% of participants classified as non-frail by the FP being classified as frail by the FI. Being older, a current smoker, and having multimorbidity and polypharmacy were associated with higher frailty levels by both tools. Female, low income, obesity and living alone were associated with the FI.
Conclusion: *Frailty prevalence was higher when assessed using the FI. Socioeconomic factors and other health determinants contribute to higher frailty levels.*

Practice Impact: It is important to be aware that there is only modest agreement between two of the most common measures used to determine frailty. Factors associated with frailty included older age, multimorbidity, polypharmacy, being female, low income, living alone, obesity and smoking.

Introduction

Frailty is a state of decreased physiological reserve in which individuals are vulnerable to stressor events resulting in adverse health outcomes such as falls, disability and death [1]. There are two main approaches to defining frailty. The Frailty Phenotype (FP) focuses on physical manifestations, and frailty is present when three of more of the following criteria are met: unintentional weight loss, weak grip strength, self-reported exhaustion, slowness and low physical activity level [2]. The cumulative deficits model is mathematically based, where frailty is the proportion of deficits present in an individual and this proportion is represented as a Frailty Index (FI) [3,4]. Despite differences, both approaches are moderately correlated [5]. Frailty increases nonlinearly with age, is predictive of mortality and is higher for women [6]. Studies which report on frailty using established FI cut-points tend to report higher frailty prevalence in comparison with the FP [7]. While the FP was designed and is most commonly used as a categorical measure, it has also been used as a continuous measure to examine the association of frailty with adverse outcomes, and for comparison with other frailty measures [1,6,8–11]. Furthermore, using a continuous FP may result in improved predictive validity of the measure [11].

Frailty has been investigated in four Australian cohort studies [12–15]. One South Australian study using 1992 data compared frailty using both the FP and FI, where frailty prevalence was reported at 9% (FP) and 18% (FI) (mean age 78.2 (6.7)) respectively [12]. Two other male studies reported a prevalence of 9% (FP; New South Wales; mean age 76.9 (5.5)) and 16% (FRAIL Scale; Western Australia, mean age 76.9 (3.8)) [13,14]. One very recent rural South Australian study looked at individuals ≥65 years and found a frailty prevalence of 25% (FI; mean age 75.9 (7.9)) [15].

The aims of this study were to determine the prevalence of frailty in the North West Adelaide Health Study (NWAHS) using two measures of frailty (FP and FI) and to determine factors associated with both of these measures. A novel feature of our study is the examination of factors associated with frailty in Australian men and women using both the FP and FI.

Methods

Sample and study design
This is a secondary analysis of data from NWAHS, a population representative longitudinal study of 4060 men and women aged ≥18 years [16]. Participants in the study were randomly selected from households in the north-west of metropolitan Adelaide and were interviewed by phone, attended a clinic for biomedical examination and completed a questionnaire. Probability of selection was known and allowed for weighting of data to the area population. Individuals living in residential care facilities were excluded from NWAHS.

Participants included in this secondary analysis were those aged ≥65 years who attended the clinic assessment at Stage 2 (2004–2006). Stage 1 weight was used to calculate baseline weight loss over four years preceding Stage 2. Variables within the data set were used to construct both the FP and FI measures [17]. Participants were excluded if they had a FP score with <3 valid responses or a FI with <27 valid responses (20% missing). We used Stage 2 data for this study, as future analysis will examine frailty state transitions and associations with quality of life and survival in Stage 3 (2008–2010). SA Health Human Research Ethics Committee (TQEH/LMH/MH) (Reference number HREC/15/TQEH/61) provided ethics approval.

Construction of the Frailty Phenotype
Data were available for the original phenotype criteria (exhaustion and weakness), and modified variables were used for the remaining three (weight loss, slow walking and low physical activity) [18] (Table 1). The FP is typically presented as three categories (non-frail, prefrail and frail). In this article, we have used a dichotomous FP, non-frail (0–2 deficits, combining non-frail and prefrail categories) and frail (3+ deficits) to examine association with cohort characteristics. Results for the FP were reported as both categorical (non-frail and frail) and continuous (proportion of deficits).

Construction of the FI
At least 30 age-related health deficits are required to calculate a FI [4]. We developed a 34-item FI based on a standard methodology [4] and excluded outcomes of interest for further analysis such as variables used in the Short Form 6D quality of life measure. Included variables were recoded to provide a score between 0, for no deficit, and 1, for maximal expression of deficit. The FI may be reported as a continuous measure between zero (extremely robust) and one (extremely frail) [3] and is also typically presented as four categories (non-frail, prefrail, frail and most frail) with a frail cut-point of 0.21 representing elevated risk of adverse health outcomes [19]. In this article, we have used a dichotomous FI: non-frail (0 to ≤0.21, combining non-frail and prefrail categories) or frail (>0.21, combining frail and most frail categories) to examine the association with cohort characteristics. The 34 variables included in the FI are reported in Table 1.

Statistical analysis
SPSS version 23 was used for all statistical analyses. Case weights for the cohort were used in analysis procedures, reporting mean scores and percentages to ensure that the sample was representative of the north-western population of Adelaide. Statistical significance was determined by an alpha value of 0.05. FP and FI scores were compared using one-way ANOVA in relation to descriptive characteristics of the sample. The 99th percentile was also calculated for both frailty measures. Regression models were used to test the best fit of association between age and frailty. Agreement between the two frailty scales was measured using the kappa statistic. Univariate and multivariate logistic regression analyses were used to examine the association between individual cohort characteristics and frailty. A 24-item FI was also constructed excluding chronic conditions to examine the association of frailty with multimorbidity.

Results
A total of 909 older participants (mean age 74.4 (6.2), 55% female) were included in this study. The 36 participants who were excluded (missing more than 20% of FI variables) were older (mean age 81.5 (6.5), $P < 0.001$) and were more likely to be female (84%, $P = 0.002$) than those included.

Using the FP criteria, 18% were classified as frail, compared to 48% using the FI (Table 2). See Table S1 (Supporting information) for three category frailty status classification. The kappa statistic for agreement between scales in classifying individuals was 0.38 (SE = 0.03, $P < 0.001$). Of those participants who were classified as frail by the FP, 91% were also classified as frail by the FI. However, among those classified as non-frail by the FP, more than one-third (37%) were classified as frail by the FI (Table 3). Categorical FP and FI prevalence is presented in Table S2 (Supporting information) for agreement between three category frailty measures. The participants who were classified as non-frail by the FP but frail by the FI had significantly

Table 1: Frailty Phenotype and Frailty Index variables

Item	NWAHS phenotype	Original phenotype†
Frailty Phenotype		
Weight loss	>10% weight loss over four years (clinic measurement: Phase 1 and Phase 2)	Unintentional weight loss of ≥10 pounds in prior year or at follow-up, of ≥5% of body weight in prior year (by direct measurement of weight)
Weakness	Original method used	Grip strength (kg) measured using dynamometer in the lowest 20% at baseline adjusted for sex and body mass index. Cut-points stratified by sex and BMI
Exhaustion	Original method used	Two questions used from the CES-D. How often in the last week did you feel:
		• I felt that everything I did was an effort • I could not get going
		Scoring: rarely or none (0), some or a little (1), moderate (2), most (3). Deficit present when answering '2' or '3' to either question
Slowness	Self-report to the question: Health limits you a lot walking 100 m (SF36 q11)	The slowest 20% of the population based on time to walk 15 feet, adjusting for sex and height
Low activity	Australian Bureau of Statistics National Health Survey, METs per week based on previously published cut-points for this cohort (<100 METs) [29]	Minnesota Leisure Time Activity questionnaire. Kilocalories per week stratified by sex. Men <383 kcal per week, women <270 kcal per week

34-item Frailty Index

Angina	Self-reported health
Heart attack	Health limits lifting or carrying groceries
Osteoporosis	Health limits climbing several flights of stairs
Osteoarthritis	Health limits climbing one flight of stairs
Rheumatoid and any other arthritis	Health limits bending, kneeling or stooping
Stroke or TIA	Health limits walking more than 1 km
Diabetes	Health limits walking 100 m
Any mental health problem	Felt lonely
10% weight loss over four years	Felt that could not get going
Systolic blood pressure	Difficulty keeping mind on what you were doing
Diastolic blood pressure	Felt everything was an effort
FEV1/FVC postratio	Physical and emotional problems interfered with social activities
Weak grip strength	Felt full of life
Falls	Felt calm and peaceful
Hospital emergency admission	Felt worn out
Low activity level (<100 METs per week)	Felt tired
Healthy as anybody I know	
Health is excellent	

†Exhaustion and weakness. BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; FEV1/FVC, forced expiratory volume/forced vital capacity; METs, metabolic equivalent of task; NWAHS, North West Adelaide Health Study; TIA, transient ischaemic attack.

higher ($P < 0.05$) rates of multimorbidity (2+ chronic conditions) (odds ratio (OR) 5.7, 95% confidence interval (CI) 4.1–7.9); polypharmacy (5+ medications) (OR 3.3, 95% CI 2.4–4.5); 2 + falls (OR 6.0, 95% CI 3.7–9.7); a hospital emergency admission in last 12 months (OR 2.5, 95% CI 1.5–4.2); physical function limitations: climbing one flight of stairs (OR 38.9, 95% CI 19.3–78.4), walking more than 1 km (OR 36.1, 95% CI 20.5–63.6), bending, kneeling or stooping (OR 23.8, 95% CI 13.1–43.2); emotional problems: feel full of life (OR 28.6, 95% CI 12.7–64.4), feel tired (OR 33.4, 95% CI 13.4–83.6), felt calm and peaceful (OR 8.9, 95% CI 4.1–19.5); and poor self-reported health (OR 24.5, 95% CI 13.9–43.1) than those classified as non-frail in both measures (data not shown).

Frailty Phenotype scores ranged from zero to five deficits (mean 1.32 (1.17)) with only one individual scoring five. The FI ranged from zero to 0.78 (mean 0.23 (0.15)). None of the measures showed a ceiling effect. The 99th percentile score for the FP was 4.0, and for the FI, it was

0.61. The FP demonstrated a floor effect with 29% of participants scoring zero, which was considerably greater than the 1% of participants scoring zero with the FI.

There was a strong correlation between mean FI scores and proportion of FP deficits present ($r = 0.76$, $P < 0.001$) (Figure 1a). The scores for both frailty measures as a proportion of the total deficits demonstrated a right skewed distribution (Figure 1b). Frequencies and histograms for each FP and FI variable are available in Table S3 (Supporting information).

Mean frailty scores were significantly higher in both measures for women, older age, lower income, obesity, and living alone and in the FP only for lower education and being widowed (Table 2). An exponential model best described the relationship between frailty and age, with a 4% natural log increase per year of age for the mean FP and a 3% natural log increase per year for the mean FI. For women, the log increase per year of age for frailty was 4% for the FP and 3% for the FI. For men, the rate was 3% per year of age for the FP (Figure 2a) and

Table 2: Relationship of frailty with descriptive characteristics

	Whole sample, n (%)	Mean FP (SD)	Mean FI (SD)	FP categories				FI categories			
				Non-frail, n (%)	Frail, n (%)	OR (95% CI), univariate	OR (95% CI), multivariate	Non-frail, n (%)	Frail, n (%)	OR (95% CI), univariate	OR (95% CI), multivariate
Total	909	1.32 (1.17)	0.23 (0.15)	759 (82)	150 (18)	—	—	496 (52)	413 (48)	—	—
Sex											
Male	453 (45)	1.12 (1.12)	0.20 (0.14)	394 (87)	59 (13)	1	1	275 (61)	178 (39)	1	1
Female	456 (55)	1.49 (1.19)*	0.25 (0.15)*	365 (78)	91 (22)	1.89 (1.33, 2.70)*	1.26 (0.76, 2.09)	221 (44)	235 (56)	1.97 (1.51, 2.58)*	1.89 (1.24, 2.89)*
Age groups											
65–74 years	554 (56)	1.07 (1.05)	0.20 (0.13)	499 (89)	55 (11)	1	1	339 (60)	215 (40)	1	1
>75 years	355 (44)	1.64 (1.25)*	0.26 (0.15)*	260 (72)	95 (28)	3.19 (2.23, 4.55)*	4.09 (2.56, 6.53)*	157 (42)	198 (59)	2.12 (1.62, 2.77)*	2.36 (1.61, 3.46)*
Education level†											
Up to secondary	569 (64)	1.40 (1.19)*	0.23 (0.14)*	467 (80)	102 (20)	2.59 (0.60, 11.20)	1.43 (0.29, 7.01)	300 (51)	269 (49)	3.84 (1.34, 10.96)*	3.20 (0.83, 12.34)
Trade/Cert/Dip	288 (31)	1.14 (1.13)	0.22 (0.15)	248 (86)	40 (14)	1.66 (0.37, 7.38)	1.03 (0.21, 5.08)	167 (53)	121 (47)	3.51 (1.21, 10.17)*	3.74 (0.97, 14.42)
Bachelor degree+	25 (3)	.67 (1.05)	0.16 (0.14)	23 (91)	2 (9)	1	1	20 (82)	5 (18)	1	1
Income groups†											
Up to $20k	462 (47)	1.50 (1.18)*	0.25 (0.15)*	371 (79)	91 (21)	7.51 (0.81, 69.73)	8.70 (0.76, 99.31)	225 (46)	237 (54)	3.73 (1.41, 9.86)*	3.66 (1.11, 12.09)*
$20–$40k	281 (34)	1.03 (1.12)	0.20 (0.14)	246 (86)	35 (14)	4.56 (0.49, 42.87)	5.00 (0.44, 56.43)	180 (61)	101 (39)	1.98 (0.74, 5.27)	1.82 (0.56, 5.94)
$40–$60k	59 (7)	0.94 (1.05)	0.20 (0.15)	53 (89)	6 (12)	3.43 (0.33, 36.22)	4.23 (0.33, 54.44)	38 (64)	21 (36)	1.81 (0.61, 5.35)	1.73 (0.46, 6.52)
More than $60k	26 (3)	0.78 (.88)	0.14 (0.10)	25 (96)	1 (4)	1	1	21 (75)	5 (25)	1	1
Smoking status†											
Never smoked	416 (48)	1.37 (1.14)	0.23 (0.15)	351 (81)	65 (19)	1	1	234 (52)	182 (48)	1	1
Former smoker	428 (45)	1.23 (1.19)	0.22 (0.14)	358 (84)	70 (17)	0.85 (0.59, 1.21)	0.76 (0.47, 1.24)	231 (52)	197 (48)	0.99 (0.75, 1.30)	0.96 (0.65, 1.42)
Current smoker	61 (6)	1.51 (1.24)	0.23 (0.16)	48 (79)	13 (21)	1.12 (0.56, 2.24)	3.24 (1.37, 7.68)*	31 (52)	30 (48)	1.03 (0.59, 1.80)	2.36 (1.12, 4.99)*
Alcohol consumption†,‡											
Not at risk	775 (85)	1.34 (1.18)	0.23 (0.15)	642 (81)	133 (19)	1	1	422 (52)	353 (48)	1	1
Excess	98 (10)	1.16 (1.09)	0.21 (0.13)	86 (89)	12 (11)	0.52 (0.26, 1.04)	0.60 (0.26, 1.42)	57 (58)	41 (42)	0.77 (0.49, 1.19)	1.27 (0.71, 2.26)
Waist circumference†,§											
Normal	426 (45)	1.12 (1.17)	0.20 (0.14)	374 (86)	52 (15)	1	1	278 (62)	148 (38)	1	1
Obese	478 (54)	1.48 (1.15)*	0.25 (0.14)*	382 (79)	96 (21)	1.60 (1.13, 2.28)*	1.07 (0.68, 1.66)	216 (43)	262 (57)	2.15 (1.65, 2.82)*	1.49 (1.04, 2.13)*
Multimorbidity†											
0–1 health conditions	622 (67)	1.13 (1.08)	0.18 (0.12)	552 (87)	70 (13)	1	1	428 (66)	194 (34)	1	1
2+ health conditions	287 (33)	1.71 (1.25)*	0.33 (0.14)*	207 (70)	80 (30)	2.94 (2.08, 4.15)*	2.05 (1.31, 3.22)*	68 (24)	219 (76)	6.18 (4.50, 8.48)*	5.59 (3.79, 8.26)*
Polypharmacy†											
0–4 medication	471 (51)	1.07 (1.03)	0.18 (0.12)	432 (91)	39 (9)	1	1	332 (68)	139 (32)	1	1
5+ medications	430 (48)	1.59 (1.26)*	0.29 (0.15)*	319 (72)	111 (28)	3.77 (2.59, 5.49)*	3.50 (2.13, 5.75)*	156 (34)	274 (66)	4.05 (3.06, 5.35)*	2.99 (2.08, 4.29)*
Living arrangements†											
Lives with others	543 (67)	1.24 (1.16)	0.22 (0.14)	462 (83)	81 (17)	1	1	314 (55)	229 (45)	1	1
Lives alone	335 (29)	1.50 (1.21)*	0.25 (0.16)*	271 (78)	64 (22)	1.35 (0.94, 1.93)	1.45 (0.64, 3.30)	166 (45)	169 (55)	1.50 (1.12, 2.01)*	2.23 (1.14, 4.34)*
Marital status†											
Married/De facto	493 (62)	1.22 (1.14)	0.22 (0.14)	421 (84)	72 (17)	1	1	285 (55)	208 (45)	1	1
Separated/Divorced	114 (8)	1.27 (1.21)	0.23 (0.18)	97 (83)	17 (17)	1.08 (0.57, 2.05)	0.47 (0.17, 1.34)	64 (53)	50 (47)	1.07 (0.66, 1.73)	0.36 (0.15, 0.86)*
Widowed	267 (27)	1.53 (1.20)*	0.24 (0.15)	213 (77)	54 (23)	1.48 (1.02, 2.15)*	0.33 (0.14, 0.77)*	134 (45)	133 (55)	1.50 (1.11, 2.03)*	0.31 (0.16, 0.61)*
Never married	26 (2)	1.29 (1.11)	0.23 (0.14)	23 (90)	3 (11)	0.49 (0.10, 2.53)	0.46 (0.06, 3.33)	12 (50)	14 (50)	1.13 (0.44, 2.88)	0.47 (0.12, 1.79)

*$P < 0.05$. Frailty Phenotype (FP) categories: 0–2, non-frail; ≥3, frail. Frailty Index (F) categories: 0 to ≤0.21, non-frail; >0.21, frail. †Not stated or missing not included. ‡Excess alcohol consumption was measured as >14 drinks per week and/or >4 drinks per session. §Obesity waist circumference: men >102 cm, women >88 cm. —, Not reported; CI, confidence interval; multivariate OR, logistic regression including all descriptive covariates; OR, odds ratio; SD, standard deviation.

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Table 3: Proportion of participants within the Frailty Phenotype and Frailty Index categories

	Frailty Index, *n* (%)		Total, *n* (%)
	Non-frail	Frail	
Frailty Phenotype, *n* (%)			
Non-frail	494 (63)	265 (37)	759 (82)
Frail	2 (2)	148 (98)	150 (18)
	496 (52)	413 (48)	909 (100)

2% for the FI (Figure 2b). See Figure S1 (Supporting information) for log increase per year based on frailty classification. Being older, a current smoker, and having multimorbidity and polypharmacy were significantly associated with both the FP and FI. Table 2 shows the results of multivariate analysis where frailty status was dichotomised as either non-frail or frail. Being female, low income, obesity and living alone were significantly associated with only the FI. Being widowed was positively associated with frailty in the univariate analysis but negatively associated in the multivariate analysis for both frailty measures. This is probably because being widowed is more likely for older women who live alone than for other population groups. When the 24-item FI, without the chronic conditions, was used in the multivariate analysis, all variables remained significantly associated with frailty, including multimorbidity (OR 2.61, 95% CI 1.80–3.79, *P* < 0.001) (data not shown).

Discussion

In this study, there was only modest agreement between the two measures when classifying individuals as either non-frail or frail, which has implications for the clinical setting. As frailty is a potentially reversible state, correct identification is necessary for individuals to be offered timely and appropriate interventions [20].

Frailty prevalence (FP: 18%, FI: 48%) was substantially higher than in a previous South Australian study which measured frailty prevalence in men and women using both measures (FP: 9%, FI: 18%, mean age 78.2 (6.7) years) [12]. In that study, exclusively self-report FI variables and a higher cut-point of 0.25 were used, which is likely to have contributed in part to the lower prevalence [19,21]. The use of self-report data was also the case for the study by Dent et al. [15] (FI: 18%, mean age 75.9 (7.9) years). Our FI used a combination of self-report and test-based health measures, and had a cut-point of 0.21, as combining both forms of measurement has been identified as best predicting adverse health outcomes [19,21]. Furthermore, when comparing our findings, using data from 2004 to 2006, with the findings by Widagdo et al. [12] who used data from 1992, there may be a cohort effect. The comparatively lower socioeconomic status (SES) of the NWAHS region might also have contributed to a higher frailty prevalence [22]. Frailty for men in the NWAHS cohort (FP: 13%) was slightly higher than the New South Wales study (FP: 9%, mean age 76.9 (5.5) years) [13]. The exclusion of individuals living in residential care from this and a number of other studies as well as the potential non-participation of home-bound older people is likely to result in an underestimation of the true prevalence of frailty [23].

Multivariate analysis of cohort characteristics identified that being older, a current smoker, and having multimorbidity and polypharmacy were associated with higher frailty levels by both frailty measures. The association with multimorbidity for the FI was maintained when health conditions contributing to multimorbidity status were excluded from the FI. Being female, a low income earner, obesity and living alone were associated with only the FI.

Our findings for the FI are consistent with other studies which have identified women as having significantly higher frailty than men, and for both measures, that frailty increases significantly with age in a nonlinear pattern [3,6,24,25]. The significant association of lower household income with the FI in this population is also similar to other studies [2,25].

Figure 1: Characteristics of the Frailty Phenotype (FP) and Frailty Index (FI). (a) Relationship between the FP (number of deficits) and the FI (mean score). The error bars represent the 95% confidence interval of the estimate of the mean FI. Error bar not shown for five phenotype deficits as only one participant had this score. (b) Distribution of FP and FI scores as a proportion of deficits present. (—○—) Frailty Index; (—●—) Frailty Phenotype.
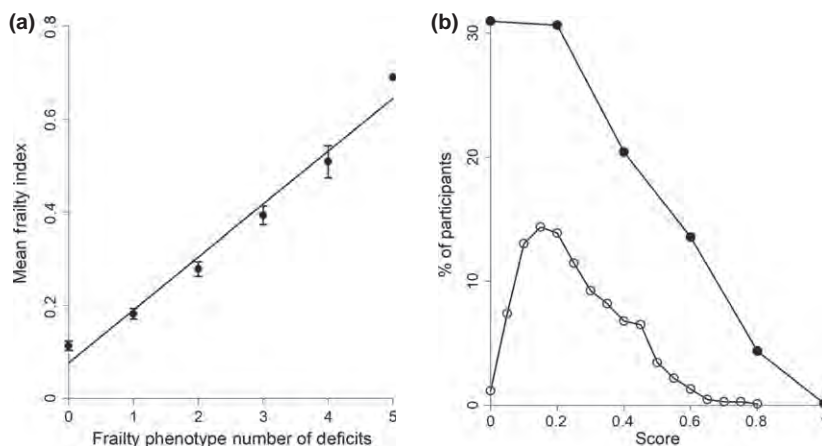
Figure 2: Relationship between average frailty scores (proportion of deficits present) and age stratified according to sex, using the (a) Frailty Phenotype and (b) Frailty Index. ○ Male; ● Female.
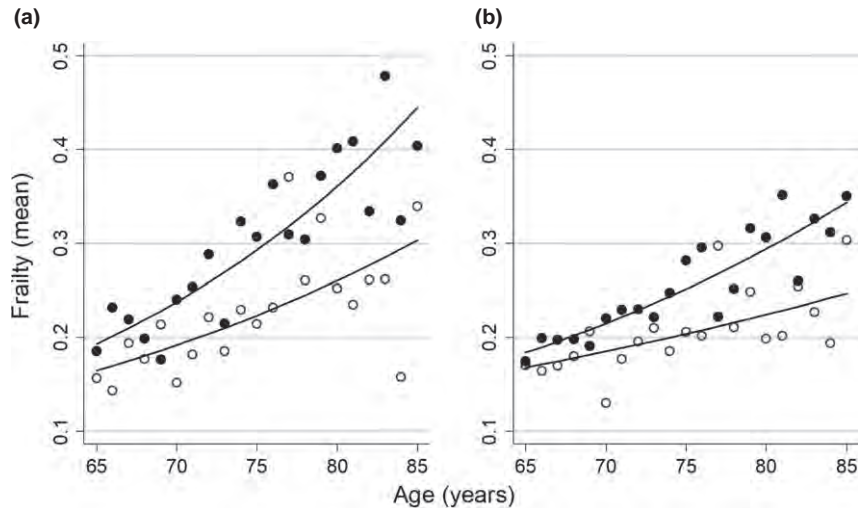
Likewise, multimorbidity has been identified elsewhere as a significant contributor to the development of frailty and was also a significant factor for both measures in our study [11,13,26]. Additionally, being a current smoker has been previously identified as a significant factor associated with frailty and is consistent with our findings [11]. These health and social determinants of frailty may be useful triggers for alerting clinicians to vulnerable older adults who might benefit from a screening, comprehensive assessment and individualised remediation or treatment of risk.

In this study, both frailty measures demonstrated a strong significant correlation in continuous scores but only a modest kappa score of 0.38 in their ability to classify individuals as either non-frail or frail, with the FI classifying a larger number of participants as frail. Agreement between measures was potentially strengthened by the use of all five FP variables in the FI as they met FI inclusion criteria [4]. Of note, over a third of individuals classified as non-frail by the FP were classified as frail by the FI. These participants had significantly higher rates of multimorbidity, polypharmacy, physical functional limitations, emotional problems and poor self-reported health than those classified as non-frail by both measures. The agreement between the FP and FI has been identified elsewhere as ranging from slight to moderate, with the FI classifying more people as frail with better discriminative ability at the lower and middle end of the frailty continuum than the FP [9,10]. The literature suggests that the FI may be a suitable scale that captures the multidimensionality of frailty and has high predictive ability of adverse outcomes [9,27]. The advantage of the FP is that it is shorter and relies on less items; however, grip strength and gait speed used in the FP are not standard components of a clinical geriatric assessment, although these measurements might potentially be considered as markers of an accumulation of deficits [27].

The main strength of this study was the use of population-based data to measure frailty using both the FP and the FI.

Limitations of the study were the availability of general population variables rather than ageing-specific variables such as cognitive impairment or gait speed. Inclusion of cognitive impairment has been highlighted as an important variable in the measurement of frailty [28]. Some researchers may disagree with using the continuous FP as this scale was originally developed to be used as a categorical variable. Even so, a number of studies have used it in continuous form, and for the purpose of this study, we decided to report both continuous and categorical findings [8–11]. However, in 2011 in a study in which Fried was a co-author, the researchers acknowledge that there is a floor effect when using the continuous 5-point FP and instead recommended a recalibrated 10-point scale to better differentiate individuals [11]. Even so, the most commonly used FP scales in the literature use either 5- or 3-point categorisation [18]. Another limitation of the study was the use of a modified FP which is recognised as having a potential impact on frailty prevalence [18]. The rate of physical inactivity in our sample is high (43%) compared to the originally published FP proportion (22%) [2] and may be a result of the low SES of the NWAHS population rather than due to modification per se [22]. However, our selection of a previously published threshold for physical inactivity in this cohort is likely to reflect an accurate proportion of physical inactivity that in turn presents an increased risk of frailty [29]. Reporting the association between frailty and multimorbidity using a FI which contains nine health conditions is another limitation of this study; we addressed this with a subanalysis using a 24-item FI which excluded these conditions. The association was weaker in this subanalysis; however, it still remained significant.

Conclusion

In this study, we successfully measured frailty prevalence in a sample of South Australian older adults using the FP and the FI. Socio-economic and other health determinants contributed to higher risk of frailty. There was only a modest

agreement between both measures in classifying individuals as either non-frail or frail, with the FI classifying a greater number of individuals as frail. This difference in sensitivity of frailty measures has clinical implications, where the choice of tool may impact the accurate identification of frailty. A FI consisting of at least 30 self-report and clinical measurements may be more appropriate to use in the clinical setting due to its sensitivity in identifying at-risk individuals, and the emergence of electronic health records may facilitate the generation of an automated FI score [30]. Further research is required to refine the process of frailty screening and assessment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Frailty categories for the Frailty Phenotype and Frailty Index based on descriptive characteristics.

Table S2. Proportion of participants within the Frailty Phenotype categories compared with the Frailty Index categories.

Table S3. Coding, frequency and histograms of included variables.

Figure S1. Relationship between proportion classified as frail and age, stratified according to sex, using the Frailty Phenotype and Frailty Index.

Frailty state transitions and associated factors in South Australian older adults

Frailty state transitions and associated factors in South Australian older adults was published in the *Journal of Geriatrics and Gerontology International*. The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 6.

6.1   Summary

Aim: Frailty is a state of decreased physiological reserve and vulnerability to stressors. Understanding the characteristics of those most at risk of worsening, or likely to improve their frailty status, are key elements in addressing this condition. This study measured frailty state transitions and factors associated with improvement or worsening frailty status in the North West Adelaide Health Study.

Methods: Frailty was measured using the frailty phenotype (FP) and a 34-item frailty index (FI) for 696 community dwelling participants aged ≥65 years, with repeated measures at 4.5 years follow-up.

Results: Improvement in frailty state was common for both tools (FP 15.5%; FI 7.9%). The majority remained stable (FP 44.4%; FI 52.6%), and many transitioned to a worse level of frailty (FP 40.1%; FI 39.5%). For both measures, multimorbidity was associated with worsening frailty among non-frail participants. Among pre-frail participants, normal waist circumference was associated with improvement, whereas older age was associated with worsening of frailty status. Among frail individuals, younger age was associated with improvement, and male sex and older age were associated with worsening frailty status.

Conclusions: Frailty is a dynamic process where improvement is possible. Multimorbidity, obesity, age and sex were associated with frailty transitions for both tools.

Statement of Authorship

Title of Paper	Frailty state transitions and associated factors in South Australian older adults
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☑ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Plan to submit to J Gerontology A submitted to Gerontology & Geriatrics International

Principal Author

Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 8/12/17

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

    i.   the candidate's stated contribution to the publication is accurate (as detailed above);

    ii.   permission is granted for the candidate in include the publication in the thesis; and

    iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Olga Theou
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation
Signature	Date 11/12/17

Name of Co-Author	Graeme Tucker
Contribution to the Paper	Supported statistical analysis and manuscript evaluation
Signature	Date 19/2/18

Name of Co-Author	Robert Adams
Contribution to the Paper	Representative of the North West Adelaide Health Study – source of data. Helped to evaluate and edit the manuscript
Signature	Date 5/3/208

Name of Co-Author	Renuka Visvanathan
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation.
Signature	Date 1/12/17

ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Frailty state transitions and associated factors in South Australian older adults

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Aim: Frailty is a state of decreased physiological reserve and vulnerability to stressors. Understanding the characteristics of those most at risk of worsening, or likely to improve their frailty status, are key elements in addressing this condition. The present study measured frailty state transitions and factors associated with improvement or worsening frailty status in the North West Adelaide Health Study.

Methods: Frailty was measured using the frailty phenotype (FP) and a 34-item frailty index (FI) for 696 community-dwelling participants aged ≥65 years, with repeated measures at 4.5-year follow up.

Results: Improvement in frailty state was common for both tools (FP 15.5%; FI 7.9%). The majority remained stable (FP 44.4%; FI 52.6%), and many transitioned to a worse level of frailty (FP 40.1%; FI 39.5%). For both measures, multimorbidity was associated with worsening frailty among non-frail participants. Among pre-frail participants, normal waist circumference was associated with improvement, whereas older age was associated with worsening of frailty status. Among frail individuals, younger age was associated with improvement, and male sex and older age were associated with worsening frailty status.

Conclusions: Frailty is a dynamic process where improvement is possible. Multimorbidity, obesity, age and sex were associated with frailty transitions for both tools. **Geriatr Gerontol Int 2018; 18: 1549–1555.**

Keywords: aged, Australia, cohort studies, epidemiology, frailty.

Introduction

Frailty represents a decline across multiple physiological systems, making individuals more vulnerable to stressor events and at a greater risk of adverse health outcomes, such as disability, hospitalization, entry to residential care and death.[1–4] Frailty is common among older adults, and the prevalence has been measured at 14% using the frailty phenotype (FP) and 24% using the frailty index (FI),[2] which are the two main approaches to the measurement of frailty. Prevalence is typically higher when measured using the FI.[5,6]

There is growing interest in how frailty changes over time, and the factors that are associated with early versus late stage frailty for possible intervention.[7–11] Frailty is a dynamic process where improvement is possible, with rates of improvement in frailty status ranging from 6% to 25%.[7–10] Improvement typically is a single-step transition to an adjacent state, such as from pre-frail to non-frail.[7–10] Even so, transition to a worse frailty level is more common than improvement,[7,8,10] and remaining in a stable frailty state is the most common outcome.[8,9]

A range of socioeconomic, clinical and behavioral factors influence frailty transitions. Increased age, cognitive impairment, obesity, the presence of multimorbidity, lower education level and hospitalization are risk factors for worsening frailty status,[7,9,10,12,13] whereas increased levels of physical activity, female sex, being overweight, low alcohol consumption, higher educational level, living alone and fewer baseline deficits increase the likelihood of improved frailty.[9,10,12,14]

The aims of the present study were to examine the transitions between frailty states for a cohort of older Australian adults using both the FP and FI, and to describe the characteristics associated with frailty status improving, remaining stable or worsening.

Although frailty state transitions have been examined internationally,[7–10] and in two Australian studies using the FP[15] and the FRAIL scale[16] respectively, to the best of our knowledge this is the

first study to report on frailty state transitions using both the FP and FI, and to describe a range of factors associated with transitions for both.

Understanding the natural course of frailty and the characteristics of those most at risk of worsening or likely to improve their frailty status might be considered key elements in maximizing the health, functioning and well-being of individuals in our aging populations.[1,17]

Methods

Sample and study design

The present study was a secondary analysis for data from the North West Adelaide Health Study, a population-based longitudinal study of community-dwelling adults living in the North West of Adelaide, South Australia.[18] As the probability of selection was known, data were weighted to the area population. Stage 2 (2004–2006) was the baseline for the present study, and only participants aged ≥65 years at the time of attending clinic stage 2 were included. Follow up of participants for stage 3 occurred in 2008–2010 (4.5 years [0.45 SD] mean follow up). Information on participant mortality was drawn from data matching to official death records. Participants were excluded from this analysis if there were missing three or more FP variables or ≥20% of FI variables at either stage, if English comprehension was inadequate and if they were lost to follow up (Fig. S1). Ethics approval for this study was granted by SA Health Human Research Ethics Committee.

FP

A modified FP was used to measure frailty status at baseline and follow up. Individuals with three or more deficits were classified as frail, while those with one or two deficits were classified as pre-frail and those with no deficits present were non-frail.[19] The FP criteria used in the present study are described in Table 1. The characteristics of the modified FP in the North West Adelaide Health Study cohort have been described previously.[6]

FI

We developed a 34-item FI following a standard methodology.[20] Based on the proportion of deficits, individuals scoring >0.21 were classified as frail, while those with scores ranging between 0.10 and 0.21 were pre-frail, and <0.10 were considered non-frail.[21] FI variables are outlined in Table 1, and the characteristics of this FI have been described previously.[6] A 24-item FI, which excluded 10 chronic conditions, was also constructed to examine the relationship between multimorbidity and FI frailty state transitions (Table 1).

Statistical analysis

SPSS version 23 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Case weights for the cohort were used in analysis procedures, reporting mean scores and percentages to ensure that the sample was representative of the population. Statistical significance was determined by an alpha value of 0.05. The number and proportion of participants classified as non-frail, pre-frail or frail using both measures were reported according to cohort characteristics. The number and proportion of those in each frailty category who remained stable, improved or worsened was also reported. Transition directions included: (i) non-frail at baseline and worse at follow up (pre-frail, frail or dead); (ii) pre-frail at baseline and improved at follow up to a non-frail state; (iii) pre-frail at baseline worsening to a frail or dead state; (iv) frail at baseline improving to pre-frail or non-frail; and (v) frail at baseline worsening to dead.

Univariate logistic regression was carried out as a first step in the purposeful selection process for identifying candidate variables for multivariate analysis (Supporting Information Tables 4,5). Any variable with *P*-value of <0.25 was included. An iterative process of variable selection was then used for multivariate logistic regression using backwards elimination of non-significant variables from the model. Covariates that were significant for only one frailty measure were included in the model for analysis of both measures. At the end of this process of deleting and verifying, the model contained significant covariates and confounders associated with frailty state transitions that were included in the final multivariate analysis.

Table 1 Frailty phenotype and frailty index variables

Frailty phenotype	34-Item frailty index	
Weight loss: >10% weight loss over 4 years (clinic measurement)	Angina[†]	Self-reported health
	Heart attack[†]	Health limits lifting or carrying groceries
	Osteoporosis[†]	Health limits climbing several flights of stairs
	Osteoarthritis[†]	Health limits climbing one flight of stairs
Weakness: Original method used	Rheumatoid and any other arthritis[†]	Health limits bending, kneeling or stooping
Exhaustion: Original method used	Stroke or TIA[†]	Health limits walking more than 1 km
	Diabetes[†]	Health limits walking 100 m
Slowness: Self-report to the question "Health limits you a lot walking 100 m." (SF36 q11)	Any mental health problem[†]	Felt lonely
	Systolic blood pressure[†]	Felt that could not get going
	Diastolic blood pressure[†]	Difficulty keeping mind on what you were doing
	10% weight loss over 4 years	Felt everything was an effort
Low activity: Australian Bureau of Statistics National Health Survey. (<100 METs per week)	FEV1/FVC post ratio	Physical and emotional problems interfered with social activities
	Weak grip strength	Felt full of life
	Falls	Felt calm and peaceful
	Hospital emergency admission	Felt worn out
	Low activity level (<100 METs per week)	Felt tired
	Healthy as anybody I know	
	Health is excellent	

[†]Variable excluded from 24-item frailty index. BMI, body mass index; METs, metabolic equivalent of task; SF36, 36-Item Short Form Health Survey.

Covariates included: sex, age group (65–74 years and ≥75 years), the presence of multimorbidity (≥2 chronic conditions), obesity (waist circumference men >102 cm, women >88 cm), polypharmacy (≥5 medications) and living arrangements (alone or with others). Covariates that were tested but not included were: education level, income group, smoking status and alcohol consumption. As the length of time between the baseline and follow-up clinics varied for each participant, we also included time between clinics as a covariate.

Results

Study participants

In the present analysis, we included 696 participants (mean age 73.4 years [6.1], 53.1% women). We excluded 93 participants due to insufficient FI or FP variables at phase 3, and 120 were lost to follow up. Baseline descriptive characteristics of participants based on the FP and FI frailty categories are presented in Table 2. At baseline, 16.3% of participants were classified as frail according to the FP, whereas 45.6% were frail based on the FI. The

213 excluded participants were more likely to be older (mean age 75.8 years [6.7]), and frail as classified by the FP (20.7%) and the FI (52.1%) at baseline, compared with those included in analysis.

Frailty state transitions

The majority of participants in this cohort either improved or remained stable over 4.5 years (FP 59.9%, FI 60.5%). Figure 1 shows the frailty state at follow up according to baseline frailty states for both measures (see also Supporting Information Tables 1–3). A number of participants improved their frailty state: FP – 23.1% of pre-frail and 21.6% of frail individuals; FI – 13.6% of pre-frail and 8.4% of frail individuals. Remaining stable was the most common frailty state transition for both the FP (47.7% of non-frail, 44.7% of pre-frail and 36.9% of frail) and the FI (54.4% of non-frail, 38.0% of pre-frail and 61.5% of frail). The next most likely state transition was to a worse frailty state (FP 40.1% and FI 39.5%), which also included death (19%). When participants transitioned to a different frailty state (improved, worsened or dead), this was most typically to a state adjacent their baseline classification.

Table 2 Baseline frailty categories for the frailty phenotype and frailty index (34-item) based on descriptive characteristics

	Whole sample, n (%)	Frailty phenotype categories			Frailty index (34-item) categories		
		Non-frail, n (%)	Pre-frail, n (%)	Frail, n (%)	Non frail, n (%)	Pre-frail, n (%)	Frail, n (%)
Total	696	233 (32.0)	357 (51.7)	106 (16.3)	175 (23.2)	219 (31.2)	302 (45.6)
Sex							
Male	353 (46.9)	127 (35.7)	179 (50.5)	47 (13.8)	98 (27.3)	115 (33.2)	140 (39.5)
Female	343 (53.1)	106 (28.5)	178 (52.9)	59 (18.6)	77 (19.4)	104 (29.4)	162 (51.2)
Age groups							
65–74 years	442 (59.9)	171 (37.3)	234 (53.3)	37 (9.4)	129 (28.6)	152 (33.7)	161 (37.7)
≥75 years	254 (40.5)	62 (24.0)	123 (49.5)	69 (26.5)	46 (15.2)	67 (27.5)	141 (57.2)
Education level[†]							
Up to secondary	427 (61.6)	125 (28.6)	229 (53.0)	73 (18.4)	89 (19.1)	144 (34.4)	194 (46.5)
Trade/certificate/diploma	229 (32.6)	97 (38.7)	104 (48.2)	28 (13.1)	75 (30.2)	64 (25.7)	90 (44.1)
Bachelor degree or higher	19 (2.5)	9 (52.9)	8 (35.3)	2 (11.8)	8 (41.2)	6 (35.3)	5 (23.5)
Income groups[†]							
Up to $20k	345 (45.6)	92 (24.8)	187 (54.5)	66 (20.6)	65 (16.5)	111 (32.6)	169 (51.0)
$20–$40k	223 (35.1)	96 (42.4)	103 (45.8)	24 (11.8)	77 (32.2)	71 (30.5)	75 (37.2)
$40–$60k	48 (7.0)	24 (41.7)	20 (50.0)	4 (8.3)	17 (34.0)	13 (27.7)	18 (38.3)
>$60k	23 (2.8)	12 (52.6)	10 (42.1)	1 (5.3)	10 (36.8)	9 (42.1)	4 (21.1)
Smoking status[†]							
Never smoked	326 (49.6)	107 (29.3)	174 (54.7)	45 (16.0)	84 (23.1)	107 (32.0)	135 (44.8)
Former smoker	327 (45.1)	116 (35.9)	159 (48.0)	52 (16.0)	80 (22.8)	99 (30.3)	148 (46.9)
Current smoker	42 (5.2)	10 (25.0)	23 (52.8)	9 (22.2)	11 (25.7)	13 (31.4)	18 (42.9)
Alcohol consumption[†,‡]							
Not at risk	593 (85.0)	201 (31.8)	299 (51.2)	93 (17.0)	146 (22.5)	190 (31.7)	257 (45.8)
Excess	75 (10.0)	22 (27.9)	42 (57.4)	11 (14.7)	21 (27.9)	22 (29.4)	32 (42.6)
Waist circumference[†,§]							
Normal	328 (45.7)	140 (40.5)	151 (46.0)	37 (13.5)	113 (30.9)	103 (32.8)	112 (37.7)
Obese	364 (53.6)	92 (24.9)	204 (56.4)	68 (18.6)	62 (16.7)	114 (28.2)	188 (56.7)
Multimorbidity[†]							
0–1 health conditions	486 (68.9)	184 (36.7)	248 (51.4)	54 (11.9)	169 (32.4)	174 (35.4)	143 (32.2)
≥2 health conditions	210 (31.1)	49 (21.7)	109 (52.4)	52 (25.9)	6 (2.8)	45 (21.8)	159 (75.4)
Polypharmacy[†]							
0–4 medication	371 (53.2)	138 (36.2)	200 (53.6)	33 (10.2)	126 (30.9)	133 (36.4)	112 (32.8)
≥5 medications	319 (46.1)	92 (26.5)	154 (49.8)	73 (23.6)	45 (13.4)	84 (25.2)	190 (61.3)
Living arrangements[†]							
Lives with others	418 (67.6)	154 (33.9)	206 (51.3)	58 (14.8)	104 (23.4)	142 (33.6)	172 (43.0)
Lives alone	257 (29.1)	74 (28.3)	137 (51.5)	46 (20.2)	65 (22.7)	71 (24.7)	121 (52.5)
Marital status[†]							
Married/de facto	386 (63.6)	145 (34.7)	189 (50.9)	52 (14.4)	102 (24.7)	126 (32.8)	158 (42.5)
Separated/divorced	87 (8.1)	32 (36.4)	46 (52.7)	9 (10.9)	29 (32.1)	24 (28.6)	34 (39.3)
Widowed	198 (25.6)	50 (24.6)	108 (53.1)	40 (22.3)	40 (17.8)	63 (28.2)	95 (54.0)
Never married	18 (1.8)	5 (30.8)	10 (53.8)	3 (15.4)	3 (16.7)	6 (41.7)	9 (41.7)

Frailty phenotype cut points (number of deficits): 0, not frail; 1–2, pre-frail; and ≥3, frail. Frailty index cut points (proportion of deficits): 0 to ≤0.10, not frail; >0.10 to ≤0.21, vulnerable; and >0.21, frail. [†]Not stated or missing not included. [‡]Excess alcohol consumption was measured as >14 drinks per week and/or more than four drinks per session. [§]Waist circumference in men >102 cm and in women >88 cm is considered obesity.

(a) Frailty phenotpye

(b) Frailty index

Figure 1 Frailty state transitions between baseline and follow up (4.5 years mean) for the (a) frailty phenotype and (b) frailty index. (□) Non-frail, (▨) pre-frail, (▦) frail and (■) dead.

Factors associated with frailty state transitions

Tables 3 and 4 examine the relationship between frailty state transitions and covariates. The reference category of "same" was used for comparison of "better" and "worse" states. Baseline frailty category and frailty state transition proportions were similar for both the 34-item and 24-item FI, which excluded chronic conditions (see supplementary file).

Improved at follow up

Pre-frail at baseline

Obese individuals were significantly less likely to improve according to both measures (FP: OR 0.37, 95% CI 0.20–0.68, P = 0.001; FI: OR 0.25, 95% CI 0.09–0.74, P = 0.013), whereas polypharmacy was negatively associated with improvement for the FP (OR 0.42, 95% CI 0.22–0.81, P = 0.009).

Frail at baseline

Older age was negatively associated with improving for the FI (OR 0.13, 95% CI 0.03–0.65, P = 0.013), as was multimorbidity (OR 0.11, 95% CI 0.02–0.67, P = 0.016).

Worsened at follow up

Non-frail at baseline

Multimorbidity was associated with worsening according to both measures (FP: OR 4.20, 95% CI 1.78–9.89, P = 0.001; FI: OR 5.74, 95% CI 1.21–27.09, P = 0.027). In addition, for the FI, obesity was associated with worsening (OR 2.24, 95% CI 1.06–4.76, P = 0.035), while people living alone were less likely to worsen (OR 0.37, 95% CI 0.15–0.93, P = 0.035). Stratified by sex, women living alone were significantly less likely to worsen (OR 0.19, 95% CI 0.05–0.67, P = 0.010) than women living with others, whereas there was no difference for men in terms of living arrangements and worsening.

Pre-frail at baseline

Older age (≥75 years) was associated with worsening state for both measures (FP: OR 3.06, 95% CI 1.72–5.47, P < 0.001; FI: OR 3.55, 95% CI 1.56–8.05, P = 0.002), whereas obese individuals were less likely to worsen for the FP (OR 0.54, 95% CI 0.30–0.97, P = 0.038).

Frail at baseline

Male sex was significantly associated with worsening for both measures (FP: OR 3.91 95% CI 1.01–15.14, P = 0.048; FI: OR 3.22, 95% CI 1.50–6.92, P = 0.003), as was older age (≥75 years; FP: OR 6.74, 95% CI 1.66–27.33, P = 0.008; FI: OR 6.40, 95% CI 2.95–13.86, P < 0.001). Living alone was significantly associated with worsening for the FI (OR 2.70, 95% CI 1.23–5.92, P = 0.013).

Discussion

Frailty, in the present study of community-dwelling Australian older adults, was identified as a dynamic condition where approximately 60% of participants either improved or remained stable over the course of 4.5 years; however, deterioration to a worse frailty state was more likely than improvement. This finding was similar to other studies that have examined frailty state transitions.[8,9]

The pattern was similar for both the FP and FI, with the FI identifying higher baseline frailty prevalence and a lower rate of improvement; however, the pattern of movement assessed by each instrument provides corroboration of the nature of changes.

Improvement to a lesser frailty state occurred for a number of pre-frail and frail individuals, as measured by both the FP and FI. Improvement in the FP for 16% of participants was slightly higher than that of other randomly sampled cohorts of similar follow-up periods where 12% and 6% of participants improved, respectively.[7,10] Improvement in the present cohort, as measured by the FI, at 8% was half that of the FP. Even so, the potential for improvement was evident for both pre-frail and frail individuals.

Normal waist circumference was a significant factor for the improvement of pre-frail individuals for both measures, whereas polypharmacy was negatively associated with improvement for the FP. In other studies, normal weight has been identified as a significant protective factor for survival,[22] and polypharmacy has been associated with increased risk of mortality.[10,15] Improvement of frail participants was significantly associated with younger age and with having less than two chronic conditions for the FI.

Worsening was most common to an adjacent frailty state. Gradual worsening to an adjacent frailty state has been identified as a common feature of frailty across a number of studies that have used a FP method.[7–10] A pattern of gradual decline has also been identified in a study that examined change in mean FI score.[11] Despite worsening of frailty level being the most common transition in this cohort, interventions exist that might prevent worsening.[1,23]

The worsening of non-frail individuals was significantly associated with the presence of multimorbidity for both measures, and

Table 3 Multivariate logistic regression examining transitions in frailty phenotype states over 4.5 years

	Odds ratio (95% confidence interval)				
Baseline frailty status	Non-frail	Pre-frail	Pre-frail	Frail	Frail
Follow-up status	Worse[†]	Improved[‡]	Worse[†]	Improved[‡]	Worse[†]
Sex					
Female	1	1	1	1	1
Male	0.76 (0.41, 1.42)	0.91 (0.49, 1.69)	1.03 (0.58, 1.85)	1.06 (0.31, 3.56)	3.91 (1.01, 15.14)*
Age group					
65–74 years	1	1	1	1	1
≥75 years	1.89 (0.97, 3.68)	0.49 (0.24, 1.00)	3.06 (1.72, 5.47)*	0.59 (0.17, 2.09)	6.74 (1.66, 27.33)*
Waist circumference[§]					
Normal	1	1	1	1	1
Obese	1.50 (0.81, 2.78)	0.37 (0.20, 0.68)*	0.54 (0.30, 0.97)*	2.60 (0.71, 9.57)	0.92 (0.26, 3.29)
Multimorbidity					
0–1 conditions	1	1	1	1	1
≥2 conditions	4.20 (1.78, 9.89)*	1.03 (0.51, 2.07)	1.58 (0.84, 2.96)	0.70 (0.21, 2.38)	0.77 (0.20, 2.91)
Polypharmacy					
0–4 medication	1	1	1	1	1
≥5 medications	0.85 (0.45, 1.60)	0.42 (0.22, 0.81)*	0.89 (0.49, 1.61)	0.35 (0.09, 1.37)	0.41 (0.10, 1.68)
Living arrangements					
Lives with others	1	1	1	1	1
Lives alone	0.92 (0.45, 1.89)	0.50 (0.24, 1.02)	1.01 (0.54, 1.90)	0.46 (0.11, 1.92)	3.35 (0.85, 13.18)

Adjusted for time between clinic measurements. Frailty phenotype cut points (number of deficits): 0, not frail; 1–2, pre-frail; and ≥3, frail. *$P < 0.05$. [†]A more severe frailty state, including death, compared with baseline state. [‡]A less severe frailty state compared with baseline state. [§]Waist circumference in men >102 cm and in women >88 cm is considered obesity.

with obesity and living with others for the FI. Chronic conditions are recognized as having an impact on physiological systems that might lead to the development of frailty.[9,10,24] The present findings on the association between obesity and the development of frailty are consistent with those of others who identified that obesity and overweight increased the risk of non-frail individuals transitioning to a worse frailty state.[10,22,25] The mechanisms by which obesity has a potential impact on frailty status include inflammatory dysregulation and sarcopenic obesity, where a mismatch exists between fat mass and muscle mass.[26] Non-frail women living alone in the present study were significantly less likely to worsen than those living with others; however, this scenario was not the case for non-frail men. This finding is similar to another

study that identified a positive effect of living alone on frailty for women.[27] The protective effects of non-frail women living alone might be linked to carer stress, which was not measured in the North West Adelaide Health Study.

Being older was associated with the worsening of pre-frail individuals for both measures, while obesity was protective for the FP. Advanced age has been identified as being associated with frailty previously in this cohort,[6] and in other studies internationally.[2] Previous studies that have reported older age being significantly associated with the worsening of any frailty characteristic,[7] the worsening of frailty in men,[9] becoming frail and dying,[10] and the worsening of a continuous FI score.[11] The protective effect of obesity has been described elsewhere as potentially associated with

Table 4 Multivariate logistic regression examining transitions in frailty index (24-item) states over 4.5 years

	Odds ratio (95% confidence interval)				
Baseline frailty status	Non-frail	Pre-frail	Pre-frail	Frail	Frail
Follow-up status	Worse[†]	Improved[‡]	Worse[†]	Improved[‡]	Worse[†]
Sex					
Female	1	1	1	1	1
Male	0.51 (0.23, 1.12)	0.44 (0.15, 1.28)	0.89 (0.42, 1.89)	1.11 (0.40, 3.08)	3.22 (1.50, 6.92)*
Age group					
65–74 years	1	1	1	1	1
≥75 years	2.13 (0.88, 5.12)	0.23 (0.04, 1.18)	3.55 (1.56, 8.05)*	0.13 (0.03, 0.65)*	6.40 (2.95, 13.86)*
Waist circumference[§]					
Normal	1	1	1	1	1
Obese	2.24 (1.06, 4.76)*	0.25 (0.09, 0.74)*	0.52 (0.24, 1.12)	0.43 (0.16, 1.15)	0.85 (0.41, 1.77)
Multimorbidity					
0–1 conditions	1	1	1	1	1
≥2 conditions	5.74 (1.21, 27.09)*	1.12 (0.30, 4.14)	1.68 (0.69, 4.08)	0.11 (0.02, 0.67)*	0.50 (0.23, 1.09)
Polypharmacy					
0–4 medication	1	1	1	1	1
≥5 medications	1.39 (0.62, 3.12)	0.82 (0.28, 2.44)	1.59 (0.74, 3.40)	0.42 (0.14, 1.31)	1.60 (0.73, 3.50)
Living arrangements					
Lives with others	1	1	1	1	1
Lives alone	0.37 (0.15, 0.93)*	0.64 (0.17, 2.46)	1.41 (0.57, 3.47)	0.99 (0.29, 3.43)	2.70 (1.23, 5.92)*

Adjusted for time between clinic measurements. Frailty index cut points (proportion of deficits): 0 to ≤0.10, not frail; >0.10 to ≤0.21, pre-frail; and >0.21, frail. *$P < 0.05$. [†]A more severe frailty state, including death, compared with baseline state. [‡]A less severe frailty state compared with baseline state. [§]Waist circumference in men >102 cm and in women >88 cm is considered obesity.

being a target of increased medical care and benefiting from higher metabolic reserves.[22]

Male sex and older age were associated with the worsening (transition to dead) of frail individuals for both measures, while living alone was significant for the FI only. Although women have higher frailty levels in this cohort,[6] their reduced mortality risk might reflect the male–female health-survival paradox, in which women have a survival advantage over men despite having a significantly higher number of disabling health conditions, including frailty.[28] For older age, the likelihood of worsening for frail individuals was sixfold that of those classified as frail in the younger age group for both measures, suggesting that advancing age has a greater impact on mortality risk in the later stages of frailty. Living alone has been described as increasing the vulnerability for frailty through mechanisms, such as undernutrition.[19]

The covariates associated with improvement or worsening frailty status presented different risks based on the stage of frailty progression. Each of these factors have a potential role in triggering or accelerating frailty through either the physiological changes of aging or by means of a pathway of disease or comorbidity.[19] However, for individuals already pre-frail and frail at baseline, frailty itself plays a more important role in influencing later-stage frailty transitions.

The two frailty measures showed similar patterns of frailty state transitions over the 4.5-year mean follow-up period. Their key differences included higher baseline frailty prevalence for the FI (45.6%) compared with the FP (16.3%), and a smaller proportion of individuals improving in frailty status for the FI (7.9%) compared with the FP (15.5%). The higher baseline prevalence for the FI has been reported elsewhere.[5,6]

Aging-specific variables, such as cognition and gait speed, were not available for the present cohort. Accordingly, we used a modified FP, which might have impacted the estimate of frailty prevalence.[29] The North West region of Adelaide has a lower socioeconomic status compared with the broader metropolitan area; therefore, the present findings might not be representative of the Australian population.[6] The exclusion of individuals living in residential care from the present study is likely to result in under-representing the baseline prevalence of frailty. A further limitation of this study was the use of FI categories to measure frailty state transitions. It is possible that smaller changes might be clinically significant, but this is yet to be determined using continuous frailty scores. Furthermore, the loss to follow up of 213 participants who were significantly older and had higher frailty prevalence based on the baseline frailty classification is likely to have impacted our findings, potentially resulting in an underestimation of frail individuals remaining stable or improving.

Frailty was identified as a dynamic process in which many individuals improved over a 4.5-year follow-up period. Most individuals improved or remained stable. For both improvement and worsening, transition to an adjacent frailty state was most likely. Among the factors that were identified as associated with frailty transitions, age and sex are non-modifiable, but multimorbidity, obesity, polypharmacy and living status might be targeted. These factors pose different risks for frailty transition at different stages of the frailty process, as does frailty classification itself and, hence, suggests a tailored approach in targeting vulnerable individuals. These findings have implications for clinicians and policymakers. Identifying individuals who are at risk of becoming frail and recognizing that there is potential for improvement of those who are already pre-frail or frail will be an important feature of maintaining healthy aging populations. This is particularly prescient, as interventions exist that might prevent, delay or reverse frailty.[1,23]

Acknowledgements

Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website: .

Figure S1 Flow diagram of participants.

Table S1 Frailty category and death status at 4.5 years mean follow up according to baseline frailty category. Percentage by baseline frailty status.

Table S2 Frailty category and death status at 4.5 years mean follow up according to baseline frailty category. Percentage of whole sample.

Table S3 Frailty state transitions: better, same and worse (worse includes dead) at 4.5 years mean follow up according to baseline frailty category.

Table S4 Univariate logistic regression for variables associated with frailty phenotype transitions in frailty states over 4.5 years, adjusted for time between clinic appointments. Reference category is "same."

Table S5 Univariate logistic regression for variables associated with frailty index transitions in frailty states over 4.5 years, adjusted for time between clinic appointments. Reference category is "same."

Diagnostic test accuracy of self-reported screening instruments in identifying frailty in community-dwelling older people:
A systematic review

Diagnostic test accuracy of self-reported screening instruments in identifying frailty in community-dwelling older people: A systematic review was published in the journal *Geriatrics and Gerontology International*. The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 7. A copy of the systematic review protocol published in the *JBI Database of Systematic Reviews and Implementation Reports* is included as Appendix B.

This publication also appeared as a chapter in the doctoral thesis of Rachel C Ambagtsheer (lead author), with Mark Q Thompson as secondary author. The contribution of each author is specified in the following statement of authorship.

7.1 Summary

Background: Against a backdrop of ageing populations worldwide, it has become increasingly important to identify frailty screening instruments suitable for community settings. Self-reported and/or administered instruments may offer significant simplicity and efficiency advantages over clinician-administered instruments but their comparative diagnostic test accuracy has yet to be systematically examined.

Aims: The aim of this systematic review was to determine the diagnostic test accuracy of self-reported and/or self-administered frailty screening instruments against two widely accepted frailty reference standards (the Frailty Phenotype and the Frailty Index) within community-dwelling older adult populations.

Methods: We conducted a systematic search of the Embase, CINAHL, MEDLINE, PubMed, Web of Science, PEDro, PsycINFO, ProQuest Dissertations, Open Grey and GreyLit databases up to April 2017 (with an updated search conducted over May-July 2018) to identify studies reporting comparison of self-reported and/or self-administered frailty screening instruments against an appropriate reference standard, with a minimum sensitivity threshold of 80% and specificity threshold of 60%.

Results: We identified 24 studies that met our selection criteria. Four self-reported screening instruments across three studies met minimum sensitivity and specificity thresholds. However, in most cases, study design considerations limited the reliability and generalisability of the results. Additionally, meta-analysis was not conducted because no more than three studies were available for any of the unique combinations of index tests and reference standards.

Conclusions: Although our study has demonstrated that a number of self-reported frailty screening instruments reported sensitivity and specificity within a desirable range for community application, additional diagnostic test accuracy studies are needed.

STATEMENT OF AUTHORSHIP

Title of Paper	Diagnostic test accuracy of self-reported screening instruments for identifying frailty in community-dwelling older people: A systematic review
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Principal Author

Name of Principal Author (Candidate)	Rachel Ambagtsheer		
Contribution to the Paper	Conceived and designed the study, collected the data, performed the analysis, drafted the manuscript, critically reviewed and edited the manuscript for submission, approved final version.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/8/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:
  i.   the candidate's stated contribution to the publication is accurate (as detailed above);
  ii.   permission is granted for the candidate in include the publication in the thesis; and
  iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mark Quinlivan Thompson		
Contribution to the Paper	Conceived and designed the study, collected the data, performed the analysis, drafted the manuscript, critically reviewed and edited the manuscript for submission, approved final version.		
Overall percentage (%)	45%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the secondary author of this paper.		
Signature		Date	16/082019

Name of Co-Author	Archibald, M.M
Contribution to the Paper	Conceived and designed the study, drafted the manuscript, critically reviewed and edited the manuscript for submission, approved final version.

Signature		Date	26/08/2019

Name of Co-Author	Casey, M.G
Contribution to the Paper	Conceived and designed the study, critically reviewed and edited the manuscript for submission, approved final version.

Signature		Date	27/08/19

Name of Co-Author	Schultz, T.J.
Contribution to the Paper	Conceived and designed the study, performed the analysis, critically reviewed and edited the manuscript for submission, approved final version, oversaw development of paper.

Signature		Date	19/8/19

REVIEW ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Diagnostic test accuracy of self-reported screening instruments in identifying frailty in community-dwelling older people: A systematic review
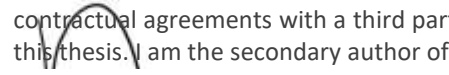
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Against a backdrop of aging populations worldwide, it has become increasingly important to identify frailty screening instruments suitable for community settings. Self-reported and/or administered instruments might offer significant simplicity and efficiency advantages over clinician-administered instruments, but their comparative diagnostic test accuracy has yet to be systematically examined. The aim of this systematic review was to determine the diagnostic test accuracy of self-reported and/or self-administered frailty screening instruments against two widely accepted frailty reference standards (the frailty phenotype and the Frailty Index) within community-dwelling older adult populations. We carried out a systematic search of the Embase, CINAHL, MEDLINE, PubMed, Web of Science, PEDro, PsycINFO, ProQuest Dissertations, Open Grey and GreyLit databases up to April 2017 (with an updated search carried out over May–July 2018) to identify studies reporting comparison of self-reported and/or self-administered frailty screening instruments against an appropriate reference standard, with a minimum sensitivity threshold of 80% and specificity threshold of 60%. We identified 24 studies that met our selection criteria. Four self-reported screening instruments across three studies met minimum sensitivity and specificity thresholds. However, in most cases, study design considerations limited the reliability and generalizability of the results. Additionally, meta-analysis was not carried out, because no more than three studies were available for any of the unique combinations of index tests and reference standards. Although the present study has shown that a number of self-reported frailty screening instruments reported sensitivity and specificity within a desirable range for community application, additional diagnostic test accuracy studies are required. **Geriatr Gerontol Int 2019; ••: ••–••.**

Keywords: aged 80 and over, frailty, geriatric assessment, primary healthcare.

Introduction

Frailty has been identified as a global public health priority in societies with aging populations.[1] Frailty is a state of decreased physiological reserve and increased vulnerability to stressor events, resulting in increased risk of adverse health outcomes, such disability, hospitalization, institutionalization and mortality.[2–4] Frailty is a dynamic condition where improvement is possible[5,6] and interventions exist that can delay or reverse frailty.[7] Identifying individuals who would benefit from timely identification and intervention, therefore, is a key priority in the management of frailty within the community.[8,9]

There are currently a large number of different frailty screening instruments in existence, many of which have proven to be reliable and valid measures of frailty within different contexts.[10]

However, only some of these are suitable contenders to be considered within the scope of self-administered instruments, taking the form of either a postal survey or a self-completed questionnaire. Several systematic reviews have examined the utility of frailty screening within community settings, from the perspective of both self-report and test-based measurement.[4,9,11–13]

Two systematic reviews have reported on the diagnostic test accuracy (DTA) of frailty screening instruments against a reference standard.[14,15] A number of publications have examined the DTA of self-reported instruments for the identification of frailty since these reviews were published, hence the need for the present review. One of the key complexities identified in these reviews regarding frailty screening is a lack of consensus on a definition of frailty, which is reflected in two separate reference standards and a large number of potential index tests.[9]

The aim of the present review was to identify the DTA of self-reported screening instruments against a frailty reference standard for community-dwelling older adults. Specifically, our review questions were:

- How accurate are self-reported screening instruments against agreed reference standards?
- How does the accuracy of self-reported instruments vary according to whether the test is self-reported or self-administered?

Methods

We consulted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Diagnostic Test Accuracy Studies tool[17] in developing the study design. The study protocol has been published previously, and the study is registered with both the PROSPERO (ID: CRD42017081379) and the JBI databases.[18]

We diverged from our original protocol with respect to the following points:

- We focused on frailty alone rather than including pre-frailty for purposes of clarity.
- We excluded Comprehensive Geriatric Assessment as a reference standard for frailty due to a lack of standardization in terms of its administration between studies and the absence of a widely recognized threshold for frailty. We have, however included studies where the Frailty Index (FI) was derived from Comprehensive Geriatric Assessment.
- We excluded studies carried out in hospital settings and emergency departments, along with patients with specific conditions; for example, cancer.
- We included studies from inception of the databases rather than studies published after 1 January 2001.
- Due to significant overlap between JBI and quality assessment of diagnostic accuracy studies (QUADAS) and time limitations, we critically appraised against the JBI framework only.
- Meta-analysis and subgroup analysis were not carried out due to substantial heterogeneity in the results.
- We excluded consideration of feasibility from our review given that our search strategy, which is focused on diagnostic accuracy, is likely to have omitted a high proportion of papers focused specifically on the feasibility of individual instruments.

Selection criteria

Types of studies
We included observational studies published in English and carried out in community settings.

Participants
The participants in our included studies were community-dwelling older adults with a minimum mean age of 65 years, or where at least half of the study participants were aged ≥65 years. Studies of participants living in residential care settings were excluded. Studies that addressed a specific diagnosis or that were carried out in an acute setting (e.g. cancer patients, surgical patients or emergency department patients) were excluded.

Index tests
Any index test purporting to measure frailty that was entirely self-reported (i.e. administered by an investigator, but including no clinical or physical measurements), or that was self-administered was included. Tests that were partially self-reported were excluded, unless test results for the self-reported items were presented independently of the non-self-reported items. We included studies in which the self-report frailty instrument was completed by a proxy, as well as studies where the older person self-completed the instrument. Studies using a self-reported FI were excluded, as any FI (self-report, test-based or combination) that meets the criteria of Searle *et al.* might be considered to be a reference standard.[19]

Reference standards
Studies were included if they applied either of two frailty reference standards: the frailty phenotype (FP; Fried *et al.*[20]) or the FI (Mitnitski *et al.* 2001).[21] Studies applying no reference standard or a reference standard other than those specified above were excluded.

Diagnosis of interest
The diagnosis of interest was frailty.

Search strategy

To identify published studies, we searched the databases MEDLINE/PubMed, PEDro, Embase, PsycINFO, CINAHL, Scopus and Web of Science from inception. The initial search was carried out between March and April of 2017, and updated in July 2018. Our search strategy was developed in consultation with an academic librarian with a specialty in medicine.

The search strategy was developed in a scaffolded manner, commencing with a CINAHL and PubMed search to inform specified keyword analysis, including MeSH terms, for subsequent database searching. We then used truncated and expanded keyword variations of the terms relating to frailty, self-report and screening, along with specific self-report screening tools (e.g. Kihon Checklist).

To identify unpublished and grey literature, we searched ProQuest, OpenGrey, The Grey Literature Report database and consulted websites of key gerontological research centers with a focus on frailty.

We also reviewed the reference lists of all included studies to identify additional studies of interest.

The search strategy syntax for individual databases is provided in Table S1.

Study selection

All studies of interest were exported from the respective databases and imported into Zotero Reference Manager version 4.0.29.17. Zotero was selected for this process because of its compatibility with the various data extraction formats from the electronic databases, its low cost, and an internal capability that made it relatively easy to identify and remove duplicates. Duplicates were identified using the inbuilt feature and manually checked before deletion by one researcher (RA).

The resulting unique records were exported into a Microsoft Excel 2016 (Redmond, WA, USA) worksheet before being assessed for title and abstract relevancy by two independent reviewers (RA and MT). We consulted a third reviewer (TS) over any differences in opinion regarding the inclusion of individual articles.

Agreed articles were extracted in full text format by one reviewer (RA), and reviewed independently by the same reviewers

(RA and MT) with recourse to the third reviewer (TS) to achieve consensus. The reason for exclusion was retained for all articles reviewed after the initial title/abstract screen.

Quality review

Two reviewers (RA and MT) subjected the included full-text articles to an initial assessment against the inclusion criteria, and a number of studies were excluded at this point. The reasons for exclusion were retained.

Box 1   JBI CRITERIA.

1. Recruitment: Was a consecutive or random sample of patients enrolled?

2. Case–control: Was a case–control design avoided?

3. Exclusions: Did the study avoid inappropriate exclusions?

4. Index test interpretation: Were the index test results interpreted without knowledge of the results of the reference standard?

5. Threshold: If a threshold was used, was it pre-specified?

6. Reference standard: Is the reference standard likely to correctly classify the target condition?

7. Reference standard interpretation: Were the reference standard results interpreted without knowledge of the results of the index test?

8. Interval: Was there an appropriate interval between index test and reference standard?

9. Same reference standard: Did all patients receive the same reference standard?

10. All patients: Were all patients included in the analysis?

Included studies were assessed against the JBI Checklist for Diagnostic Test Accuracy Studies.[17] This Checklist is based on the QUADAS 2 signaling questions and relate to the design and conduct of the study (see Box 1).[22]

Two reviewers (RA and MT) then assessed included studies independently against the JBI criteria. We recorded a value of "Yes," "No" or "Unclear" against each criterion, and made additional notes where appropriate.

Data extraction

We developed an initial data extraction template, which was based on the JBI Data Extraction tool[17] and was finalized in consultation with the research team. We extracted country of origin, sample size, mean age of participants, percentage male/female, index test and reference standard, test thresholds, and self-report or self-administration status. Data was extracted independently by two reviewers (RA and MT) and then discussed to achieve consensus. Where necessary, we sought additional clarification or data from study authors, especially with respect to 2 × 2 data to allow calculation of diagnostic characteristics.

Statistical analysis

We used Microsoft Excel and SPSS version 25 (IBM Corporation, Armonk, NY, USA)[23] to carry out descriptive analysis of the data.

We calculated sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios along with their associated 95% confidence intervals within the Review Manager (RevMan) version 5.3 software (The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark). We used Revman to construct forest plots of the data to show heterogeneity.

For the purposes of the present study, we adopted 80% as a minimum sensitivity threshold[9,24,25] and 60% as a minimum specificity threshold[24] as being acceptable. Although good screening tests have both high sensitivity and specificity (i.e. results close to 1), in practice there is often a trade-off in favor of one over the other.[26] In the case of frailty screening within community settings, high sensitivity and low specificity tends to be the more preferable scenario where identification of as many frail individuals as possible is a priority.[27] Following this logic, it might be more desirable to have a higher number of false positives than false negatives, signifying that there is a greater chance of potentially identifying as frail people who are not frail rather than missing those who are.

Additionally, we used Microsoft Excel to construct the Youden Index (sensitivity + specificity-1). The Youden Index is a single summary measure reflecting how closely the DTA result matches the ideal of no false positives or false negatives.[28] Although the Youden Index adds additional interpretive information (as a kind of balancing mechanism across the sensitivity and specificity values), it is not appropriate to consider it in isolation, especially in the context of the present study. For example, the Youden Index, as a single statistic, does not take into consideration decisions such as prioritization of high sensitivity over high specificity into account.

The "metandi" command in Stata (StataCorp, College Station, TX, USA) requires a minimum of four studies for meta-analysis of DTA studies.[29] However, the present review did not identify more than three studies comparing the same index test and reference standard. Consequently, we did not carry out meta-analysis, and have synthesized results in tabular and narrative formats.

Results

All results presented below are descriptive in nature. Across all possible comparisons of index and reference tests, the highest number of included studies per comparison was just three. In this single instance, a comparison of the Tilburg Frailty Indicator (index test) versus FP, the bivariate model was not calculated as the number of studies was below the minimum required (n = 4). Therefore, as meta-analysis was not possible, all comparisons are presented in tabular and graphical format, along with a narrative synthesis.

Search results and study characteristics

The search results (including the updated search) returned 18 034 results in total. The large number of results returned was due to a number of factors, including carrying out the search from the inception of the databases, the large number of databases searched, extensive duplication between databases and the need to allow for numerous combinations of the search term "self" in relation to screening. Study results are shown in the flow diagram in Figure 1. Of the total records identified, 10 579 duplicates were identified and removed, leaving 7455 records to be screened by title and abstract. Initial agreement between reviewers was 77.8%; where assessments differed, these were resolved through discussion or occasionally referred to the third reviewer.

After title and abstract screening, 7164 articles were excluded due to lack of relevance or because they could not be sourced in full text format. In all, 291 studies were assessed in full-text format
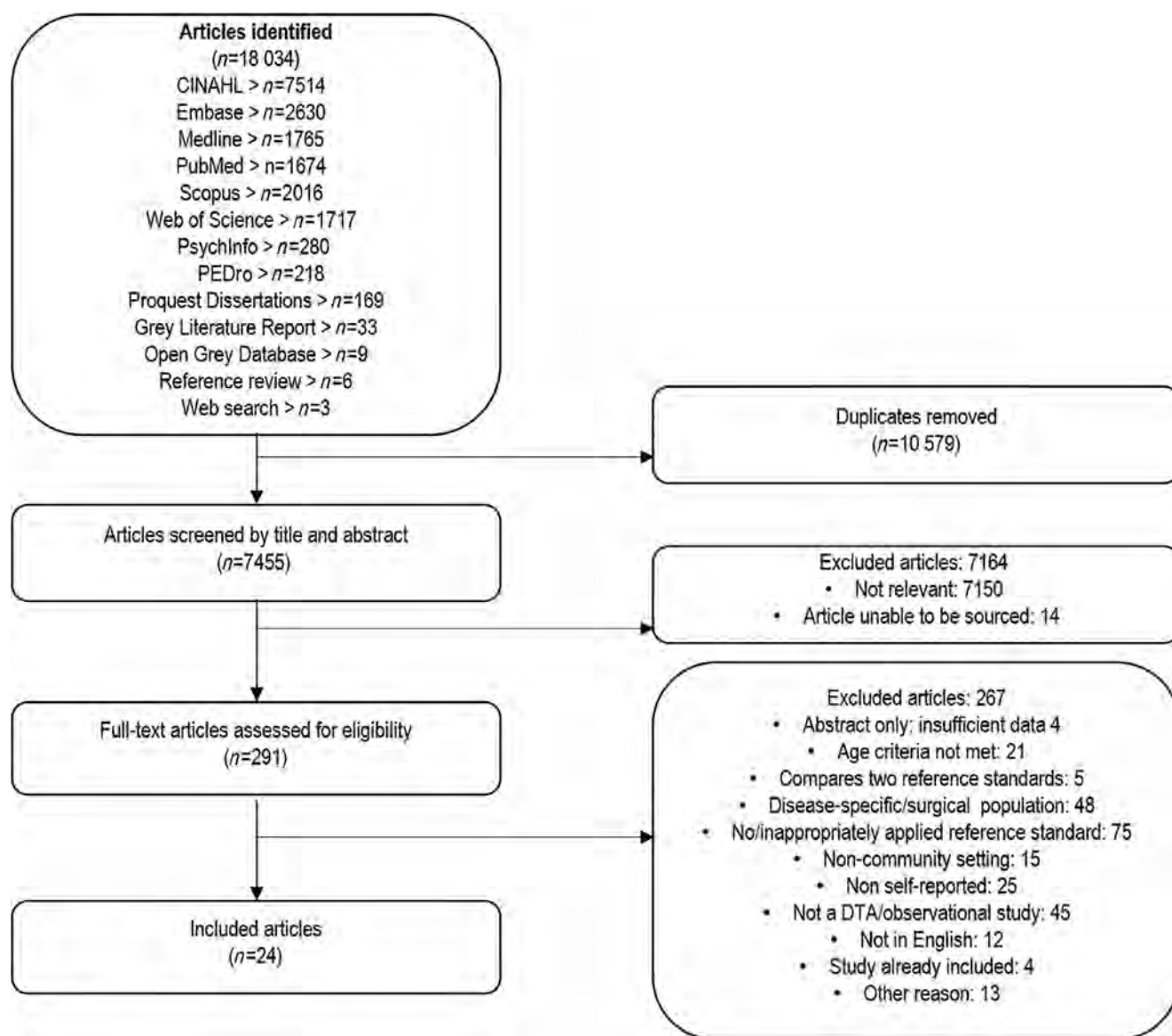
Figure 1 Study flow diagram. DTA, diagnostic test accuracy.

against the inclusion/exclusion criteria. Of these, 267 were subsequently excluded. Key reasons for exclusion included not having a reference standard or an inappropriate reference standard applied (28.1%), focus on a specific disease (18.1%), being a non-DTA or observational study (16.9%), using non-self-reported instruments (9.4%) and not meeting the age criteria (7.9%). Ultimately, 24 studies were deemed to have met the inclusion/exclusion criteria and underwent JBI critical appraisal.

Included studies

Across the 24 included studies, the sample size ranged from 52 to 27 527, with a total of 84 984 participants. The characteristics of included studies are summarized in Table 1. The mean age of participants, where stated, ranged from 65.3 years up to 85.7 years.

In all, there were 31 instances of screening instruments compared against a frailty reference standard across the included studies, with some studies having more than one combination of index test and reference standard. The most frequently

implemented instruments were the fatigue, resistance, ambulation, illnesses, and loss of weight (FRAIL) scale (22.6% of instances), the Groningen Frailty Indicator (12.9%) and Self-Reported Health (12.9%), representing a mix of multidimensional and unidimensional indicators.

Almost two-thirds (64.5%) of all comparisons were made against the FP alone as a reference standard, 19.4% against both the FP and the FI, and 16.1% against the FI alone.

The most common mode of administration was self-reporting to an external interviewer (54.8% of instances). Approximately one-quarter of cases involved self-administration of the instrument (25.8%). Finally, 19.4% of instances did not specify the mode of administration.

Methodological quality

We assessed the 24 included articles against the JBI quality criteria. The results of the methodological quality assessment against the JBI criteria for included studies are shown in Table 2.

Table 1 Key characteristics of studies included in the systematic review by reference standard

Study	Country	Sample size	Sample source & sampling strategy	Mean age (SD), sex % female	Reference standard threshold	Index test(s) and threshold	SA or SR[†]
Reference standard: FP							
Auyeung et al.[30]	China (Hong Kong)	4000	Community, convenience, selected (age group stratified)	Mean age NS, 50.0% female	≥3	Self-reported exhaustion: "yes" to a little of the time feeling like a having a lot of energy; self-reported physical activity: PASE questionnaire lowest quintile.	SR SR
Bongue et al.[31]	France	1643	Population, selected (insurer)	78.7 (7.9) years, 50.2% female	≥3	Groningen Frailty Indicator: ≥4; Vulnerable Elders Survey: ≥3	SR SR
Cawthon et al.[32]	USA	5993	Population, convenience, selected	Mean age NS, 0.0% female	≥3	Self-reported health: health compared with others of your age rated "fair, poor or very poor"	SA
De Llano et al.[33]	Brazil	820	Primary care, random.	Mean age NS, 56.1% female	≥3	Self-reported health: poor or bad	SA
Hoogendijk et al.[34]	the Netherlands	102	Primary care, selected (frail individuals over-sampled)	78.6 (7.1) years, 56.9% female	≥3	Groningen Frailty Indicator: ≥4; PRISMA-7: ≥3; Self-Rated Health: ≤6	SR SR SR
Jouanny[35]	France	64	Primary care, convenience.	Mean age and sex NS	≥3	Subjective fatigue: NS	SR
Mijnarends et al.[36]	the Netherlands	227	Population, random	74.9 years, sex NS	≥3	FRAIL Scale: ≥3	U
Mossello et al.[37]	Italy	1037	Population, convenience	Mean age and sex NS	≥3	Frailty Postal Questionnaire: ≥6.5	SA
Ng et al.[38]	Singapore	1685	Population, random	66.7 (7.8) years, 64.3% female	≥3	FRAIL Scale: ≥3	SR
Nunes et al.[27]	Brazil	433	Population, random	85.7 (5.1) years, 65.4% female	≥3	Self-reported Frailty Phenotype: ≥3	SR
Roppolo et al.[39]	Italy	267	Community, convenience	73.4 (6.0) years, 59.9% female	≥3	Tilburg Frailty Indicator: ≥5	SA
Satake et al.[40]	Japan	190	Geriatric outpatient, consecutive	76.4 (6.2) years, 33.5% female	≥3	Kihon Checklist: ≥8	U
Sternberg et al.[41]	Israel	235	Community, selected (insurer) and convenience	77.6 (5.4) years, 100% female	≥3	Vulnerable Elders Survey: ≥3	U
Szlejf et al.[42]	Mexico	434	Community, convenience	71.3 (9.5) years, 100% female	≥3	FRAIL Scale: ≥3	SA
Yamada et al.[43]	Japan	13 294	Population, random	73.7 (6.4) years, 55.2% female	≥3	Kihon Checklist: ≥7	SA
Reference standard: FI							
Drubbel et al.[44]	the Netherlands	638	Primary care, consecutive	73.4 (9.2) years, 52.8% female	≥0.08	Groningen Frailty Indicator: ≥4	SA
Jung et al.[45]	Korea	103	Geriatric outpatient, consecutive	76.8 (6.1) years, 53.4% female	≥0.35	Korean FRAIL Scale: ≥3	SR
McCaul et al.[46]	Australia	10 305	Population, random	Mean age NS, 0.0% female	≥0.25	FRAIL Scale: ≥3	U
Orkaby et al.[47]	USA	12 043	Community, selected (male physicians), convenience, first responders	69.4 (60–101) years, 0.0% female	≥0.21	Modified Study of Osteoporotic Fractures: ≥2	U

(Continues)

Table 1 Continued

Study	Country	Sample size	Sample source & sampling strategy	Mean age (SD), sex % female	Reference standard threshold	Index test(s) and threshold	SA or SR[†]
Qiao *et al.*[48]	China	1235	Population, selected (stratified by district economic development)	69.5 (6.7) years, 69.4% female	>0.25	Comprehensive Frailty Assessment Instrument: ≥39	SR
Reference standard: both FP and FI							
Braun *et al.*[49]	Germany	52	Outpatient physiotherapy clinic, recruitment method NS	73 (6) years, 63% female	FP ≥3 FI ≥0.25	PRISMA-7: ≥3 FRAIL Scale: ≥3 Groningen Frailty Indicator: ≥4	SR SR SA
Dong *et al.*[50]	China	917	Primary care, consecutive	68.6 (6.6) years, 63.8% female	FP ≥2 FI >0.35	Tilburg Frailty Indicator: ≥5 Self-Rated Health: rated fair or poor	SR SR
Ntanasi *et al.*[51]	Greece	1740	Population, random	73.4 (5.4) years, 59.0% female	FP ≥3 FI >0.25	Modified Tilburg Frailty Indicator (13 of 15 items used): ≥5	SR
Theou *et al.*[52]	11 European Countries	27 527	Population, random	65.3 (10.5) years, 54.8% female	≥3	FRAIL Scale: ≥3	U

FI, Frailty Index; FP, frailty phenotype; FRAIL, fatigue, resistance, ambulation, illnesses, and loss of weight; NS, not specified; PASE, Physical Activity Scale for the Elderly; PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument; SA, self-administered; SR, self-reported (administered by others); U, unknown.

Methodological quality of studies ranged from a low of 30% up to 90%, with almost 90% of included studies meeting ≥50% of quality criteria. The JBI criteria were designed for DTA-specific studies; however, in the present review, we have also applied them to population studies. Quality should therefore be interpreted in light of the study design. We encourage readers to refer to Table 1 for context-specific information regarding study setting and design when interpreting the DTA results.

Test accuracy

We were able to obtain sufficient data to calculate diagnostic test accuracy from 14 of the included studies (Tables 3, S2, S3; Fig. S1). The sensitivity and specificity of frailty screening instruments against the two reference standards varied widely between included studies that provided DTA data (Table 3).

Self-reported screening instruments meeting the minimum sensitivity and specificity thresholds included the PRISMA-7 against the FP (two studies; sensitivity 100.0%, specificity 80.0%[49] and sensitivity 93.3%, specificity 78.2%[34]), the GFI against the FP (sensitivity 100.0%, specificity 80.0%[49]); Self-Rated Health against the FP (sensitivity: 85%, specificity:73%[34]); and Self-Reported Physical Activity against the FP (sensitivity:80.6%, specificity:84.2%[30]) (Table 4). All instruments scoring high sensitivity also returned a Youden index value above 0.5.

Of the results reported above, most (5 of 6) were based on self-reported rather than self-administered instruments. Only the Groningen Frailty Indicator against the FP (sensitivity 100.0%, specificity 80.0%), as reported in the study by Braun *et al.*, was self-administered.[49] However, as the sample size was small (*n* = 52), this result should be interpreted with caution.

Discussion

We did not find strong and reliable evidence in support of the DTA of self-reported instruments for the identification of frailty included within the present study. Two candidates (the PRISMA-7 and the Groningen Frailty Indicator) developed specifically for the identification of frailty met our minimum sensitivity and specificity requirements against the FP,[34,49] as did Self-Reported Health (Hoogendijk *et al.*[34]). However, the studies from which they were drawn were characterized by wide confidence intervals and relatively small sample sizes, and in the case of one study (Hoogendijk *et al.*[34]), a higher prevalence of frailty than would be expected to be found within the community due to study design. Only Self-Reported Physical Activity, not a frailty screening instrument per se, but rather a single self-reported criterion of the FP, simultaneously met our sensitivity and specificity criteria, and was based on a relatively large sample size (*n* = 4000).[30] However, none of the studies described above met the JBI criterion for random or consecutive recruitment and/or were deliberately structured to achieve an overrepresentation of frail individuals, limiting their reliability and generalizability.

The present review found very high heterogeneity with respect to DTA, study design, index test and reference standard between the included studies. This is an important consideration, because study methodology, sample size, setting, and selection of both index test and reference standard are all likely to have influenced DTA results. Very few studies compared the same index test and reference standard, making a meta-analysis statistically unviable. In this respect, the present results were consistent with other studies in finding substantial variability for the DTA of frailty screening instruments.[11,14,15]

In the included studies, the reference standard was commonly modified, which complicates interpretation of the present results. The majority of studies that used the FP as a reference standard in this review included variables that differed from the original formulation specified by Fried *et al.*[20] The FP is commonly modified due to the availability of variables or ease of data collection across studies, and the modification of variables has implications for frailty prevalence, and thus also DTA findings.[53] Furthermore, we observed considerable variation in terms of the threshold for frailty used for the FI across a number of studies, which ranged from 0.08 up to 0.35. These factors impacted on our ability to

Table 2 Methodological quality of included studies (against Joanna Briggs Institute criteria)

Study	Criteria										
	1 Recruitment	2 Case control	3 Exclusions	4 Index interpretation	5 Threshold	6 Appropriate reference standard	7 Reference standard interpretation	8 Interval	9 Same reference standard	10 All patients	% Yes
Reference standard: FP											
Auyeung et al.[30]	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	70%
Bongue et al.[31]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	80%
Cawthon et al.[32]	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	70%
de Llano et al.[33]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	80%
Hoogendijk et al.[34]	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	60%
Jouanny[35]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	30%
Mijnarends et al.[36]	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	70%
Mossello et al.[37]	Yes	Yes	No	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	50%
Ng et al.[38]	Unclear	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	60%
Nunes et al.[27]	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	70%
Roppolo et al.[39]	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	70%
Satake et al.[40]	No	Yes	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	50%
Sternberg et al.[41]	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	60%
Szlejf et al.[42]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	70%
Yamada et al.[43]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Unclear	Yes	60%
Reference standard: FI											
Drubbel et al.[44]	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	60%
Jung et al.[45]	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	60%
McCaul et al.[46]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	80%
Orkaby et al.[47]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	70%
Qiao et al.[48]	Unclear	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Yes	60%
Reference standard: both FP and FI											
Braun et al.[49]	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	80%
Dong et al.[50]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	No	70%
Ntanasi et al.[51]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	80%
Theou et al.[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	90%

FI, Frailty Index; FP, frailty phenotype.

make definitive recommendations regarding the DTA of various self-reported instruments in their ability to identify frailty, and this also impacts healthcare providers and policymakers in determining whether a particular instrument is sufficiently accurate to apply for population level or clinic in frailty screening.

No conclusive statement can be made regarding the accuracy of self-reported versus self-administered tests. In the present review, the screening tests were interviewer-administered in the majority of instances (54.8%), a much smaller proportion were self-administered (25.8%) and 19.4% had an unknown mode of administration. In a number of studies, screening tests were either interviewer or self-administered concurrent to a broader assessment, which included a range of questions covering geriatric syndromes, health conditions and disability. Different methods of questionnaire administration have been identified as impacting the quality of data collected, with differences most marked between interview and self-administration.[54] Factors, such as cognitive burden of questionnaires, control over pace of interview, rapport between interviewer and respondent, and social desirability bias, are recognized as contributing to potential differences in responses.[54] Therefore, the accuracy of using self-reported, but not self-administered, frailty screening tools within community-based frailty screening, particularly in populations with low levels of education or literacy, is unclear.

The key strength of the present review is to deliver the first (to our knowledge) comprehensive appraisal of the DTA of self-reported and/or self-administered screening instruments for the identification of frailty. Consequently, we anticipate that the data presented within this review will be particularly relevant to those seeking to implement surveys carried out by post, online or in waiting room-type environments. It has also greatly expanded the number of studies and instruments included in previous reviews. Furthermore, we have calculated and reported comprehensive DTA statistics for each of the included studies. For a number of studies, these data were not reported in the original publications, and have been sourced through direct communication with authors.

The present review also identified a number of novel measures that might be further explored in future DTA studies of instruments for the identification of frailty; for example, the inclusion of instruments not specific to frailty, such as self-reported health and self-reported physical exhaustion, both of which returned higher sensitivity results than some of the instruments designed specifically to identify frailty. In addition, the present study makes a range of new contextual and diagnostic information available, including the Youden Index, which is of potential clinical relevance in making decisions about screening.

There were a number of limitations associated with the present study. The most significant of these was the heterogeneity characterizing our included studies (particularly with regard to the FI, where multiple thresholds have been applied), making interpretation challenging. However, in the absence of consensus within the field on many aspects of frailty screening, we believe that it remains important to present the full range of results, so that policymakers and practitioners can come to their own conclusions about the appropriateness of various instruments based on their intended context of use. Additionally, we acknowledge that a number of the included studies were not explicitly designed as DTA studies, but rather, might have been designed for another purpose, such as population-level cohorts. A further limitation is that we did not include self-reported FI as index tests within our study. Despite the fact that a self-reported FI can be used for frailty screening, it also meets the criteria of being a reference standard for frailty,[19] and hence was outside the scope of the present review. Finally, although we focused this review on older adults aged ≥65 years, we acknowledge the possibility that a potential source of the heterogeneity we observed in the results might be due to differences in functional ability between younger and older age groups within this cohort.

In order to focus the review, we deliberately excluded studies focusing on certain populations (cancer and surgical patients) and settings (residential care, acute care and emergency departments). Therefore, our findings do not extend beyond community settings. Furthermore, studies that focused on the feasibility of tool administration and predictive, rather than diagnostic, accuracy were outside the scope of this review. Where the DTA information on the accuracy of screening instruments is limited, it might be optimal to also consider the predictive accuracy of these instruments (mortality, hospitalization, institutionalization etc.) before implementing them at a population level or in a clinical setting. The ability of self-reported instruments to predict adverse outcomes is an important feature of screening instruments that should be considered where DTA findings are inconclusive. Finally, despite the comprehensiveness of our search strategy, it might be possible that we have inadvertently omitted studies that were relevant to our review.

There are a number of implications for frailty screening using self-reported or self-administered instruments that can be drawn from our results. First, the relatively low accuracy of many of the formal screening instruments currently in wide use potentially restricts the field of choice; however, this decision is largely dependent on the purpose for screening. The appropriate sensitivity for a self-reported instrument in the identification of frailty might vary according to the context in which such an instrument is used. Although a lower sensitivity might be appropriate in a primary care setting where follow-up investigation can more readily occur, the presence of a large number of false positive results might be problematic in larger-scale population-level screening of frailty. The ethics of frailty screening require follow-up consultation with a health professional in the event of a positive result;[55] therefore, the DTA of a screening instrument has implications in terms of health resource utilization. Other outcomes, such as predictive validity, might need to be considered alongside DTA when considering a self-report instrument for the identification of frailty.

Alternatively, another option is to consider whether a self-reported reference standard could be practically applied in preference to a frailty screening instrument. Frailty screening instruments are commonly developed as alternatives to reference standards for purposes of efficiency, but this might come at the expense of clinical relevance and accuracy.[56] A fully self-reported FI has been identified as having similar characteristics to a test-based FI.[53] Requiring a minimum of 30 variables, this could be considered as a viable alternative. Otherwise, in contexts where self-reporting is not possible, and where equipment and space allow, the FP, a combined test-based and self-report FI or a non-self-reported instrument (such as gait speed) meeting accuracy requirements might be able to be administered.

Regardless, any decision on a frailty screening instrument depends on the purpose for selecting the instrument, and which approach to frailty best fits the requirements of the health organization or practitioner recommending the test. It is widely recognized within the frailty literature that the FP and FI approaches to measuring frailty are essentially different (although complementary).[57] For example, the FP has been proposed as more amenable to a "first contact" with an individual, as it relies on general signs and symptoms, and does not readily signify what should be done by way of therapeutic follow up. In contrast, the FI, as a

Table 3 Diagnostic test accuracy statistics for selected studies

Study	Index test (reference standard)	Self-reported vs self-administered	Sample size	Prevalence, % (reference standard)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Youden index
Atyeung et al.: SREx	SREx (FP)	SR	4000	5.4	33.0 (0.27–0.40)	95.3 (0.95–0.96)	28.3
Atyeung et al.: SRPA	SRPA (FP)	SR	4000	5.4	80.6 (0.75–0.85)	84.2 (0.83–0.85)	64.8
Braun et al. (1)	PRISMA-7 (FP)	SR	52	3.9	100.0 (0.34–1.00)	80.0 (0.67–0.89)	80.0
Braun et al. (2)	FRAIL (FP)	SR	52	3.9	50.0 (0.10–0.91)	92.0 (0.81–0.97)	42.0
Braun et al. (3)	GFI (FP)	SA	52	3.9	100.0 (0.34–1.00)	80.0 (0.67–0.89)	80.0
Braun et al. (4)	PRISMA-7 (FI)	SR	52	23.1	75.0 (0.47–0.91)	92.5 (0.80–0.97)	67.5
Braun et al. (5)	FRAIL (FI)	SR	52	23.1	33.3 (0.14–0.61)	97.5 (0.87–1.00)	30.8
Braun et al. (6)	GFI (FI)	SA	52	23.1	50.0 (0.25–0.75)	85.0 (0.71–0.93)	35.0
de Llano et al.	SRH (FP)	SA	820	43.6	20.3 (0.16–0.25)	95.6 (0.93–0.97)	15.9
Dong et al. (1)‡	TFI (FP)	SR	917	5.1	73.8 (0.59–0.85)	84.8 (0.82–0.87)	58.6
Dong et al. (2)‡	TFI (FI)	SR	917	8.0	68.2 (0.56–0.78)	86.2 (0.84–0.88)	54.4
Drubbel et al.	GFI (FI)	SA	638	60.0	55.1 (0.50–0.60)	84.7 (0.79–0.89)	39.8
Hoogendijk et al.: PRISMA-7‡	PRISMA-7 (FP)	SR	102	11.6	93.3 (0.70–0.99)	78.2 (0.68–0.86)	71.5
Hoogendijk et al.: GFI‡	GFI (FP)	SR	102	11.6	73.3 (0.48–0.89)	52.9 (0.43–0.63)	26.2
Hoogendijk et al.: SRH†,‡	SRH (FP)	SR	102	11.6	85	73	58.0
McCaul et al.: Wave 2‡	FRAIL (FI)	U	10 305	24.4	52.4 (0.50–0.55)	96.3 (0.96–0.97)	48.7
McCaul et al.: Wave 3‡	FRAIL (FI)	U	10 305	33.8	63.8 (0.61–0.66)	91.8 (0.90–0.93)	55.6
Mijnarends et al.	FRAIL (FP)	U	227	8.4	68.4 (0.46–0.85)	96.2 (0.93–0.98)	64.6
Mossello et al.	FPQ (FP)	SA	1037	36.6	74.7 (0.70–0.79)	69.3 (0.66–0.73)	44.0
Ntanasi et al. (1)‡	TFI (FP)	SR	1740	4.2	76.3 (0.66–0.85)	76.7 (0.75–0.79)	53.0
Ntanasi et al. (2)‡	TFI (FI)	SR	1740	18.5	67.5 (0.62–0.72)	84.0 (0.82–0.86)	51.5
Orkaby et al.‡	MSOF (FI)	U	12 043	20.1	33.2 (0.31–0.35)	95.7 (0.95–0.96)	28.9
Qiao et al.‡	CFAI (FI)	SR	1235	20.4	65.3 (0.59–0.71)	81.2 (0.79–0.84)	46.5
Roppolo et al.	TFI (FP)	SA	267	12.7	79.4 (0.63–0.90)	60.5 (0.54–0.67)	39.9
Theou et al.: RS = SHARE-FI (70 item)‡	FRAIL (FI)	U	27 527	18.1	25.9 (0.24–0.26)	99.0 (0.99–0.99)	24.9
Theou et al.: RS = SHARE-FI-CGA (44 item)‡	FRAIL (FI)	U	27 527	21.6	25.6 (0.24–0.27)	99.0 (0.99–0.99)	24.6

†Confidence intervals not available for these results. ‡Based on unpublished data supplied by the author. CFAI, Comprehensive Frailty Assessment Instrument; CGA, Comprehensive Geriatric Assessment; CI, confidence interval; FI, Frailty Index; FP, frailty phenotype; FPQ, Frailty Postal Questionnaire; FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight; FRAIL Scale; GFI, Groningen Frailty Indicator; MSOF, Modified Study of Osteoporotic Fracture Frailty Score; PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument; RS, reference standard; SHARE, survey of health, ageing and retirement in europe; SREx, Self-Reported Exhaustion; SRH, Self-Rated Health; SRPA, Self-Reported Physical Activity; TFI, Tilburg Frailty Indicator; U, unknown.

Table 4 Summary table showing instruments meeting minimum sensitivity (>80%) and specificity (>60%) thresholds

Index test	No. studies in which the index test met the minimum Se, Sp threshold	
	Reference standard	
	FP	FI
Groningen Frailty Indicator	1	–
PRISMA-7	2	–
Self-Reported Health	1	–
Self-Reported Physical Activity	1	–

PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument; Se, sensitivity; Sp, specificity.

multidimensional frailty assessment (often based on a comprehensive assessment), can indicate where clinicians or health service providers might need to focus their intervention.[57] This difference can influence the motivation for selecting a screening instrument;[10] for example, if the instrument is to be used within a large, population-based study, further investigation will be a priority. Conversely, if it is to be used for diagnostic screening and assessment, for example, within a primary care context, the ability to intervene based on information collected will be important.

Although the body of literature on frailty is expanding rapidly, it appears that there remain an insufficient number of high-quality, sufficiently-powered DTA studies to enable meaningful conclusions to be drawn about the performance of individual frailty screening instruments.[58] More studies are required examining the DTA of self-reported frailty screening instruments for the identification of frailty in community settings. In the present review, we have combined large population-based studies and smaller clinical studies of community-dwelling participants. The justification for this choice was to maximize the available evidence on screening instruments, and centralize the results to inform research and practice. However, as the frailty evidence base grows, it might be useful to narrow the inclusion criteria to DTA studies only in a future review.

The present study has identified several self-reported instruments with potential for application within community settings. However, despite four screening instruments across three studies reporting sensitivity and specificity within a desirable range, diagnostic accuracy was clouded by study design and sampling issues, in particular participant selection. The current evidence for the DTA of many screening instruments does not support their widespread use to identify frailty in community-dwelling adults. Predictive validity, which was outside the scope of this review, might be an alternative outcome to inform health policy and practice decision-making regarding instrument selection for this population. Further well-designed DTA studies of self-reported screening instruments to identify frailty are required.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Search syntax by database

Table S2. 2 × 2 Table data for selected studies

Table S3. Additional diagnostic test accuracy results

Figure S1. Forest plots, diagnostic test accuracy statistics

Recurrent measurement of frailty is important for mortality prediction: Findings from the North West Adelaide Health Study.

Recurrent measurement of frailty is important for mortality prediction: Findings from the North West Adelaide Health Study is a paper published in the J*ournal of the American Geriatrics Society*. The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 8.

8.1   Summary

Background: Frailty places individuals at greater risk of adverse health outcomes, however, it is a dynamic condition and may not always lead to decline.

Objectives: To determine the relationship between frailty status (at baseline and follow-up) and mortality using both the frailty phenotype (FP) and frailty index (FI).

Design and setting: Population-based cohort of community-dwelling older adults

Participants: 909 individuals aged $\geq$ 65 years (55% female), mean age 74.4 (6.2) years, had frailty measurement at baseline. 549 participants had frailty measurement at 2 time points.

Measurements: Frailty was measured using the FP and FI, with a mean 4.5 years between baseline and follow-up. Mortality was matched to official death records with a minimum of 10 years follow-up.

Results: For both measures, baseline frailty was a significant predictor of mortality up to 10 years, with initially good predictive ability (AUC 0.8-0.9) decreasing over time. Repeated measurement at follow-up resulted in good prediction compared to lower (AUC: 0.6-0.7) discrimination of equivalent baseline frailty status. In a multivariable model, frailty measurement at follow-up was a stronger predictor of mortality compared to baseline. Frailty change for the Continuous FI was a significant predictor of decreased or increased mortality risk based on corresponding improvement or worsening of score (HR = 1.04, 95%CI = 1.02-1.07, p = .001).

Conclusions: Frailty measurement is a good predictor of mortality up to 10 years, however, recency of frailty measurement is important for improved prediction. A regular review of frailty status is required in older adults.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 14/2/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

   i.   the candidate's stated contribution to the publication is accurate (as detailed above);

   ii.   permission is granted for the candidate in include the publication in the thesis; and

   iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution

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Contribution to the Paper	Supervised development of work, supported data interpretation and manuscript evaluation.		
Signature		Date	11/2/2019

Recurrent Measurement of Frailty Is Important for Mortality Prediction: Findings from the North West Adelaide Health Study

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OBJECTIVES: Frailty places individuals at greater risk of adverse health outcomes. However, it is a dynamic condition and may not always lead to decline. Our objective was to determine the relationship between frailty status (at baseline and follow-up) and mortality using both the frailty phenotype (FP) and frailty index (FI).

DESIGN: Population-based cohort.

SETTING: Community-dwelling older adults.

PARTICIPANTS: A total of 909 individuals aged 65 years or older (55% female), mean age 74.4 (SD 6.2) years, had frailty measurement at baseline. Overall, 549 participants had frailty measurement at two time points.

MEASUREMENTS: Frailty was measured using the FP and FI, with a mean 4.5 years between baseline and follow-up. Mortality was matched to official death records with a minimum of 10 years of follow-up.

RESULTS: For both measures, baseline frailty was a significant predictor of mortality up to 10 years, with initially good predictive ability (area under the curve [AUC] = .8-.9) decreasing over time. Repeated measurement at follow-up resulted in good prediction compared with lower (AUC = .6-.7) discrimination of equivalent baseline frailty status. In a multivariable model, frailty measurement at follow-up was a stronger predictor of mortality compared with baseline. Frailty change for the Continuous FI was a significant predictor of decreased or increased mortality risk based on corresponding improvement or worsening of score (hazard ratio = 1.04; 95% confidence interval = 1.02-1.07; *P* = .001).

CONCLUSIONS: Frailty measurement is a good predictor of mortality up to 10 years; however, recency of frailty measurement is important for improved prediction. A regular review of frailty status is required in older adults. **J Am Geriatr Soc 00:1-7, 2019.**

Key words: frailty; Australia; mortality; longitudinal study; older adults

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Frailty represents a state of decreased physiologic reserve that places individuals at a greater risk of adverse outcomes such as disability, institutionalization, and death.[1,2] Despite the negative perceptions associated with frailty, it is possible for frailty status to improve or to remain stable over time.[3,4] This finding is pertinent because interventions exist that may slow or reverse the frailty process.[1,5] The routine assessment of the frailty status of older adults has been highlighted as a key activity in primary care so these interventions might be offered in a timely manner.[6-8]

The two main approaches to describing frailty are the frailty phenotype (FP) that defines frailty as a biological syndrome based on five physical variables,[9] and the accumulation of deficit approach that represents the proportion of deficits present across a range of systems and is represented as a frailty index (FI).[10] A number of studies examined the relationship between frailty and mortality, and they identified that when compared with non-frail individuals, those classified as frail by either the FP or FI have a greater risk of death.[2,11-14] The method of frailty measurement has an impact on both frailty prevalence and mortality risk, with the more encompassing definition of the FI generating a higher prevalence.[2] Additionally, there is a cumulative effect where the presence of an increased number of deficits is associated with greater mortality risk.[13]

Frailty was identified as a significant long-term predictor of mortality, with predictive strength best over a shorter

follow-up,[2] potentially due to the dynamic nature of frailty where change is likely over time.[12] The relationship between change in frailty classification and mortality was explored in single studies for the FP[15] and the FI.[16] Although clinicians increasingly recognize the need for assessing frailty status,[8] review of frailty status following intervention requires just as much attention. Understanding the relationship between changing frailty status and mortality may help provide the evidence base that clinicians need to be convinced that both assessment and review of frailty status may be of benefit to their patients.

The aim of this study was to examine the predictive ability of frailty classification on mortality over 10 years and the effect of recency of frailty measurement (at follow-up 4.5 y later) on mortality prediction for both the FP and FI in the North West Adelaide Health Study (NWAHS).

METHODS

Sample

This study is a secondary analysis of the NWAHS, a longitudinal population survey consisting of community-dwelling adults randomly selected from households in the northwest region of metropolitan Adelaide.[17] Participants attended a clinic and completed a written and telephone survey for each study stage. Because the probability of selection was known, data were weighted to the area population. The South Australia Health Human Research Ethics Committee (reference no. HREC/15/TQEH/61) provided ethics approval for this study.

The baseline cohort of this study included participants aged 65 years or older who completed stage 2 (2004-2006) (baseline). We excluded participants who had a FP score with fewer than three valid responses or a FI with fewer than 27 (20% missing) valid responses at baseline. To examine the effect of recency of frailty measurement, we analyzed a returning sample of participants who attended both stage 2 (baseline) and stage 3 (2008-2010) (follow-up) with the same exclusion criteria for FP and FI valid responses as at baseline. Participant mortality information was drawn from data matched to official death records and used to calculate number of years survived from follow-up, with all participants having a minimum of 10 years of follow-up from baseline.

Frailty Phenotype

A modified FP was used in this study with identical variables used at baseline and follow-up (Table S1). Three iterations of the FP were used: a Continuous FP; a 5-Category FP (0 characteristics, 1 characteristic, 2 characteristics, 3 characteristics, 4-5 characteristics); and a 3-Category FP (individuals with three or more characteristics were classified as frail; those with one or two characteristics were classified as pre-frail; and those with no characteristics present were non-frail).[9] The modified FP used in NWAHS was described previously.[18] Although the FP was originally designed as a categorical variable, it has been used in continuous form.[18,19]

Frailty Index

We developed a 34-item FI following a standard methodology[20] (Table S1). Three iterations of the FI were used: a Continuous FI; a 10% Increment FI (0-10%, 10-20%, 20-30%, 30-40%, 40-50%, and >50% proportion of deficits); and a 3-Category FI (>.21 proportion of deficits = frail; .10 and .21 = pre-frail; and <.10 non-frail). The FI used in NWAHS was described previously.[18]

Data Analysis

We used SPSS v.23 software (IBM Corp, Armonk, NY) for all statistical analysis. Cohort case weights were used in analysis and for reporting percentages to ensure the sample was representative of the population of North West Adelaide. Weighting was rescaled to sum to the sample size for the returning sample to adjust for attrition. An α value of .05 was used for determining statistical significance. Participants in the cohort were matched against death records to determine the time of death. All-cause mortality was analyzed. Descriptive characteristics and the number and proportion of participants classified as non-frail, pre-frail, and frail were reported according to mortality rate at 1, 2, 4, 6, 8, and 10 years from baseline. State transitions including participants lost to follow-up were reported. Complex samples procedures were used in SPSS to allow for the effect of the sample design on the standard error of estimates. We performed significance testing of cross-tabs using a Pearson χ^2 test and tests for linear by linear association. Survival was modeled using complex samples Cox regression to allow for the design of the sample, and we reported the hazard ratio. Multivariable analysis included combined frailty classification at baseline and follow-up, sex, age group, education level, and income level. A predictive probability of surviving 1, 2, 4, 6, 8 and 10 years from baseline was generated through logistic regression to generate an area under the curve (AUC) value for frailty classification at baseline as well as at follow-up.

RESULTS

This study included 909 participants (mean age = 74.4 [SD 6.2] y; 55% female) at baseline (Table 1). We excluded 36 participants from analysis at baseline due to insufficient FI or FP variables. For the returning cohort analysis, we included 549 participants who had frailty measurement at both stages 2 and 3. Of those excluded from the returning cohort, 147 had died between baseline and follow-up, and a further 213 were either lost to follow-up or had insufficient FI or FP variables. The 360 participants excluded from the returning cohort were significantly more likely to be older (mean age = 76.9 [SD 6.2] y), have lower income status, and higher baseline frailty prevalence (FP = 29.1% frail; FI = 62.0% frail) than the whole sample (Table S2). All participants at baseline had a minimum of 10 years of survival data.

Over a 10-year period, 292 (33.8%) participants died, with men having significantly higher mortality rates (40.1%) compared with their female counterparts (28.6%) (Table 1, Figure 1, and Table S3). Likewise, for older age group, 10-year mortality for those aged 75 years or older (54.3%) was significantly higher than for those aged 65 to 74 years (17.8%). Low-income category was also significantly associated with mortality at the 10-year mark, at 35.5% for the lowest income group compared with 11.6% for the higher group.

The 3-Category FP classified 18.3% of participants as frail at baseline; 48.1% were frail according to the 3-Category FI. Mortality was significantly higher for increasing levels of

Table 1. Descriptive Characteristics of Sample at Baseline and Frailty Status for the Frailty Phenotype and Frailty Index

	Whole sample n (%) 909	3-Category FP, n (%)			3-Category FI, n (%)		
		Non-frail 289 (30.1)	Pre-frail 470 (51.6)	Frail 150 (18.3)	Non-frail 211 (21.5)	Pre-frail 285 (30.4)	Frail 413 (48.1)
Sex							
Male	453 (45.2)	165 (36.5)	229 (50.2)	59 (13.3)*	124 (27.0)	151 (34.1)	178 (38.9)*
Female	456 (54.8)	124 (24.8)	241 (57.2)	91 (22.5)	87 (16.9)	134 (27.4)	235 (55.7)
Age groups, y							
65-74	554 (56.3)	204 (35.7)	295 (53.4)	55 (10.8)*	147 (26.1)	192 (33.9)	215 (40.0)*
≥75	355 (43.7)	85 (22.8)	175 (49.2)	95 (28.0)	64 (15.5)	93 (25.9)	198 (58.5)
Education level[a]							
Up to secondary	569 (63.5)	159 (26.9)	308 (52.9)	102 (20.3)*	110 (17.8)	190 (33.3)	269 (48.9)*
Trade/Certificate/Diploma	288 (30.6)	115 (37.0)	133 (49.0)	40 (14.0)	87 (28.1)	80 (25.3)	121 (46.6)
≥Bachelor's degree	25 (2.5)	13 (58.2)	10 (32.9)	2 (8.9)	10 (41.6)	10 (38.4)	5 (19.9)
Income groups[a]							
Up to $20 k	462 (46.5)	117 (23.1)	254 (55.5)	91 (21.4)*	81 (15.6)	144 (30.1)	237 (54.3)*
$20-$40 k	281 (33.5)	117 (41.2)	129 (44.6)	35 (14.2)	87 (29.1)	93 (32.3)	101 (38.6)
$40-$60 k	59 (6.8)	29 (43.6)	24 (45.3)	6 (11.1)	21 (33.1)	17 (30.4)	21 (36.5)
>$60 k	26 (2.6)	13 (47.1)	12 (49.4)	1 (3.5)	11 (36.8)	10 (39.1)	5 (24.2)

Abbreviations: FI, frailty index; FP, frailty phenotype.
Note: n, unweighted; % reported using cohort case weights. The 3-Category FP, no. of characteristics: 0, non-frail; 1-2, pre-frail, ≥3, frail; 3-Category FI, proportion of deficits: 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
*P < .05 (main effects reported).
[a]Missing nor included.

frailty for both the FP and FI. For the 3-Category FP, 60.2% of individuals classified as frail had died at 10 years compared with 26.3% of those who were non-frail. Of those classified as frail by the 3-Category FI, 45.1% had died at 10 years, in comparison with 21.4% of non-frail individuals. Frailty state transitions for this cohort are presented in Table S4 and were discussed in detail elsewhere.[4]

FP and FI classification at baseline significantly predicted the probability of surviving 1, 2, 4, 6, 8, and 10 years from baseline (Table 2) through AUC analysis. Mortality prediction was strongest at 1 year with good discrimination (AUC = .8-.9) for all iterations of FP and FI measures: All iterations retained acceptable discrimination (AUC = .7-.8) at 2 and 4 years and low (AUC: .6-.7) but significant prediction of mortality at 6, 8, and 10 years. Repeated frailty measurement at follow-up, for the returning cohort of 563 participants, resulted in good discriminative ability for all iterations of the FP and FI at 6, 8, and 10 years from baseline (that equates to approximately 2, 4, and 6 years post follow-up), compared with low discrimination for equivalent baseline measurement (Table 2).

In a multivariable model that included frailty status at both baseline and follow-up for the returning sample of 563 participants, frailty measurement at follow-up, but not at baseline, was significantly associated with mortality for all iterations of the FP and the 3 Category FI; however, both time points were significant for the Continuous FI and the 10% Increment FI (Table 3). The significant negative coefficient for the latter measures at baseline is a masked result due to possible suppression by the stronger predictor at follow-up. Addressing this by including frailty change (Continuous FI: follow-up minus baseline) in the model, each 1% improvement or worsening in the Continuous FI was associated with a corresponding 4% significant increase or decrease,

respectively, in mortality risk (hazard ratio [HR] = 1.04; 95% confidence interval [CI] = 1.02-1.07; P = .001). The Continuous FI at follow-up remained a significant mortality predictor in this model. Analysis of the returning sample examining baseline and follow-up frailty classification separately illustrated the stronger association between follow-up frailty measurement and mortality in comparison with baseline measurement (Tables S5, S6, and S7).

Compared with a reference category of 0 characteristics, significant elevated mortality risk was identified at three characteristics for the 5-Category FP at follow-up (HR = 2.97; 95% CI = 1.33-6.63; P = .008). For the 10% increment FI, with a reference category of 0% to 10%, a marginally significant elevation of mortality risk was observed for a 10% to 20% proportion of deficits at follow-up (HR = 2.55; 95% CI = 1.00-6.46; P = .49), and significant for the 20% to 30% proportion (HR = 4.82; 95%CI = 1.83-12.69; P = .002). HRs at higher proportions of characteristics/deficits increased exponentially and were highly significant for both the FP and FI.

DISCUSSION

Frailty classification was a significant predictor of mortality up to 10 years in this cohort of community-dwelling Australian older adults, with predictive ability strongest immediately after measurement and gradually decreasing over time. Mortality prediction was improved by repeated frailty measurement at follow-up.

Approximately one-third of participants died over 10 years, with mortality significantly higher for men, those in the older age group (≥75 y), and those on the lowest income group (<$20 000 per annum), consistent with other studies.[2,12,21]
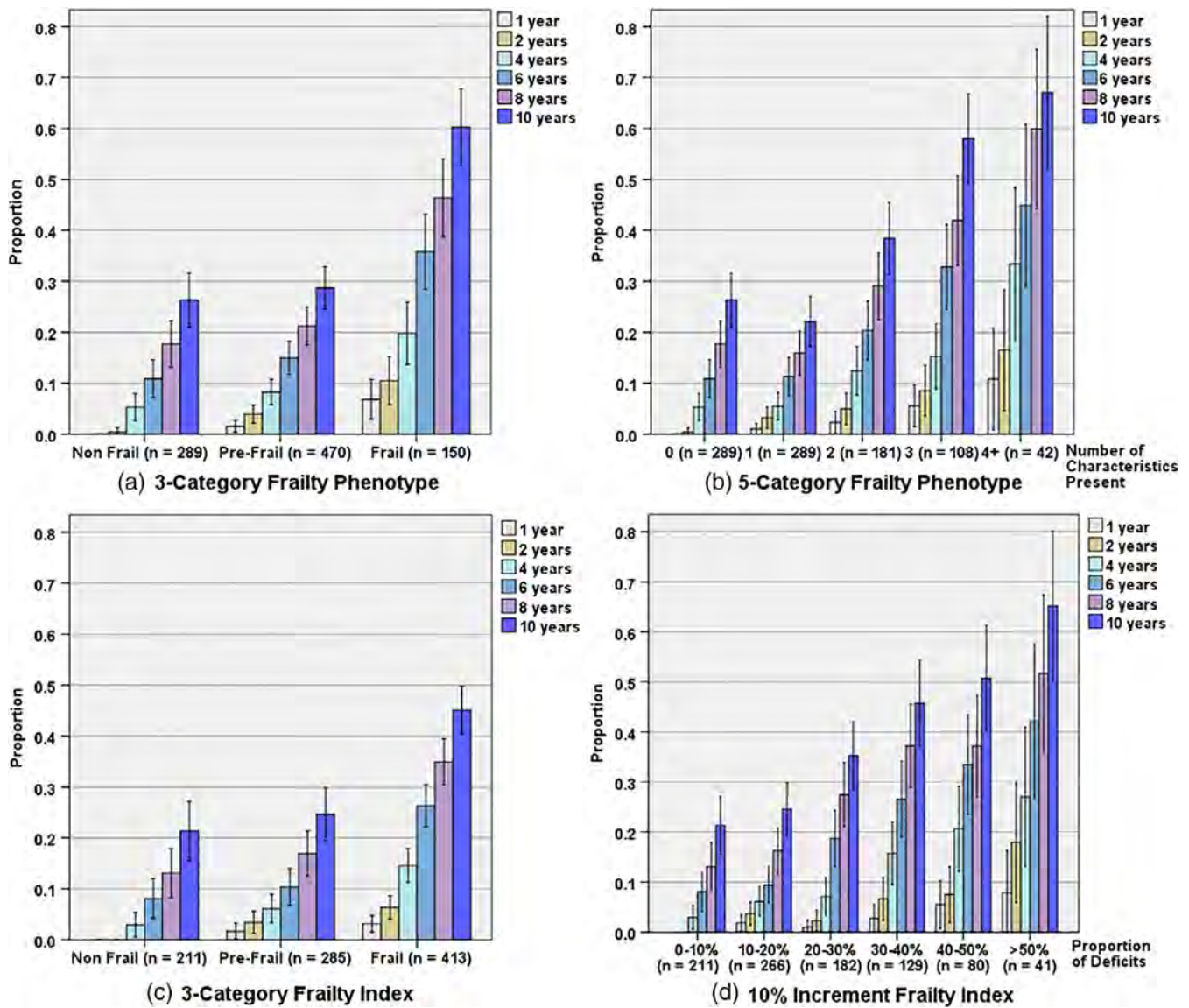
Figure 1. Mortality rates (proportion dead) over 10 years by baseline frailty status for the frailty phenotype (FP) and frailty index (FI). Proportions reported using cohort case weights. Error bars represent 95% confidence intervals. Note: 3-Category FP, no. of characteristics present: 0, non-frail; 1-2, pre-frail; ≥3, frail; 5-Category FP, no. of characteristics present: 0, 1, 2, 3, 4-5; 3-Category FI, proportion of deficits: 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail; 10% Increment FI: 0%-10%, 10%-20%, 20%-30%, 30%-40%, 40%-50%, >50%.

We examined various iterations of the FP (Continuous, 5-Category, and 3-Category) and the FI (Continuous, 10% Increment, and 3-Category) with 18.3% of individuals classified as frail by the 3-Category FP and 48.1% by the 3-Category FI. Both frailty measures in all their iterations demonstrated significant discriminative ability in predicting mortality over 10 years, with AUC prediction initially excellent (AUC = .8-.9), decreasing incrementally over time to low (AUC = .6-.7).[22] Frailty measurement for all iterations of the FP and FI at follow-up had excellent discriminative ability for mortality, compared with the low AUC of corresponding baseline measurements. This finding is consistent with the literature, where the strongest association with mortality is immediately after the frailty measurement, remaining predictive up to 11 years.[2] These findings are likely due to the dynamic nature of frailty where individuals

are more likely to worsen with increasing age; hence mortality prediction is better over shorter follow-up periods.[12]

When we examined each iteration of the FP and the FI in multivariable analysis that included both baseline and follow-up measurement, frailty measurement at follow-up, but not at baseline, was significantly associated with mortality for all iterations of the FP and the 3-Category FI; measurements at both time points were significant for the Continuous FI and 10% Increment FI. The separate analysis of the returning sample also illustrated the stronger association of follow-up measurement, countering the effect of bias of being more likely to lose those who were frail at baseline.

Frailty change (between baseline and follow-up) for the Continuous FI was a significant predictor of decreased or increased mortality risk in this study based on corresponding improvement or worsening of frailty, consistent with the

Table 2. Discriminative Ability of Frailty Phenotype and Frailty Index at Baseline and at Follow-up for Predicting Mortality[a]

Whole sample (n = 909)	AUC (95% CI)					
	1 y	2 y	4 y	6 y	8 y	10 y
FP at baseline						
Model 1: Continuous FP	.87 (.81-.94)*	.78 (.71-.85)*	.73 (.68-.79)*	.68 (.63-.73)*	.66 (.62-.71)*	.67 (.62-.71)*
Model 2: 5-Category FP	.87 (.80-.93)*	.78 (.71-.85)*	.73 (.68-.80)*	.69 (.64-.74)*	.67 (.63-.72)*	.67 (.63-.71)*
Model 3: 3-Category FP	.85 (.77-.93)*	.77 (.69-.84)*	.71 (.66-.78)*	.68 (.63-.73)*	.67 (.62-.71)*	.66 (.62-.71)*
FI at baseline						
Model 4: Continuous FI	.83 (.74-.92)*	.76 (.69-.84)*	.73 (.67-.79)*	.68 (.63-.73)*	.65 (.61-.70)*	.66 (.62-.70)*
Model 5: 10% Increment FI	.82 (.73-.92)*	.79 (.72-.86)*	.76 (.71-.81)*	.71 (.66-.76)*	.68 (.64-.73)*	.68 (.64-.72)*
Model 6: 3-Category FI	.80 (.70-.90)*	.75 (.68-.83)*	.73 (.68-.79)*	.70 (.65-.74)*	.68 (.64-.72)*	.68 (.64-.72)*
Returning sample (n = 549) [b]						
FP at follow-up				1.6 y[c]	3.6 y[c]	5.6 y[c]
Model 1: Continuous FP	-	-	-	.85 (.80-.91)*	.82 (.76-.88)*	.80 (.74-.85)*
Model 2: 5-Category FP	-	-	-	.88 (.83-.94)*	.84 (.78-.90)*	.80 (.75-.85)*
Model 3: 3-Category FP	-	-	-	.87 (.83-.91)*	.83 (.77-.88)*	.79 (.73-.84)*
FI at follow-up						
Model 4: Continuous FI	-	-	-	.87 (.82-.92) *	.82 (.77-.87)*	.80 (.75-.85)*
Model 5: 10% Increment FI	-	-	-	.87 (.82-.92)*	.85 (.80-.89)*	.81 (.76-.86)*
Model 6: 3-Category FI	-	-	-	.85 (.80-.89)*	.83 (.78-.87)*	.80 (.75-.85)*

Abbreviations: AUC, area under the curve; FI, frailty index; FP, frailty phenotype.

Note: 5-Category FP, no. of characteristics: 0, 1, 2, 3, 4-5; 3-Category FP, no. of characteristics: 0, non-frail; 1-2, pre-frail; ≥3, frail; 10% Increment FI: 0%-10%, 10%-20%, 20%-30%, 30%-40%, 40%-50%, >50%; 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.

*P < .001.

[a]AUC for years survived from baseline. Adjusted for age, sex, education, and income. Follow-up mean = 4.5 years.

[b]AUC for the returning sample at follow-up is based on survival years from baseline.

[c]Mean years between follow-up measurement and survival years from baseline.

findings of Chamberlain and colleagues.[16] Although not significant in this study, worsening of FP status was identified elsewhere with increased mortality risk.[15] The FI was described as being more sensitive to change and having more precise mortality risk prediction compared with the FP due to its more comprehensive nature.[12,16]

The findings of our research for the FP were consistent with those of the original FP study in which three characteristics was identified as a significant cut point for elevated mortality risk,[9] and furthermore, that each increase in the number of FP characteristics is associated with elevated mortality risk.[23]

However, our finding that those classified as frail by the 3-Category FP at follow-up had over triple the mortality risk compared with those who were non-frail was slightly higher than that of a systematic review by Chang and Lin[11] (pooled HR = 2.00) but was within the range of included studies. The FP has good predictive ability of mortality, and with only five variables for measurement, this approach is clinically feasible but limited in terms of the scope of characteristics measured compared with the FI.[23]

Likewise, our findings for the FI reflected those of other studies that demonstrated a dose-response relationship between higher proportions of FI deficits of worse survival.[10,14,24,25] In this study, the 7% increase in mortality risk for each 1% increase in proportion of deficits at follow-up for the Continuous FI was higher than the pooled risk of 4% per 1% increase in FI described in a systematic review by Kojima and colleagues.[12] However, it was within the upper range of studies included in that review. The FI was described as both pragmatic and flexible in terms of frailty measurement, and its graded system of measurement as valuable in providing a more sensitive risk prediction for adverse health outcomes.[12,25] The higher mortality rates for the FP and FI in this study may be associated with the lower socioeconomic status (SES) of the NWAHS region compared with the Australian population.[26] The use of routinely collated data from electronic health records in both the primary care and acute settings are likely to enhance the feasibility of automated repeat measurements of frailty,[27,28] and evolving wearable technologies may provide real-time data on the dynamic nature of the frailty syndrome.[29,30] These developments call for a new generation of dynamic frailty studies.

Strengths of this study were the use of population-based data for both the FP and FI, and 10 years of follow-up matched to official death records. Limitations of this study included a lack of some aging-specific variables such as walking speed or cognitive impairment in the data set, the use of a modified FP, and the lower SES of the NWAHS in comparison with the broader Adelaide metropolitan area. Additionally, the inclusion of only community-dwelling participants in this study, and the exclusion of 360 participants from the returning cohort who were more likely to be older, have lower income status, and higher baseline frailty prevalence than those included, is likely to have resulted in an underestimation of frailty prevalence at baseline and follow-up, and it may have weakened the mortality prediction for frailty at follow-up. Furthermore, the 4.5-year interval between baseline and follow-up allows the effect of time to become more evident with participants in the returning sample more likely

Table 3. Frailty Classification (FP and FI) at Baseline and Follow-Up and Mortality Risk (Hazard Ratio) for the Returning Sample[a]

Returning sample (n = 549) FP	Baseline		Follow-up	
	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value
Model 1: Continuous FP per 1 score	.96 (.76-1.21)	.741	1.59 (1.27-2.00)	<.001*
Model 2: 5-Category FP				
0 characteristics (n = 207)	1	-	1	-
1 characteristic (n = 188)	.86 (.47-1.58)	.623	.91(.45-1.86)	.804
2 characteristics (n = 100)	.68 (.33-1.40)	.297	1.98 (.96-4.07)	.063
3 characteristics (n = 45)	1.05 (.47-2.37)	.899	2.97 (1.33-6.63)	.008*
4-5 characteristics (n = 9)	.62 (.14-2.66)	.515	6.24 (2.47-15.81)	<.001*
Model 3: 3-Category FP				
Non-frail (n = 207)	1	-	1	-
Pre-frail (n = 288)	.90 (.53-1.55)	.713	1.28 (.69-2.37)	.426
Frail (n = 54)	1.16 (.55-2.43)	.696	3.35 (1.65-6.79)	.001*
FI				
Model 4: Continuous FI per .01 score	.96 (.94-.98)	<.001*	1.07 (1.04-1.09)	<.001*
Model 5: 10% increment FI				
0%-10% (n = 160)	1	-	1	-
10%-20% (n = 177)	.62 (.31-1.24)	.178	2.55 (1.00-6.46)	.049*
20%-30% (n = 106)	.63 (.29-1.40)	.261	4.82 (1.83-12.69)	.002*
30%-40% (n = 59)	.46 (.18-1.18)	.105	5.53 (1.92-15.95)	.002*
40%-50% (n = 36)	.31 (.10-.98)	.047*	9.52 (3.16-28.69)	<.001*
>50% (n = 11)	.30 (.06-1.51)	.144	21.62 (6.11-76.47)	<.001*
Model 6: 3-Category FI				
Non-frail (n = 160)	1	-	1	-
Pre-frail (n = 191)	.67 (.34-1.33)	.251	2.42 (.95-6.15)	.063
Frail (n = 198)	.72 (.35-1.49)	.373	6.08 (2.38-15.57)	<.001*

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; FI, frailty index; FP, frailty phenotype.
Note: 5-Category FP, no. of characteristics: 0, 1, 2, 3, 4-5; 3-Category FP, no. of characteristics: 0, non-frail; 1-2, pre-frail; ≥3, frail; 10% Increment FI: 0%-10%, 10%-20%, 20%-30%, 30%-40%, 40%-50%, >50%; 3-Category FI, proportion of deficits: 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of September 30, 2016 (minimum of 10 y of mortality data for all participants).
*P < .05.
[a]Weighted multivariable analysis adjusted for frailty at both time points, age, sex, education, and income.

to have higher levels of frailty at follow-up, which is to be expected for an aging cohort. Additionally, the Continuous FP is an ordinal measure that does not fulfill the preconditions of most parametric statistical tests; however, nearly all articles treat this as a continuous measure, as we have done.

In conclusion, this study identified that recency of frailty measurement is important for predicting survival. Although frailty measurement was a significant predictor of mortality risk up to 10 years, recency of measurement was a stronger predictor. Routine assessment of frailty in older adults was highlighted as important in the clinical setting,[7,8] which can feasibly be measured using routinely collected data.[6,27,28] The findings from this study have implications for the clinical setting where a more recent frailty assessment is likely to provide the best information about the health status of older adults, taking into account the dynamic nature of the frailty condition and that regular reevaluation is necessary to keep this frailty profile up to date.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1: Frailty Phenotype and Frailty Index Variables.

Table S2: Baseline Descriptive Characteristics and Frailty Classification of Participants Who Died Before July 31, 2018, or Who Were Lost to Follow-Up.

Table S3: Mortality Rates by Baseline Descriptive Characteristics, Frailty Status for the Frailty Phenotype (FP) and Frailty Index (FI).

Table S4: Frailty Status at Baseline and Follow-Up Status for the 3-Category Frailty Phenotype and Frailty Index

Table S5: Mortality Rates by Baseline Descriptive Characteristics, Frailty Status (Frailty Phenotype [FP] and Frailty Index [FI]) for the Returning Sample (n = 549).

Table S6: Frailty Classification (Frailty Phenotype and Frailty Index) at Baseline and Follow-Up and Mortality Risk (Hazard Ratio) for the Returning Sample (n = 549). Baseline and Follow-Up Frailty Classification are Considered separately. Weighted multivariable analysis adjusted for age, sex, education, and income.

Table S7: Frailty Classification (Frailty Phenotype and Frailty Index) at Baseline and Mortality Risk (Hazard Ratio) for the Whole Sample (n = 909). Weighted Multivariable Analysis Adjusted for Age, Sex, Education, and Income.

The combination of frailty and sarcopenia is an important mortality predictor: North West Adelaide Health Study findings

This chapter is a reproduction of a paper submitted to the *Journal of Gerontology Series A*. The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 9.

9.1 Summary

Background: Frailty and sarcopenia are age-related conditions with shared features and associated with adverse health outcomes. Relatively little is known about outcomes of these conditions in combination. The aim of this study was to examine the predictive ability of frailty and sarcopenia classification on mortality.

Methods: Frailty was measured in this cohort of 716 community-dwelling adults (mean age 74.1 (6.1) years, 55.5% female) using the frailty phenotype (FP) and frailty index (FI), and sarcopenia using the revised European consensus definition. Participants were classified as: neither frail nor sarcopenic; frail-only; sarcopenic-only; or both frail and sarcopenic. All participants had a minimum of 10-years mortality follow-up.

Results: Classification as both frail and sarcopenic resulted in a multivariable model resulted in significantly elevated mortality risk for the FP (HR = 4.78, p<.001) and FI (HR = 4.90, p<.001), which was over four times that of those neither frail nor sarcopenic. Frail-only was also a significant mortality predictor for both the FP (HR = 1.78, p=.010) and FI (HR = 2.05, p<.001), while sarcopenic-only approached significance in the FP model (HR = 1.71, p=.100) and the FI model (HR = 2.01, p=.081). Significant associations were maintained in a sensitivity analysis that excluded weak grip strength from both the FP and FI.

Conclusions: Individuals identified as frail would benefit from screening and assessment for sarcopenia, and vice versa for those identified as sarcopenic, as the mortality risk for individuals with these syndromes in combination is more than double that of each in isolation.

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Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 23/1/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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The combination of frailty and sarcopenia is an important mortality predictor: North West Adelaide Health Study findings

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Contribution to the Paper	Representative of the North West Adelaide Health Study – source of data. Helped to evaluate and edit the manuscript.		
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Contribution to the Paper	Supervised development of work, supported data interpretation and manuscript evaluation.		
Signature		Date	18/10/2019

The combination of frailty and sarcopenia is an important mortality predictor: North West Adelaide Health Study findings

Introduction

Frailty and sarcopenia are two common conditions experienced by older adults, with evidence to suggest that both are associated with adverse outcomes such as hospital admission, disability, and mortality (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Cruz-Jentoft & Sayer, 2019). Frailty is described as a state of reduced physiological reserve and failure of homeostatic mechanisms (Clegg et al., 2013), while sarcopenia is a skeletal muscle disorder characterized by loss of muscle mass and function (Cruz-Jentoft & Sayer, 2019). Increasingly, frailty and sarcopenia are being examined together, as these conditions share features in common, in particular in relation to lower lean mass and physical function (Cesari, Landi, Vellas, Bernabei, & Marzetti, 2014).

Internationally, frailty prevalence in community-dwelling adults aged ≥65 years has been estimated as ranging between 4% to 17% (9.9% weighted mean) using the FP approach, and between 4% to 59% (13.6% weighted mean) using an accumulated deficits approach (i.e., Frailty Index [FI]) which classifies frailty based on a proportion of deficits present (Collard, Boter, Schoevers, & Oude Voshaar, 2012). The FI typically classifies a higher proportion of individuals as frail compared to the more physical definitions of frailty as it relies on a more comprehensive approach (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Thompson, Theou, Adams, Tucker, & Visvanathan, 2018). While both approaches to measurement are strongly correlated, there is only modest agreement in terms of frailty classification (Thompson, Theou, Yu, et al., 2018). We have previously described that both the FP and FI are significantly predictive of mortality up to 10 years in this cohort, where frailty prevalence was 18.3% FP and 48.1% FI (Thompson, Theou, Tucker, Adams, & Visvanathan, 2019).

Sarcopenia prevalence has been estimated at 10% in adults aged ≥60 years (Shafiee et al., 2017). We have previously reported the prevalence of sarcopenia as being 6.2% for men and 9% for women aged ≥ 65 years in the North West Adelaide Health Study (NWAHS) cohort (Yu et al., 2014). Prevalence varies on the method of measurement utilised, and in this cohort sarcopenia has been defined as the lowest 20% of the study population for low appendicular muscle mass (ASM) (male: < 7.36 kg/m2, female: < 5.81 kg/m2), and < 30kg (male) and < 20kg (female) for weak grip. The significant association between sarcopenia and increased mortality risk has been established internationally (pooled HR = 1.60, p = .216) (Liu et al., 2017), however, this relationship is yet to be examined in an Australian cohort.

The prevalence of frailty and sarcopenia in combination has been explored in a small number of studies. Mori et al (2019) identified 3.6% of participants in a

population of Japanese community-dwelling adults (n=331, mean age 71.5 [SD 5.1] years, 72% female) as being both frail (using FP approach) and sarcopenic, while Yoshimura and colleagues (2019) identified 2.1% as being both frail (FP) and Sarcopenic in a Japanese community-dwelling cohort (n=963, mean age 72.2 [SD 7.6] years, 67% female). This proportion was higher (18%, FP) for a Spanish sample of either hospitalized or geriatric outpatient attending adults (n=444, mean age 77.3 [SD 8.4] years, 45% female) (Bernabeu-Wittel et al., 2019), and for a sample of participants attending a Dutch geriatric outpatient clinic (n = 299, mean age 82.4 [SD 7.1] years, 65% female) at 42% (n=8) FP and 25% (n=1) FI (Reijnierse et al., 2016). This is the only study to date that has examined frailty, using both approaches, and sarcopenia.

The adverse health outcomes associated with frailty and sarcopenia individually have been described in a number of studies, with frail participants having a significantly higher mortality risk than their non-frail counterparts (pooled RR = 1.50, $p < .001$ for FP, and RR = 1.15, $p < .001$ for FI) (Shamliyan, Talley, Ramakrishnan, & Kane, 2013), and likewise for survival of sarcopenic individuals (pooled RR = 3.60, $p < .001$) (Beaudart, Zaaria, Pasleau, Reginster, & Bruyere, 2017). However, to the best of our knowledge, no study to date has examined the relationship between the combination of frailty and sarcopenia and survival in a community-based cohort of men and women. It is important to understand the nature of this relationship for prognostication as well as when determining a treatment regimen.

The aims of this study were to report on the combined prevalence of frailty and sarcopenia, and to examine the predictive ability of frailty alone, sarcopenia alone and sarcopenia in combination with frailty on mortality over 10 years in adults aged ≥65 years from the North West Adelaide Health Study (NWAHS) for both the FP and FI.

Methods
Sample
This study was a secondary analysis of the North West Adelaide Health Study (NWAHS), a longitudinal population survey of community-dwelling adults randomly selected from households in the North-West region of Adelaide (Grant et al., 2009). At each study stage, participants attended a clinic and completed phone and written surveys. As the probability of selection was known, data were weighted to the area population. SA Health Human Research Ethics Committee (Reference number HREC/15/TQEH/61) provided ethics approval.

Participants in this study were aged ≥65 years who completed stage 2 (2004-2006). Stage 2 data were used as the basis of all frailty and sarcopenia markers. We excluded participants who were lacking 3 or more valid FP characteristics, with <27 valid FI responses (20% missing) or who were lacking DEXA data. Excluded participants were significantly older (mean age 75.9 (SD 6.9) years) than those

included. Participants were matched to official death records in order to determine mortality, and all participants had a minimum of 10 years of follow-up from baseline.

Frailty Phenotype (FP)

Frailty for the FP was measured in this study using a modified version of that proposed by Fried and colleagues (Fried et al., 2001). A dichotomous FP classification was used, where participants with three or more of the following characteristics present were classified as frail: weight loss, weak grip strength, exhaustion, slowness, and low physical activity level, while participants with 0-2 characteristics were classified as non-frail (See Supplementary Table S1 for cut points of each FP characteristic). Grip strength (kg) was based on the mean of three measurements of the dominant hand using a grip dynamometer (Lafayette Instrument Company, IN, USA). For sensitivity analysis, a 4-variable FP was used which excluded grip strength. The characteristics of the FP used in this study have been described elsewhere (Thompson, Theou, Yu, et al., 2018).

Frailty Index (FI)

We developed a 34-item FI following a standard methodology (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008), with variables coded as between 0, for no deficit, and 1, for maximum expression of deficit. A dichotomous FI classification was used where participants with 0 to ≤ 0.21 were classified as non-frail; and those with > 0.21 deficits were frail. (See Supplementary Table S1 for FI variables included). Grip strength, a sarcopenia biomarker, was a FI variable in this study, and used the same cut points as the FP. For sensitivity analysis, a 33-item FI was used which excluded grip strength. The characteristics of the FI used in this study have been described elsewhere (Thompson, Theou, Yu, et al., 2018).

Sarcopenia

Individuals were classified as sarcopenic if both of the following criteria were present: weak grip strength and low SMI. (See Supplementary Table S1 for cut points of each sarcopenia characteristic).

Weak grip strength for sarcopenia was stratified by sex as: Male, < 30kg; Female, < 20kg (Yu et al., 2014). Appendicular skeletal muscle mass (ASM) in this study was measured using Dual Energy X-Ray Absorptiometry (DXA), and was defined as the sum of lean soft-tissue masses for arms and legs, assuming that all non-fat and nonbone tissue are skeletal muscle. A Lunar PRODIGY scanner (GE Medical Systems, Madison, WI) in conjunction with Encore 2002 software and a DPX+ (GE Medical Systems, Madison, WI) scanner in conjunction with LUNAR software version 4.7e were used.

Low SMI cut points were based on the lowest 20% of the study population stratified by sex: Male, < 7.36 kg/m2; Female, < 5.81 kg/m2 (Yu et al., 2014). The characteristics of sarcopenia used in this study meet the revised European consensus definition (Cruz-Jentoft et al., 2019), and have been described elsewhere (Yu et al., 2014).

Data Analysis

We used SPSS version 23 (IBM Corporation, Armonk, NY) for statistical analysis in this study. Case weights for the cohort were used in reporting percentages and for analysis to ensure that the sample was representative of the population. An alpha value of 0.05 was used for statistical significance. We reported descriptive characteristics of the sample for the number and proportion classified as frail by the FP (FP-frail), frail by the FI (FI-frail), and sarcopenic.

Complex samples procedures were used in SPSS to allow for the effect of the sample design on the standard error of estimates. Complex samples Cox regression was used to model survival, which allowed for the sample design, and we reported the hazard ratio.

Multivariable analysis was performed separately for FP-frailty, FI-frailty, and sarcopenia, adjusting for sex, age, education level, and income. Multivariable analyses were also performed in models which classified participants as: neither frail or sarcopenic; frail-only; sarcopenic-only; and both frail and sarcopenic, for both the FP and FI. Pearson's correlation was performed between both frailty measures and sarcopenia, as continuous variables. In order to minimize measurement overlap between frailty and sarcopenia, a sensitivity analysis was conducted by excluding frailty cases for which weak grip strength was part of the qualifying criteria, for both the FP and FI. Additionally, we examined the interaction between frailty and sarcopenia for both the FP and FI by fitting a Cox model that included the main effects of frailty and sarcopenia as well as an interaction term between frailty and sarcopenia. We performed ANOVA with post hoc multiple comparisons to compare mean FP and FI values for those classified as frail only or both frail and sarcopenic, to examine the severity of frailty for each classification.

Results

In this longitudinal cohort of 716 community-dwelling Australian adults aged ≥65 years (mean age 74.1 (6.1) years, 55.5% female), 18.3% were classified as frail using the FP, 49.3% frail using the FI, and 9.8% Sarcopenic. Descriptive characteristics of the sample and relationship with frailty and sarcopenia classification are reported in Table 1. (see Supplementary Table S2 for descriptive characteristics by classification as neither, only or both frail and sarcopenic) The proportion of participants classified according to FP or FI frailty status, and FP or FI frailty status with sarcopenia is presented in Figure 1. While the FP and FI were strongly correlated (r = .764, p < .001), there was a moderate significant correlation between both the FP and sarcopenia (r = .479, p < .001), and the FI and sarcopenia (r = .330, p = .003). There was no significant difference in mean frailty scores between those classified as FP frail-only and both FP-frail and sarcopenic. However, FI frail-only participants had a significantly lower proportion of deficits compared to those both FI-frail and sarcopenic (Supplementary Table S3).

Table 1. Descriptive characteristics of sample and relationship with frailty (frailty phenotype and frailty index) and sarcopenia classification.

	Whole sample n (%)	FP Frailty Status		FI Frailty Status		Sarcopenia Status	
		Non-Frail n (%)	Frail n (%)	Non-Frail n (%)	Frail n (%)	Non-Sarcopenic n (%)	Sarcopenic n (%)
Total	716	598 (81.7)	118 (18.3)	387 (50.7)	329 (49.3)	646 (90.2)	70 (9.8)
Sex							
Male	352 (44.5)	305 (86.4)	47 (13.6)*	211 (60.0)	141 (40.0)*	315 (89.5)	37 (10.5)
Female	364 (55.5)	293 (77.9)	71 (22.1)	176 (43.3)	188 (56.7)	331 (90.8)	33 (9.2)
Age Groups							
65-74 years	449 (58.3)	405 (89.5)	44 (10.5)*	273 (58.9)	176 (41.1)*	427 (95.2)	22 (4.8)*
>75 years	267 (41.7)	193 (70.8)	74 (29.2)	114 (39.4)	153 (60.6)	219 (83.2)	48 (16.8)
Education Level†							
Up to secondary	454 (64.3)	373 (79.8)	81 (20.2)	233 (49.4)	221 (50.6)*	405 (89.3)	49 (10.7)
Trade / Cert / Dip	220 (29.8)	190 (86.4)	30 (13.6)	131 (53.6)	89 (46.4)	201 (91.0)	19 (9.0)
Bachelor degree+	23 (2.9)	21 (90.2)	2 (9.8)	18 (78.2)	5 (21.8)	22 (94.1)	1 (5.9)
Income Groups†							
Up to $20k	365 (46.9)	296 (79.9)	69 (20.1)	176 (45.2)	189 (54.8)*	325 (87.9)	40 (12.1)
$20-$40k	232 (35.5)	202 (84.9)	30 (15.1)	146 (58.9)	86 (41.1)	216 (93.4)	16 (6.6)
$40-$60k	42 (5.9)	37 (87.9)	5 (12.1)	26 (60.8)	16 (39.2)	39 (91.2)	3 (8.8)
More than $60k	20 (2.4)	19 (95.2)	1 (4.8)	15 (67.2)	5 (32.8)	18 (92.2)	2 (7.8)
Multimorbidity†							
0-1 health conditions	494 (67.0)	440 (87.6)	54 (12.4)*	341 (65.4)	153 (34.6)*	446 (89.9)	48 (10.1)
2+ health conditions	222 (33.0)	158 (69.6)	64 (30.4)	46 (20.9)	176 (79.1)	200 (90.9)	22 (9.1)
Living Arrangements†							
Lives with others	434 (68.6)	371 (83.6)	63 (16.4)*	245 (52.8)	189 (47.2)	402 (92.1)	32 (7.9)*
Lives alone	265 (29.2)	213 (77.7)	52 (22.3)	134 (45.8)	131 (54.2)	228 (85.4)	37 (14.6)

Note. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. † Not stated or missing not included.

* p < 0.05 (overall effect reported)

a) FP Frailty and FI Frailty
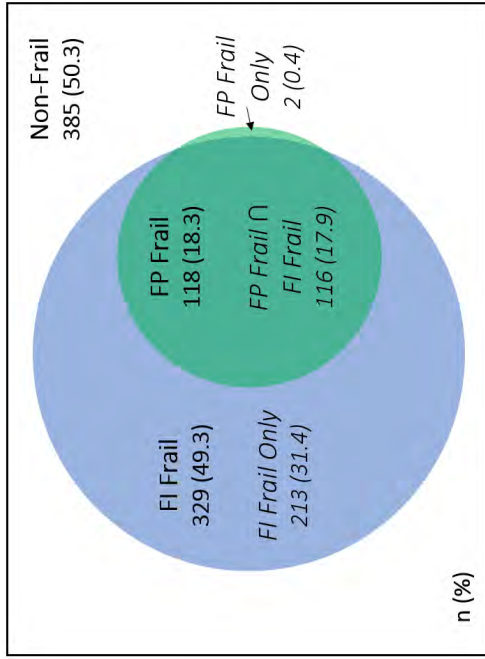
b) FP Frailty and Sarcopenia
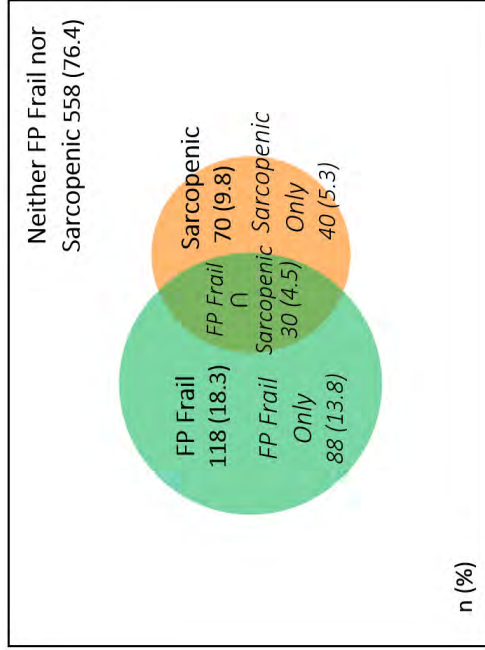
c) FI Frailty and Sarcopenia
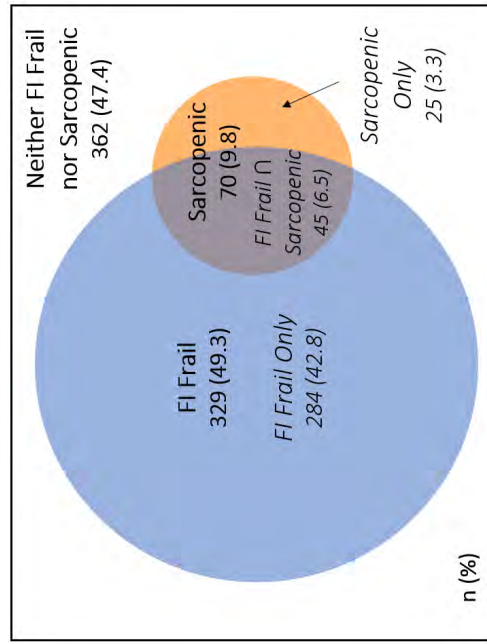
d) FP Frailty, FI Frailty, and Sarcopenia
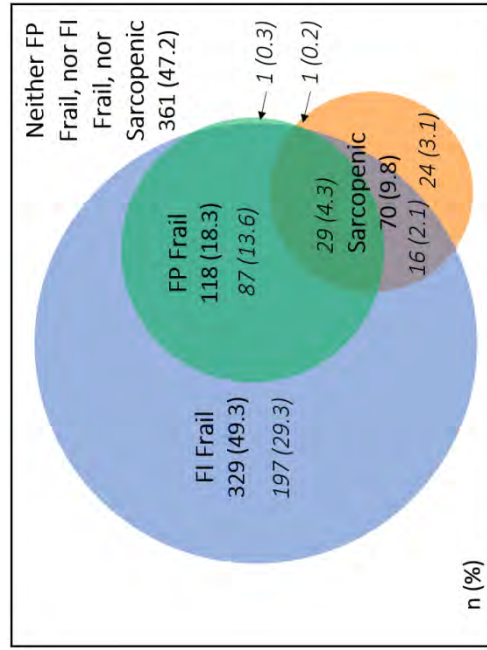
Figure 1. **Proportion of participants (n=716) classified as either FP frail, FI Frail or sarcopenic. Classification by: a) FP Frailty and FI Frailty; b) FP Frailty and Sarcopenia; c) FI Frailty and Sarcopenia; d) FP Frailty, FI Frailty, and Sarcopenia. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21, non-frail; > 0.21 = frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. Set n (%) reported in bold text. Intersection (∩) and relative complement n (%) reported in italics.**

Mortality Risk - Frailty & Sarcopenia Separate

Participants who were classified as FP-frail had over double the adjusted mortality risk (HR = 2.23, 95%CI -= 1.55-3.22, p < .001) of their non-frail counterparts, which was also the case for FI-frail participants (HR = 2.18, 95%CI = 1.55-3.07, p < .001), and sarcopenic participants (HR = 2.45, 95%CI = 1.57-3.81, p < .001) (Table 2). (See supplementary Table S4 for results stratified by sex).

Table 2. **Relationship of frailty classification (Frailty Phenotype and Frailty Index) and Sarcopenia with survival (over 10 years), with FP frailty, FI frailty, and sarcopenia analysed individually. Complex samples Cox regression, adjusted for: age, sex, income, education.**

	n (%)	Unadjusted HR (95%CI) p-value	Adjusted HR (95%CI) p-value
Total	716	-	-
FP Frailty			
Non-Frail	598 (81.7)	1	1
Frail	118 (18.3)	2.87 (2.09, 3.93) p < .001*	2.23 (1.55,3.22) p < .001*
FI Frailty			
Non-Frail	387 (50.7)	1	1
Frail	329 (49.3)	2.31 (1.72, 3.12) p < .001*	2.18 (1.55, 3.07) p < .001*
Sarcopenia			
Non-Sarcopenic	646 (90.2)	1	1
Sarcopenic	70 (9.8)	3.59 (2.45, 5.25) p < .001*	2.45 (1.57, 3.81) p < .001*

Note. HR, Hazard Ratio; 95%CI, 95% Confidence Interval. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants.

* p < 0.05

Mortality risk - Frailty & Sarcopenia Combined

For the FP and sarcopenia examined together, 4.5% of participants were classified as both FP-frail and sarcopenic, while 13.8% were FP-frail-only and 5.3% sarcopenic-only, with the remaining 76.4% as neither FP-frail nor sarcopenic (Table 3). For the FI and sarcopenia examined together, 6.5% were classified as both FI-frail and sarcopenic, while 42.8% were FI-frail-only and 3.3% sarcopenic-only, with the remaining 47.4% as neither FI-frail nor sarcopenic (Table 3). 4.3% of participants were classified as frail and sarcopenic by both frailty instruments. (See supplementary Table S5 for results stratified by sex).

Table 3. Relationship of frailty and sarcopenia status with survival (over 10 years). Complex samples Cox regression. Adjusted for: age, sex, income, education.

|	n (%)	Unadjusted HR (95% CI) p-value	Adjusted HR (95%CI) p-value
Total	716	-	-
FP Frailty & Sarcopenia Status			
Neither frail nor sarcopenic	558 (76.4)	1	1
Frail only	88 (13.8)	2.48 (1.71, 3.61) p < .001*	1.78 (1.15, 2.76) p = .010*
Sarcopenic only	40 (5.3)	2.96 (1.71, 5.14) p < .001*	1.71 (.90, 3.23) p = .100
Both frail and sarcopenic	30 (4.5)	6.66 (4.05, 10.97) p < .001*	4.78 (2.79, 8.19) p < .001*
FI Frailty & Sarcopenia Status			
Neither frail nor sarcopenic	362 (47.4)	1	1
Frail only	284 (42.8)	2.18 (1.57, 3.03) p < .001*	2.05 (1.42, 2.96) p < .001*
Sarcopenic only	25 (3.3)	3.26 (1.65, 6.43) p < .001*	2.01 (.91, 4.83) p = .081
Both frail and sarcopenic	45 (6.5)	7.16 (4.40, 11.67) p < .001*	4.90 (2.84, 8.47) p < .001*

Note. HR, Hazard Ratio; 95%CI, 95% Confidence Interval. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants.

* $p < 0.05$

Classification as both FP-frail and sarcopenic resulted in a more than quadrupled mortality risk (HR = 4.78 95%CI = 1.15-2.76, p < .001) compared to the reference category of neither FP-frail nor sarcopenic, in a multivariable analysis that adjusted for age, sex, income and education.

This was also the case for those who were FI-frail and sarcopenic (HR = 4.90, 95%CI = 2.84-8.47, p < .001). Figure 2 presents survival curves based on frailty or sarcopenia classification for both FP and FI models. Mortality risk was also significantly elevated for frail-only participants for both the FP (HR = 1.78 95%CI = 2.79-8.19, p = .010) and FI (HR = 2.05, 95%CI = 1.42-2.96, p < .001). Classification as sarcopenic-only approached significance in both the FP model (HR = 1.71, 95%CI = .90-3.23, p = .100) and the FI model (HR = 2.01, 95%CI = .91-4.83, p = .081). Survival patterns with similar significant associations were evident in a sensitivity analysis which excluded frailty cases for which weak grip strength was part of the qualifying criteria, for both the FP and FI (Supplementary Table S6). In a model which included an interaction term between frailty and sarcopenia, the interaction was non-significant (p = .749) (data not shown).
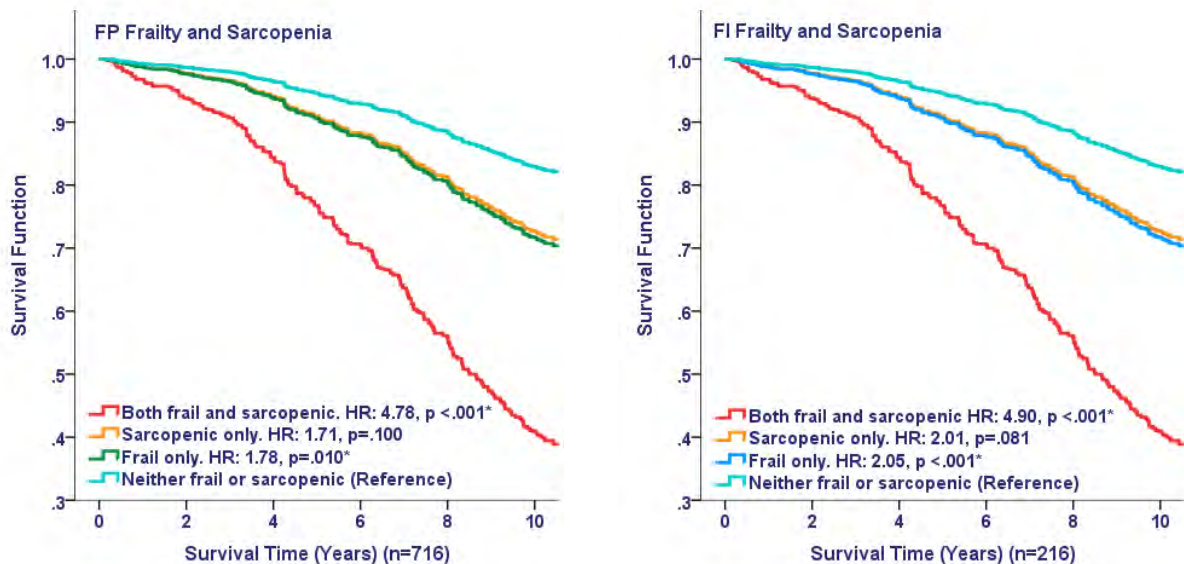
Figure 2. Survival curves for frailty and sarcopenia classification predicted from complex samples Cox regression (n=716), for: a) Frailty Phenotype (FP) and Sarcopenia; b) Frailty Index (FI) and Sarcopenia. Adjusted for age, sex, income, education. A minimum of 10 years of mortality data was available for all participants. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. HR, Hazard Ratio; 95%CI, 95% Confidence Interval. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants. * p < 0.05

Discussion

The combined presence of frailty and sarcopenia (for both the FP and FI) in this population sample of community-dwelling adults aged ≥65 years resulted in a quadrupled mortality risk compared to those classified as neither frail nor sarcopenic. This risk was exponentially higher than those classified as frail-only (both FP and FI), and sarcopenic-only (for both FP and FI models), which were still both significantly higher at around double that of the reference group of neither frail nor sarcopenic.

In this study 4.5% of participants were classified as both frail and sarcopenic using the FP approach while the proportion was 6.5% using the FI. The combined prevalence in this study is similar to that of two Japanese cohorts of older adults at 3.6% and 2.1% respectively which both used the FP approach (Mori & Tokuda, 2019; Yoshimura et al., 2019), although the comparatively higher mean age of our cohort may account for a slightly higher rate. The proportion of participants classified as either frail (FP or FI) or sarcopenic in this cohort (Figure 1) illustrates the notion of the FP being a 'physical subset' of frailty as a whole as proposed by Cruz-Jentoft (2019), and while sarcopenia might be closely related to frailty, and be considered a biological substrate of frailty, not all sarcopenic individuals were frail. The sarcopenia biomarker of grip strength was included in the FI in this study. It is important to note that the variables used to construct a FI, particularly those that are also sarcopenia biomarkers, are likely to affect the combined prevalence of FI frailty and sarcopenia. This might account for difference between prevalence of 6.5% in our

study, compared with 0.3% a geriatric outpatient cohort with a FI that did not include any sarcopenia variables (Reijnierse et al., 2016).

Those classified as sarcopenic in this cohort also had a more than doubled mortality risk over 10 years of follow up in a multivariable analysis. This finding is similar to that of DeBuyser et al (2016) where mortality was significantly higher (HR: 2.50, p = .006) for community-dwelling men with sarcopenia over 15 years follow-up. To the best of our knowledge, however, this is the first description of the relationship between sarcopenia and survival in a population cohort of both men and women.

Notably, when we classified participants as frail-only (for both the FP and FI), sarcopenic-only, and both frail and sarcopenic and compared to the reference category of neither frail nor sarcopenia, we identified an almost five-fold increase in mortality risk for those classified as both frail and sarcopenic (both FP and FI) in a multivariable analysis. Findings were similar in a sensitivity analysis which identified that frailty and sarcopenia acted independently, and with no significant difference in frailty severity for frail-only compared versus both frail and sarcopenic for the FP, however, there was a significant difference in FI proportion of deficits between groups. The implications for the clinical setting are that each condition needs to be identified separately in order to build an accurate patient prognostic profile, and severity of frailty, particularly for the FP, is not necessarily indicative of the presence of sarcopenia. Very few studies have examined the combination of frailty and sarcopenia and associated mortality risk, with the exception of a sample of hospitalized older adults with multimorbidity (Bernabeu-Wittel et al., 2019), and a sample of outpatient geriatric clinic participants (Reijnierse et al., 2016).

Bernabeu-Wittel and colleague's (2019) study of hospitalized or geriatric outpatient attending older adults with multimorbidity identified that participants with combined frailty (FP) and sarcopenia had a similar significantly worse 12-month survival profile to frail-only participants compared to non-frail individuals. However, the multimorbidity profile of this cohort makes it difficult to compare findings with our population cohort, as multimorbidity is independently associated with poor survival (Nunes, Flores, Mielke, Thume, & Facchini, 2016). The only population-level study of frailty and sarcopenia survival analysis by DeBuyser and colleagues (2016), using the Study of Osteoporotic Fractures (SOF) frailty index method, did not report on the combined classification of both frail and sarcopenic as such. To the best of our knowledge, our study is the first to report on the combined presence of frailty and sarcopenia and associated mortality in a community-based population cohort of Australian older adults.

Our findings highlight the adverse effect of the combined presence of frailty and sarcopenia on the survival of older adults. These results have important clinical implications, where frail individuals should be screened and assessed for sarcopenia, and vice versa, in order to identify those at greatest risk of mortality, and to use prognosis to guide discussion around management of these conditions. As

weakness, is a shared criterion of frailty and sarcopenia, its presence is likely indicative of the loss of lean muscle mass. A stepwise approach to screening and assessment should be considered to enhance the feasibility of identifying either condition in the clinical setting, as simple screening instruments exist for both frailty or sarcopenia that can be used to identify individuals who would benefit from a comprehensive geriatric assessment (Cesari et al., 2016; A. Clegg, Rogers, & Young, 2015; Yu, Khow, Jadczak, & Visvanathan, 2016). Both frailty and sarcopenia can be either delayed or reversed through similar, complementary interventions consisting of exercise in combination with other strategies such as protein supplementation (Dent et al., 2018; Puts et al., 2017).

This study has a number of limitations. Firstly, as a general population study, some ageing specific variables were not available for analysis such as cognition and gait speed. Furthermore, the lower socioeconomic status of the North West region of Adelaide in comparison to the larger metropolitan area may have resulted in a higher proportion of frail and sarcopenic individuals.

The proportion of participants classified as frail is likely to vary for the FI based on the number and range of FI variables included (Theou et al., 2015); for the FP based on modifications to the FP variables (Theou et al., 2015); and for both approaches based on the characteristics of the population studied. The implications of modifications to the FP for this cohort have been discussed in detail elsewhere (Thompson, Theou, Yu, et al., 2018).

Conclusions

The small proportion of participants in this study who were both frail and sarcopenic experienced a more than doubled mortality risk in comparison with those with either condition individually. Weakness, which is a sheared feature of both frailty and sarcopenia, is likely indicative of loss of lean muscle mass and represents a particularly heightened state of vulnerability for older adults.

Individuals who are identified as frail in the clinical setting should also be screened and assessed for sarcopenia, and vice versa, and offered appropriate intervention.

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FRAIL Scale: Predictive validity and diagnostic test accuracy

This chapter is a reproduction of a paper submitted for publication to the *Australasian Journal on Ageing,* and is currently under review.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 10.

10.1 Summary

Objectives: Frailty is a common geriatric syndrome, and older adults would benefit from screening for this condition which can be delayed or prevented. This study examined the predictive validity of the FRAIL Scale for mortality over 10 years, and diagnostic test accuracy (DTA) against the reference standard of the frailty phenotype (FP).

Design: Population-based cohort.

Setting: Community-dwelling Australia.

Participants: 846 participants aged ≥65 years (mean age 74.3 [SD 6.3] years, 54.8% female).

Measurement: Frailty was measured using a modified FRAIL Scale (≥3 characteristics) and a modified FP (≥3 characteristics). Mortality was matched to official death records with a minimum 10 years follow-up.

Results: The FRAIL Scale demonstrated significant predictive validity for mortality up to 10 years in an adjusted analysis (Frail HR: 2.60, p < .001). The FRAIL Scale and FP were significantly correlated (r=.619, p<.001). The FRAIL Scale demonstrated acceptable DTA findings against the FP for Specificity (86.8%) and Youden index (0.50), but not Sensitivity (63.6%), or area under receiver operator curve (auROC) (0.75) for ≥3 characteristic cut-point. All DTA estimates were acceptable when a cut-point of ≥2 characteristics was used instead (Sensitivity: 95.6%, Specificity: 64.1%, Youden Index: 0.60, auROC: 0.80).

Conclusion: The FRAIL Scale is a valid predictor of mortality. DTA estimates of FP frailty were maximised when a FRAIL Scale cut point of ≥2 characteristics was used, making this instrument a potentially useful screening tool for frailty in the community setting.

Statement of Authorship

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Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i.   the candidate's stated contribution to the publication is accurate (as detailed above);

ii.   permission is granted for the candidate in include the publication in the thesis; and

iii.   the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Supervised development of work, supported data interpretation and manuscript evaluation.
Signature		Date	2/12/19.

10.3 Submission to the *Australasian Journal on Ageing*

FRAIL Scale: Predictive validity and diagnostic test accuracy

Introduction

Frailty is a geriatric syndrome common among older adults that is amenable to intervention (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Puts et al., 2017). There have been calls for frailty to be routinely screened among this population (Theou & Rockwood, 2012), primarily due to the dynamic nature of the condition where deterioration is not always an inevitable outcome (Thompson, Theou, Adams, Tucker, & Visvanathan, 2018).

Frailty is a state of decreased physiological reserve which places individuals at greater risk of adverse outcomes following stressor events (Clegg et al., 2013). One of the most commonly used definitions of frailty is the phenotype approach of Fried and colleagues (2001) which defines frailty as being present when 3 or more of the following 5 characteristics are present: weak grip strength, slow gait speed, exhaustion, low physical activity, and unintentional weight loss.

There are a number of frailty screening instruments which have been identified as being reliable and valid across various settings (Apostolo et al., 2017; Dent, Kowal, & Hoogendijk, 2016; Drubbel et al., 2014; Pijpers, Ferreira, Stehouwer, & Nieuwenhuijzen Kruseman, 2012; Sutton et al., 2016), and two systematic reviews have examined the diagnostic test accuracy (DTA) of frailty screening instruments against a frailty reference standard (Clegg, Rogers, & Young, 2015; Pialoux, Goyard, & Lesourd, 2012).

Good screening tests should have high sensitivity and specificity, however, in reality there may be a compromise of one estimate against the other (Leeflang, Deeks, Gatsonis, Bossuyt, & Group, 2008). When screening for geriatric conditions, such as frailty, higher sensitivity is preferred over specificity, as it is preferable to incorrectly classify individual as frail and rule out a diagnosis after further assessment, than miss individuals (Nunes, Duarte, Santos, & Lebrao, 2015). Other useful estimates in evaluating the DTA of screening instruments include the Youden index which is a summary of DTA estimates, and the area under the receiver operator curve (auROC) which quantifies the overall ability of a test to discriminate between two outcomes (Carter, Pan, Rai, & Galandiuk, 2016).

The FRAIL Scale, developed by Morley and colleagues (2012), is a self-reported screening instrument for frailty. This is a short and easy to administer tool which has been identified as practical for use in identifying frailty in the general practice setting, and has been recommended as a preferred instrument in the Australian primary care setting (Burgess & Hercus, 2017). The FRAIL Scale has demonstrated preliminary evidence in favour of its predictive validity for mortality (Kojima, 2018).

A few studies have validated the FRAIL Scale in populations of Australian women (Gardiner, Mishra, & Dobson, 2015; Lopez, Flicker, & Dobson, 2012; Susanto, Hubbard, & Gardiner, 2018) and men (Hyde et al., 2010) separately. Individuals with three or more FRAIL characteristics present are classified as frail, while those with 1-2 characteristics are pre-frail, and those with no characteristics are non-frail (Morley et al., 2012).

Three studies have examined the diagnostic test accuracy (DTA) of the FRAIL Scale against the FP. DTA estimates were similar in a study by Braun and colleagues (2018) (Sensitivity: 50.0%, Specificity: 92.0%) and by Mijnarends et al (2015) (Sensitivity: 68.4%, Specificity: 96.2%), while sensitivity estimates were considerably lower in a recent Australian study by Ambagtsheer and colleagues (2019) (Sensitivity: 30.0%, Specificity 94.2%). These findings suggest that the FRAIL Scale performed well at ruling out the presence of frailty through high specificity, but fails to correctly identify an adequate number of those who were frail due to low sensitivity. Differences in DTA estimates across these studies may be attributable to differing sample sizes, and different study populations. Further examination of the psychometric properties of the FRAIL Scale is required in a variety of settings, and the Australian context in particular, where it has been proposed as a preferred screening instrument for frailty (Burgess & Hercus, 2017).

The aim of this study was to examine the predictive validity for mortality and diagnostic test accuracy of the FRAIL Scale against a reference standards of the frailty phenotype in a community-dwelling cohort of Australian older adults.

Methods

Sample

This study was a secondary analysis of the North West Adelaide Health Study (NWAHS), a randomly selected longitudinal population survey of community-dwelling adults drawn from households in the North-West region of Adelaide (Grant et al., 2009). Participants attended a clinic and completed both phone and written surveys. As the probability of selection was known, data were weighted to the area population. SA Health Human Research Ethics Committee (Reference number HREC/15/TQEH/61) provided ethics approval.

Participants included in this study were aged ≥65 years who completed stage 2 (2004-2006).

We excluded participants (n = 99) who were lacking any FRAIL Scale or FP variables. Participants were matched to official death records in order to determine mortality, and all participants had a minimum of 10 years of follow-up from baseline.

The index tests and reference standards used in this study were not 'administered' as such in NWAHS, rather, variables were drawn from available data to construct each measure. Therefore, the results of neither index tests, nor

reference standards were available to assessors. We are unable to report on the interval between administration of index test and reference standard for the same reason.

Index test: FRAIL Scale

The FRAIL Scale is comprised of five characteristics: fatigue, resistance, ambulation, illnesses, and loss of weight (Morley et al., 2012). We used some modified variables in the construction of the scale (see Supplementary Table S1 for details of variables). Each FRAIL Scale characteristic was scored 0-1, and scores ranged from 0 (best) to 5 (worst). Individuals with ≥3 characteristics were categorised as frail, 1-2 characteristics as pre-frail, and no characteristics as non-frail.

Reference Standard: Frailty Phenotype

A modified FP was used in this study, where participants with three or more of the following characteristics present were classified as frail: weight loss, weak grip strength, exhaustion, slowness, and low physical activity level, while participants with 0-1 characteristics were classified as pre-frail, and those with no characteristics as non-frail (Fried et al., 2001). Modifications to FP variables are reported in Supplementary Table S1. The characteristics of the FP used in our study have been described previously (Thompson, Theou, Yu, et al., 2018).

Diagnostic Test Accuracy Minimum Thresholds

In this study we used the following acceptable minimum thresholds: ≥80% for sensitivity (Apostolo et al., 2017; Forti et al., 2012), ≥60% for specificity (Forti et al., 2012), ≥0.50 for Youden Index (Carter et al., 2016), and ≥80.0% for auROC (Sutorius, Hoogendijk, Prins, & van Hout, 2016).

Analysis

We used SPSS version 23 (IBM Corporation, Armonk, NY) for statistical analysis in this study.

Case weights for the cohort were used in reporting percentages and for analysis to ensure that the sample was representative of the population. An alpha value of 0.05 was used for statistical significance. We reported descriptive characteristics of the sample for the number and proportion classified as frail by the FRAIL Scale, frail by the FP (FP-frail), and sarcopenic. We performed significance testing of cross-tabs using a Pearson chi-squared test.

Correlation was calculated between continuous versions of the FRAIL Scale and FP to examine their relationship. Complex samples procedures were used in SPSS to allow for the effect of the sample design on the standard error of estimates. Survival was modelled using complex samples cox regression which allowed for the sample design, and was reported as a hazard ratio. Multivariable analysis was performed adjusting for sex, age, education level, and income. We cross-tabulated the results of index tests against references standards with case weighting applied and used Stata Statistical Software Release 15 (StataCorp LLC, College Station, TX) to calculate estimates of diagnostic accuracy and their precision (95% confidence intervals).

Results

Frailty prevalence

We included 846 participants from this community-dwelling population of older adults (mean age 74.3 (SD 6.3) years, 54.8% female). Frailty prevalence was measured at 22.5% by the FRAIL Scale, and 18.7% for the FP (Table 1). Frail individuals were significantly (p<.05) more likely to be female and older age group (≥75 years) across all frailty measures compared with their non-frail counterparts. There was a strong significant correlation between continuous versions of the FRAIL Scale and the FP (r=.619, p<.001).

Table 1. Descriptive characteristics of sample at baseline and classification by frailty status (FRAIL Scale, Frailty Phenotype and Frailty Index).

	n (%)	FRAIL Scale			Frailty Phenotype		
		Non-frail n (%)	Pre-frail n (%)	Frail n (%)	Non-frail n (%)	Pre-frail n (%)	Frail n (%)
Whole Sample	846	303 (33.7)	374 (43.7)	169 (22.5)	276 (30.9)	427 (50.4)	143 (18.7)
Sex							
Male	419 (45.2)	172 (40.9)	180 (42.6)	67 (16.5)*	154 (36.6)	209 (49.8)	56 (13.6)*
Female	427 (54.8)	131 (27.7)	194 (44.7)	102 (27.6)	122 (26.3)	218 (50.9)	87 (22.9)
Age Groups							
65-74 years	522 (57.3)	213 (40.5)	231 (42.8)	78 (16.7)*	196 (36.2)	271 (52.3)	55 (11.5)*
≥75 years	324 (42.7)	90 (24.6)	143 (45.0)	91 (30.4)	80 (23.9)	156 (47.9)	88 (28.3)
Education Level [a]							
Up to secondary	524 (62.6)	171 (30.7)	241 (45.6)	112 (23.7)	151 (28.0)	275 (51.1)	98 (20.9)*
Trade / Cert / Dip	275 (31.4)	117 (39.7)	110 (39.9)	48 (20.4)	111 (37.0)	127 (49.4)	37 (13.6)
≥Bachelor degree	23 (2.5)	10 (49.4)	9 (33.5)	4 (17.1)	12 (57.9)	9 (32.7)	2 (9.4)
Income Groups [a]							
Up to $20k	425 (46.2)	122 (25.3)	210 (51.2)	93 (23.5)*	111 (23.5)	227 (54.6)	87 (21.9)*
$20-$40k	270 (34.7)	117 (41.4)	109 (39.1)	44 (19.5)	114 (41.7)	121 (43.4)	35 (14.8)
$40-$60k	55 (6.8)	26 (48.7)	19 (32.3)	10 (19.0)	28 (46.3)	22 (43.1)	5 (10.6)
>$60k	25 (2.7)	15 (59.7)	6 (23.4)	4 (16.9)	12 (45.4)	12 (51.0)	1 (3.6)
Multimorbidity [a]							
0-1 health conditions	577 (66.6)	250 (40.9)	251 (43.9)	79 (15.2)*	218 (36.0)	294 (51.5)	65 (12.5)*
2+ health conditions	269 (33.4)	53 (19.3)	123 (43.5)	93 (37.2)	58 (20.8)	133 (48.1)	78 (31.1)
FRAIL Scale Characteristics Present [b]							
Fatigue	171 (21.6)	0 (0)	61 (32.6)	110 (67.4)*	19 (9.9)	87 (48.8)	65 (41.3)*
Resistance	429 (53.8)	0 (0)	261 (58.4)	168 (41.6)*	65 (15.0)	230 (52.2)	134 (32.8)*
Ambulation	339 (42.7)	0 (0)	176 (48.8)	163 (51.2)*	34 (10.2)	170 (48.5)	135 (41.3)*
Illnesses	34 (4.4)	0 (0)	7 (20.2)	27 (79.8)*	3 (8.0)	16 (42.9)	15 (49.1)*
Loss of Weight	50 (5.4)	0 (0)	22 (42.3)	28 (57.7)*	0 (0)	27 (49.7)	23 (50.3)*
Frailty Phenotype Characteristics Present [b]							
Weight Loss	50 (5.4)	0 (0)	22 (42.3)	28 (57.7)*	0 (0)	27 (49.7)	23 (50.3)*
Weakness	320 (40.6)	68 (18.5)	151 (47.4)	101 (34.1)*	0 (0)	198 (59.9)	122 (40.1)*
Exhaustion	123 (15.1)	7 (5.6)	61 (47.8)	55 (46.6)*	0 (0)	49 (39.6)	74 (60.4)*
Slowness	223 (29.0)	1 (0.5)	101 (43.4)	121 (56.2)*	0 (0)	96 (41.7)	127 (58.3)*
Low Physical Activity	350 (42.1)	87 (23.4)	159 (44.6)	104 (31.9)*	0 (0)	225 (62.5)	125 (37.5)*

n unweighted. % reported using cohort case weights. FRAIL Scale (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥3, frail. Frailty Phenotype (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥3, frail.

[a] missing nor included.

[b] measurement method and cut points for each characteristic are described in Supplementary File S1.

* p < 0.05 (main effects reported)

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FRAIL Scale validity and DTA

Individuals classified as frail by the FRAIL Scale had significantly more than double the mortality risk (HR: 2.60, 95% CI: 1.78-3.80, p<.001) over 10 years of follow up in an analysis adjusted for age, sex, education, and income compared with their non-frail counterparts (Table 2 and Figure 1). Stratified by sex, the hazard ratio for frail men was 2.26 (95%CI: 1.39-3.69, p < .001) while frail women had more than triple the mortality risk of those who were non-frail (HR: 3.19, 95%CI: 1.57-6.51, p = .001) Cross-tabulation of the FRAIL Scale frailty classification against the reference standard of the FP, were used to generate estimates of DTA (see Supplementary Table S2 for 2x2 tables).

The FRAIL Scale produced acceptable estimates of Specificity (86.8%, 95%CI: 84.0%-89.2%) and Youden Index (0.50) against the FP using a cut point of ≥3 characteristics, however Sensitivity (63.6 95%CI: 55.3%-70.8%) and AUC (0.75 95%CI: 0.71, 0.79) were below acceptable thresholds (Table 3). When a cut point of ≥2 characteristics was used, all estimates were acceptable (Sensitivity: 95.6%, Specificity: 64.1%, Youden Index: 0.60, auROC: 0.80).

Table 2. **FRAIL Scale classification and mortality risk (Hazard Ratio). Weighted multivariable analysis adjusted for age, sex, education and income.**

	Unadjusted		Adjusted	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Whole Sample (n = 846)				
FRAIL Scale – Whole Sample				
Non-frail (n = 303)	1	-	1	-
Pre-frail (n = 374)	1.40 (1.03, 1.91)	.031*	1.32 (0.95, 1.84)	.095
Frail (n = 169)	2.63 (1.88, 3.68)	<.001*	2.60 (1.78, 3.80)	< .001*
FRAIL Scale – Male				
Non-frail (n = 172)	1	-	1	-
Pre-frail (n = 180)	1.29 (0.90, 1.84)	.170	1.24 (0.85, 1.81)	.254
Frail (n = 67)	2.44 (1.59, 3.77)	<.001*	2.26 (1.39, 3.69)	.001*
FRAIL Scale – Female				
Non-frail (n = 131)	1	-	1	-
Pre-frail (n = 194)	2.07 (1.14, 3.77)	.017*	1.51 (0.74, 3.09)	.255
Frail (n = 102)	4.35 (2.40, 7.87)	<.001*	3.19 (1.57, 6.51)	.001*

HR, Hazard Ratio. 95%CI, 95% confidence interval. FRAIL Scale categories (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥3, frail. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016. (Minimum of 10 years of mortality data for all participants).

* p < 0.05
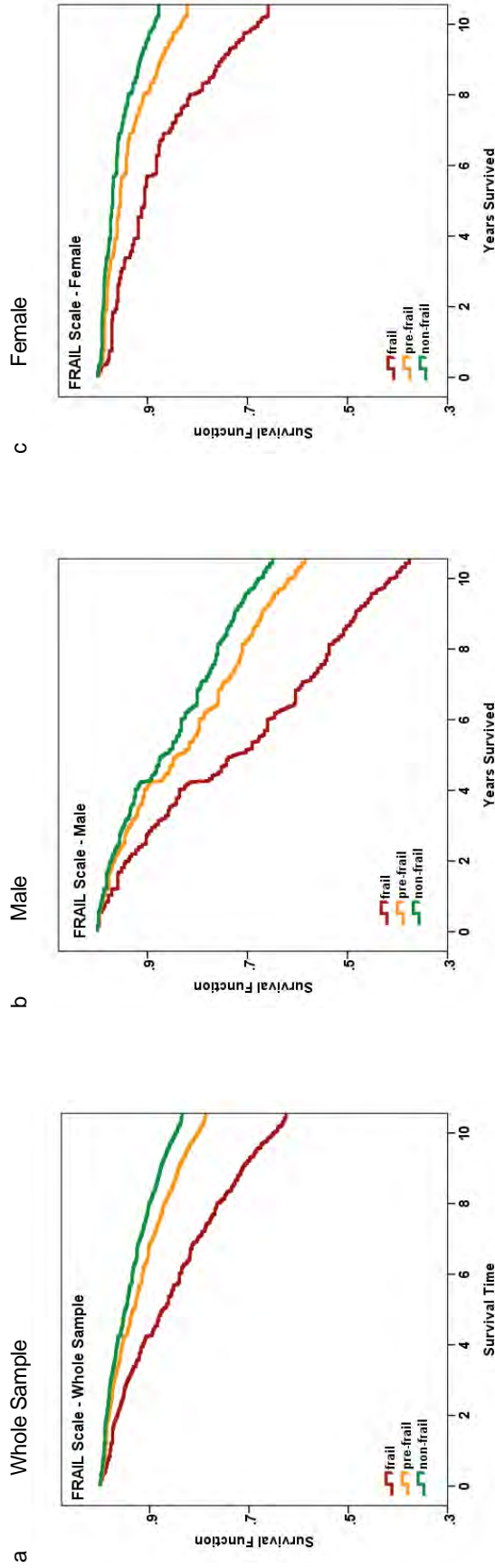
Figure 1. Survival curves for FRAIL Scale classification predicted from complex samples Cox regression, adjusted for age, sex, income, education. A minimum of 10 years of mortality data was available for all participants. FRAIL Scale categories: 0, non-frail; 1-2, pre-frail; ≥3 characteristics, frail. SARC-F categories: 0-3 points, healthy; 4-10 points symptomatic. HR, Hazard Ratio; 95%CI, 95% Confidence Interval. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants. * p < 0.05

Table 3. Diagnostic test accuracy: FRAIL Scale (number of characteristics present) by frailty phenotype (FP) ≥3 characteristics.

	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV (95%CI)	NPV (95%CI)	Area Under Curve (95%CI)	Youden Index
FRAIL Scale ≥1 vs FP	98.7 (95.5, 99.8)	41.1 (37.4, 44.9)	27.8 (24.1, 31.7)	99.3 (97.5, 99.9)	0.70 (0.68, 0.72)	0.40
FRAIL Scale ≥2 vs FP	95.6 (91.1, 98.2)	64.1 (60.4, 67.7)	37.9 (33.2, 42.9)	98.4 (96.8, 99.4)	0.80 (0.77, 0.82)	0.60
FRAIL Scale ≥3 by FP	63.3 (55.3, 70.8)	86.8 (84.0, 89.2)	52.4 (45.0, 59.6)	91.1 (88.7, 93.2)	0.75 (0.71, 0.79)	0.50

PPV, positive predictive value. NPV, negative predictive value. auROC, area under receiver operator curve. 95%CI, 95% confidence interval. FRAIL Scale (number of characteristics): 0 to 2, non-frail; ≥ 3, frail. Frailty Phenotype (number of characteristics): 0 to 2, non-frail; ≥3 = frail. SARC-F (number of characteristics): 0 to 3, healthy; ≥4, symptomatic. Sarcopenia (number of characteristics): 0 to 1, healthy; 2, sarcopenic.

Discussion

The FRAIL Scale demonstrated significant predictive validity (frail HR: 2.60) against mortality up to 10 years in this cohort of community-dwelling older adults. The FRAIL Scale produced acceptable Specificity, and Youden Index estimates only against the reference standard of the FP using the FRAIL Scale cut point of ≥3 characteristics. All DTA estimates were acceptable when ≥2 characteristics was used as a cut point for the FRAIL Scale.

When stratified by sex, our mortality findings for FRAIL Scale for women (HR: 3.19) were similar to an age-equivalent Australian cohort of women (3 characteristics HR: 3.15; 4+ characteristics HR: 4.52) (Lopez et al., 2012). Likewise for men in this study (HR: 2.26), where findings were similar to those of an equivalent cohort of Australian men (3 characteristics HR: 2.27; 4+ characteristics HR: 3.97) (Hyde et al., 2010). Importantly, this is the first study to report on FRAIL Scale validity for mortality in an Australian cohort of both men and women. The clinical implications of our findings are that individuals identified as frail using the FRAIL Scale have an elevated mortality profile and would benefit from further investigation of their frailty status, and targeting with appropriate intervention.

The acceptable DTA estimates for specificity of the FRAIL Scale against the FP reference standard in this study (86.8%) are similar to those reported in other studies which also examined FRAIL Scale DTA against the FP, with estimates ranging from 92.0% to 96.2% (Ambagtsheer et al., 2019; Braun et al., 2018; Mijnarends et al., 2015). Our sensitivity estimate (63.3%), which was below the acceptable threshold, was in the higher range compared to values reported elsewhere (30.0% to 68.4%). Variability in DTA estimates across studies may be attributable to population source and baseline frailty prevalence, sample size, and method of index test and reference standard measurement. This last point is particularly applicable to this study where several variables were modified in both measures. Additionally, we note that DTA acceptability criteria used in this study were based on the work, and readers should use their discretion in interpreting findings. For clinicians, our findings indicate that the FRAIL Scale, while effective at ruling out FP frailty, is likely to miss a number of individuals who are frail as measured by the FP.

The DTA estimates of the FRAIL Scale were improved and all met acceptability criteria when a FRAIL Scale cut point of ≥2 characteristics was used. There is potential value in trading off higher sensitivity for lower specificity in the clinical setting where it is preferable to identify as many frail individuals as possible, accepting a higher number of false positives, rather than to miss those who are actually frail (Nunes et al., 2015). A strategy for maximising the feasibility of this approach to frailty screening in primary care would be to use a stepwise process of increasingly more detailed assessment which may result in a comprehensive geriatric assessment (Theou & Rockwood, 2012). In the clinical setting, a FRAIL Scale score of 2 or more characteristics may be a useful indicator for further frailty assessment, as it is less likely to miss individuals who are FP frail than a cut-point of

3 characteristics. However, this finding should be confirmed in other studies before widespread use.

There were a number of important limitations with our study. As a secondary analysis of an already existing dataset of a general population study, some important ageing specific variables were not collected, therefore, modifications were made to some FRAIL Scale and FP variables. The use of modified measures is likely to affect prevalence, predictive validity and DTA findings, and therefore generalisability of results. In particular, we used self-reported difficulty walking 100m for slowness in the FP, and used measured weight loss over 4.5 years for both the FRAIL Scale and FP instead of self-reported weight loss for each. We have attempted to partly address this limitation by providing information on variable definitions and cut-points in Supplementary TableS1, and distribution of individual variables based on frailty classification in Table 1. We, therefore, urge caution in the interpretation and generalisability of these DTA findings to other populations and settings.

Another limitation of this study was that as the FRAIL Scale and FP were not administered as individual tests, and instead were operationalised during secondary analysis, we were unable to report on feasibility of administration. Further research is required investigating the DTA of the FRAIL Scale, which also examines different cut-points, against the FP, as well as examining predictive mortality over short time periods.

Conclusion

The FRAIL Scale was a significant predictor of morality up to 10 years in this sample of community-dwelling older adults, however, the measure did not meet a number of key DTA acceptability criteria against the reference standard of the FP. Predictive validity is an important indicator of an instrument's usefulness, despite less than acceptable DTA findings. When a FRAIL Scale cut-point of ≥2 characteristics was used, all DTA estimates were acceptable. The FRAIL Scale is a potentially useful tool in the primary care setting.

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Frailty state utility and minimally important difference: Findings from the North West Adelaide Health Study

This chapter is a reproduction of a paper submitted for publication to *Age and Ageing*. The statement of authorship and paper (.pdf) follow over the page.

Additional table(s) and/or figure(s) are provided in the Supplementary material for Chapter 11.

11.1 Summary

Background: Frailty is a dynamic condition for which a range of interventions is available. Health state utilities are based upon the preference that individuals place on health states and outcomes and form a critical component for economic evaluation. This is a topic yet to be examined in detail for frailty. Likewise, little has been reported on minimally important difference (MID), the extent of change in frailty status that individuals consider to be important.

Objectives: The objectives of the study were to examine the relationship between frailty status, for both the frailty phenotype (FP) and frailty index (FI), and utility (preference-based health state), and to determine a minimally important difference (MID) for both frailty measures.

Design and setting: Population-based cohort of community-dwelling Australian older adults.

Participants: 874 individuals aged $\geq$ 65 years (54% female), mean age 74.4 (6.2) years.

Measurements: Frailty was measured using the FP and FI. Utilities were calculated using the six-dimensional (SF-6D) Health Survey, with Australian and UK weighting applied.
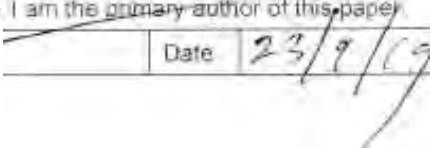
Results: For both the FP and FI, frailty was significantly statistically associated ($p < .001$) with lower utility in an adjusted analysis (age, sex, education, and income) using both Australian and UK weighting. Between person MID for the FP was identified as 0.59 (SD 0.31) (anchor-based) and 0.59 (distribution-based), while for the FI, MID was 0.11 (SD 0.05) (anchor-based) and 0.07 (distribution-based).

Conclusions: Frailty is significantly associated with lower preference-based health state utility. Frailty MID can be used to inform design of clinical trials and their economic evaluation, as well as providing useful clinical information on patient progress.

Statement of Authorship

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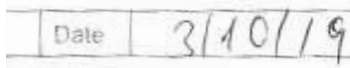
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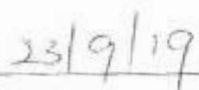
Name of Principal Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Performed analysis on cohort data, interpreted data, wrote manuscript
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 23/9/19

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11.3 Submission to *Age and Ageing*

Frailty state utility and minimally important difference: Findings from the North West Adelaide Health Study

Introduction

Frailty is increasingly recognised as a dynamic and potentially modifiable condition where a range of interventions for treatment, prevention or delay are available (Kojima, Taniguchi, Iliffe, Jivraj, & Walters, 2019; Puts et al., 2017). Frailty may be considered as a state of decreased functional reserve and resistance to stressors as a result of a cumulative decline in multiple physiological systems (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Fried et al., 2001). Frailty is common among older adults and is associated with a range of adverse outcomes including mortality, disability, falls and hospitalisation (Fried et al., 2001; Joosten, Demuynck, Detroyer, & Milisen, 2014; Shamliyan, Talley, Ramakrishnan, & Kane, 2013).

Frailty has a demonstrated inverse association with quality of life (QOL) (Crocker et al., 2019; Kojima, Iliffe, Jivraj, & Walters, 2016). The association reflects a dose-response effect with increasing frailty accounting for substantially lower QOL (Kojima et al., 2016). QOL can be represented in terms of utilities, which represent preferences that individuals or groups place on a set of health outcomes, such as frailty status. Utilities range between 1 (perfect health) and 0 (dead) and are important outcomes that may be used in evaluating the comparative effectiveness of health interventions (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). However, general utility measures can suffer from floor effects which makes identifying changes in health status for those in poorer health status difficult (Turner, Campbell, Peters, Wiles, & Hollinghurst, 2013).

Despite a range of studies describing the association between frailty and QOL at a population level (Crocker et al., 2019; Kojima et al., 2016), to the best of our knowledge there have been no population level estimates using preference-based measures of health-state utility, which can be used in health economic evaluation of frailty interventions (Neumann, Goldie, & Weinstein, 2000). Drawing utility data from a range of sources, particularly cohort surveys, is an important component of economic evaluation, particularly when coupled with health state transition data as it improves the reliability and generalisability of estimates (Drummond et al., 2005; Neumann et al., 2000).

A challenge remains for clinicians and researchers in interpreting statistically significant changes in frailty status when examining frailty interventions, namely, what level of incremental change in utility is sufficient to be considered as clinically meaningful? Minimally Important Difference (MID) is the smallest change in a treatment outcome which an individual would perceive as being important (Wyrwich et al., 2005). MID may be useful in providing a patient perspective that informs clinical decision making regarding the effectiveness of frailty interventions

(Sloan, Cella, & Hays, 2005). As far as we are aware, no studies have yet published frailty MID findings, which is an additional unique feature of our study.

The aims of this study were to examine the relationship between frailty status, for both the frailty phenotype (FP) and frailty index (FI), and utility (preference-based health state) in a community dwelling cohort, and to determine a MID for both frailty measures.

Methods

The North West Adelaide Health Study (NWAHS) is a representative longitudinal study of the population of the North-West region of Adelaide, South Australia (Grant et al., 2006; Grant et al., 2009). This study included participants aged ≥65 years who were interviewed and attended a clinic for a biomedical examination. Individuals unable to answer questions in English at the initial recruitment stage were excluded from the study, as were individuals living in residential institutions, such as nursing homes. Stage 2 (2004-06) data were used in this study.

This study was approved by the Queen Elizabeth Hospital Ethics Committee (HREC/15/TQEH/6)

Frailty phenotype

A modified FP was used in this study where individuals with 3+ characteristics (out of five) variables (weight loss, weakness, slowness, exhaustion, and low activity) were classified as frail, those with 1-2 characteristics as pre-frail, and those with no characteristics present as non-frail (Fried et al., 2001). The modified FP used in this study has been described previously (Thompson, Theou, Yu, et al., 2018). FP variables are detailed in Supplementary Table S1. The FP is scaled on a 0-5 integer scale with 0 indicating no frailty characteristics present and a maximum of five frailty characteristics being present.

Frailty index

We developed a FI consisting of 34 variables following a standard methodology (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). (Supplementary Table S1). Recoding procedures were applied for categorical, ordinal and interval variables such that they could be mapped to the interval 0–1, where 0 = absence of a deficit, and 1= full expression of the deficit. These individual deficit scores were combined in an index, where 0 = no deficit present, and 1 = all 34 deficits present. Individuals with >0.21 proportion of deficits were classified as frail, 0.10 and 0.21 deficits as pre-frail, and <0.10 deficits as non-frail. The FI used has been described previously (Thompson, Theou, Yu, et al., 2018).

Utility (preference-based health state)

Health state utility was captured by using the short-form (SF-36) health survey (Ware et al., 1993). Data from the SF-36 were used to generate utilities for each study participant by applying the SF-6D preference based scoring algorithm (Brazier, Roberts, & Deverill, 2002). We reported SF-6D values using both the original UK weighting (Brazier et al., 2002), and Australian weighting (Model B) as reported by Norman and colleagues (Norman et al., 2013). The utility scores of the UK SF-6D range from 0.29 to 1.00 compared to -0.363 to 1.00 for the Australian weighting. With the Australian weighting, certain states are rated worse than being dead. SF-36 variables used in generating Sf-6D utility scores were excluded from the FI.

Minimally important difference

There is no single measure of MID, rather, multiple approaches may be used to identify a plausible range within which MID falls (King, 2011; Revicki, Hays, Cella, & Sloan, 2008; Sloan et al., 2005), two of which include anchor-based and distribution-based methods. The use of multiple approaches and triangulation of methods is recommended to address the variability of instruments and estimates in varying populations (Sloan et al., 2005).

Anchor-based methods to MID link changes in the outcome variable to another important variable, called an 'anchor' (Revicki et al., 2008; Sloan et al., 2005). Such an anchor should be easily interpretable, used to measure health status, and moderately correlated (at least 0.30) with the variable of interest (King, 2011). Self-reported health is one such anchor which provides valuable information on an individual's global health status and is predictive of mortality (Idler & Benyamini, 1997). We used question 1 from the SF-36: "In general, would you say your health is: excellent, very good, good, fair, poor." as the anchor in this study (which is not part of the SF-6D). We took a weighted average of the difference in both FP (scores of 0 to 5) and FI (scores of 0 to 1) continuous scores between each successive category of SF36-q1. The average was weighted by the number of observations contributing to each mean score. The use of cross-sectional data in this study allows for estimation of between-group and between-person MID, however, longitudinal data is required to report within-person estimates of minimally important change (King, 2011).

Distribution-based methods reflect the concept of using a distribution of observed scores in a sample as the basis for estimating MID (Revicki et al., 2008). The distribution method is considered to be a convenient proxy for MID, however, it has no external reference point to an anchor (King, 2011). A ½ SD estimate has been suggested as an appropriate distribution based measurement of MID, and while not this is not necessarily "minimal", it is a useful conservative estimate for a clinically meaningful difference (i.e., it is obviously important) (Revicki et al., 2008; Sloan et al., 2005). A ½ SD was the distribution method used in this study for both the FP and FI.

Statistical analyses

All statistical analyses were performed using SPSS version 23 (IBM Corporation. Armonk, NY). Cohort case weights (weighted by number in the household, age group, sex and Estimated Resident Population data) were used in analysis, and reporting mean scores and percentages to ensure the sample was representative of the North West Adelaide population (Grant et al., 2006). Descriptive characteristics were reported as percentages. Analysis of variance testing of statistical significance between frailty classification levels and QOL was measured using an alpha value of 0.05, and post hoc mean comparison was performed using Tukey's least significant difference. We also performed a means comparison using complex samples general linear model to adjust for other covariates. Correlation analysis was performed between continuous frailty measures and the self-reported health anchor.

Results

In this longitudinal cohort of community-dwelling Australian older adults (n = 874, mean age 74.4 (SD 6.2) years, 54% female), 18.5% (146/874) of participants were classified as frail by the FP, and 48.8% (400/874) frail by the FI (Table 1).

Health state utility was significantly lower for frail individuals as well as pre-frail individuals in comparison to their non frail counterparts for both the FP and FI, using Australian and UK weighting for the SF-6D, for both unadjusted and adjusted analyses. (Table 2) Tukey analyses demonstrated significant differences between all levels of frailty (non-frail, pre-frail, and frail) for both the FP and FI in unadjusted analysis (data not shown). Likewise, for each level of frailty classification in complex samples general linear regression model adjusting for covariates: age, sex, education, and income (data not shown).

Table 1. Baseline descriptive characteristic and frailty status (frailty phenotype and frailty index).

	n (%)	Frailty Phenotype n (%)			Frailty Index n (%)		
		Non-frail	Pre-Frail	Frail	Non-frail	Pre-Frail	Frail
Total sample	874	281 (30.5)	447 (51.1)	146 (18.5)	204 (21.6)	270 (29.6)	400 (48.8)
Sex							
Male	437 (45.5)	160 (36.6)	219 (49.9)	58 (13.5)*	119 (26.9)	146 (34.0)	172 (39.1)*
Female	437 (54.5)	121 (25.3)	228 (52.0)	88 (22.7)	85 (17.2)	124 (25.9)	228 (56.9)
Age Groups							
65-74 years	531 (56.4)	198 (35.9)	279 (53.0)	54 (11.0)*	141 (26.0)	184 (34.0)	206 (40.0)*
≥75 years	343 (43.6)	83 (23.4)	168 (48.5)	92 (28.1)	63 (16.0)	86 (23.8)	194 (60.2)
Education Level [a]							
Up to secondary	545 (63.1)	157 (27.9)	289 (51.7)	99 (20.5)*	109 (18.7)	176 (31.6)	260 (49.8)*
Trade / Cert / Dip	280 (31.1)	110 (36.2)	130 (49.4)	40 (14.4)	82 (27.0)	79 (25.7)	119 (47.3)
≥Bachelor degree	24 (2.5)	13 (61.5)	10 (34.7)	1 (3.8)	10 (44.0)	10 (40.6)	4 (15.4)
Income Groups [a]							
Up to $20k	442 (46.2)	115 (23.7)	240 (55.2)	87 (21.1)*	79 (16.0)	136 (29.6)	227 (54.4)*
$20-$40k	274 (34.3)	114 (40.9)	125 (44.6)	35 (14.5)	85 (28.9)	90 (32.1)	99 (39.0)
$40-$60k	58 (6.8)	29 (45.5)	23 (42.9)	6 (11.6)	21 (34.5)	16 (27.5)	21 (38.1)
>$60k	25 (2.6)	12 (46.3)	12 (50.2)	1 (3.6)	10 (35.8)	10 (39.7)	5 (24.5)

n unweighted. % reported using cohort case weights. FP (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥ 3, frail. FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.

[a] missing nor included.

* p < 0.05 (main effects reported)

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Table 2. Frailty classification (frailty phenotype and frailty index) and SF-6D utility scores (Australian and UK weighting)

	n (%)	Unadjusted SF-6D Utility Score		Adjusted[a] SF-6D Utility Score	
		Australian Weighting mean (SE)	UK Weighting mean (SE)	Australian Weighting mean (SE)	UK Weighting mean (SE)
Frailty Phenotype					
Non-frail	281 (30.5)	0.72 (0.01)*	0.80 (0.01)*	0.73 (0.02)*	0.81 (0.01)*
Pre-frail	447 (51.1)	0.60 (0.01)	0.75 (0.01)	0.62 (0.02)	0.76 (0.01)
Frail	146 (18.5)	0.32 (0.02)	0.62 (0.01)	0.34 (0.03)	0.63 (0.01)
Frailty Index					
Non-frail	204 (21.6)	0.83 (0.01)*	0.86 (0.00)*	0.83 (0.01)*	0.86 (0.01)*
Pre-frail	270 (29.6)	0.70 (0.01)	0.79 (0.00)	0.70 (0.01)	0.79 (0.01)
Frail	400 (48.8)	0.41 (0.01)	0.66 (0.00)	0.40 (0.02)	0.65 (0.01)

n unweighted. % reported using cohort case weights. FP (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥ 3, frail. FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail. SF-6D, short-form six-dimensional health survey. SE, Standard Error.

[a] Adjusted for age, sex, education, and income.

* p < 0.001 (main effects reported)

The anchor of self-reported health was significantly correlated with both the FP (r = 0.43, p < .001) and FI (r = 0.69, p < .001). Using the anchor-based approach of the weighted average of the difference in both FP and FI continuous scores between each successive category of SF36 question 1 (self-reported health status), 0.59 (SD 0.31) was the MID for the FP, while 0.11 (SD 0.05) was the MID for the FI (Table 3). Using a distribution-based approach of ½ SD of mean frailty scores, 0.59 was a MID for the FP, and 0.07 was the MID for the FI (Table 3).

Table 3. Minimally important difference (MID) for the frailty phenotype and frailty index.

	Minimally Important Difference	
	Anchor Method [a] Mean (SD)	Distribution Method [b] ½ SD
Frailty Phenotype	0.59 (0.31)	0.59
Frailty Index	0.11 (0.05)	0.07

Mean and SD reported using cohort case weights.

The FP is scaled on a 0 to 5 integer scale with a score of 0 indicating no frailty characteristics and a maximum of five characteristics.

The FI is scored on a 0 to 1 scale where 0 = no deficit present, and 1 = all 34 deficits present.

[a] Anchor method: a weighted average of the difference in both FP and FI continuous scores between each successive category of SF36 question 1. "In general, would you say your health is: excellent, very good, good, fair, poor".

[b] Distribution method, ½ standard deviation of mean continuous frailty measures.

Discussion

The novel findings from this study were the identification of frailty and pre-frailty classification as being significantly associated with lower preference-based health state utility for both the FP and FI compared to their non-frail counterparts in this cohort of South Australian older adults. This association applied to both the UK and Australian weightings of the SF-6D in adjusted analysis. Additionally, we have reported the first group-level MID for frailty for both the FP and FI.

Our findings are consistent with a number of studies that have previously examined the relationship between increased frailty and lower QOL (Crocker et al., 2019; Kojima et al., 2016), however, our study is the first to report the QOL finding as a utility value for a population cohort. This is important as utilities are a requirement for cost utility analysis, the most prevalent form of economic evaluation and health economic modelling. Frailty state utilities have been reported in within-trial economic evaluations of frailty interventions (Fairhall et al., 2015; Sandberg, Jakobsson, Midlov, & Kristensson, 2015), and a model-based economic evaluation by Karnon and colleagues (2017) using a sample from a harmonised population cohort of frail individuals matched to the participant characteristics of a frailty intervention study. The adjusted SF-6D utility values (UK weighting) for FP pre-frail and frail individuals in our study (FP pre-frail: 0.75 and FP frail: 0.62) were similar to

those reported by Karnon et al (2017) (FP Pre-frail: 0.65, FP frail: 0.57). These findings of population level frailty state utility data, in combination with the longer time horizons of state transition data, previously reported for the NWAHS cohort (Thompson, Theou, Adams, Tucker, & Visvanathan, 2018), provide important data for model-based economic evaluation of frailty interventions (Drummond et al., 2005; Neumann et al., 2000). However, caution should be used in the generalisability of findings to other populations and settings, and ideally, multiple data sources should be used to inform model-based economic evaluations.

MID estimates for both the FP and FI were identified using cross-sectional anchor-based and distribution-based methods in this cohort. For the FP, 0.59 was an important difference based on both anchor-based and distribution-based methods. As 1 point is the smallest increment of the FP, it can be assumed that a change of this magnitude is minimally important. For the FI, MID ranged from 0.07 (distribution method) to 0.11 (anchor method). The anchor of self-reported health status was moderately correlated with the FP and strongly with the FI in this study, meeting an anchor requirement of being moderately correlated with the outcome of interest (King, 2011). We suggest researchers use the anchor-based estimate as this is based on an external reference, over the distribution-based estimate which may be considered a useful proxy (King, 2011). It is important to note that these MID values are specific to self-reported health and the ½ SD method. Results may be different if different outcomes are used. We caution against overinterpretation of these MID findings as our estimates represent a 'plausible range' of difference for continuous frailty scores (King, 2011). Additionally, our cross-sectional analysis does not allow us to report within-person estimates of minimally important change in frailty, which require change over time (King, 2011).

We believe that this is the first time that MID has been reported for frailty for either the FP or FI. Typically, findings from studies that have examined frailty interventions, have reported change in frailty status or change in the number of frailty characteristics or proportion of deficits present (Liu, Ng, Seah, Munro, & Wee, 2019; Puts et al., 2017). Our MID results allow these findings to be re-interpreted from the perspective of meaningful difference as rated by older adults themselves, although with caution due to the between-person nature of our estimates. When the results of a multifactorial frailty intervention RCT by Cameron and colleagues (2013) are examined from the MID perspective of our study, the non-significant FP change in the intervention group over 0-3 month of 0.56 (SD 1.10) approaches minimal importance, while the significant change of 0.80 (SD 1.19) over 0-12 months meets the criterion of a MID from a population perspective. Our MID findings will be of interest to clinicians evaluating frailty intervention outcomes as MID is important for assessing effectiveness from a consumer perspective. Additionally, researchers might use our MID results when looking to perform power calculations for participant numbers for future frailty intervention studies.

There were a number of limitations with our study. Aging specific variables such as cognition and gait speed were not available for this cohort, therefore, we used a modified FP which may have affected frailty prevalence estimate. The lower socioeconomic status (SES) of the North West region of Adelaide, compared with the broader metropolitan area, suggests our findings may not be representative of the Australian or other population. The exclusion of individuals living in residential care from this study means that our frailty utility and MID findings do not apply to this group. An additional limitation is that we looked at the MID cross sectionally, whereas minimally important change requires longitudinal data for change over time. This is an important topic for future research.

In conclusion, we identified that frailty was significantly associated with lower utility for both the FP and FI. Additionally, we identified MIDs for both measures. These findings are relevant to the design of frailty RCTs, health economic evaluations of frailty interventions, and to clinicians evaluating patient responsiveness to frailty interventions.

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Chapter 12

Discussion, future directions, and conclusions

12.1 Discussion

The goal at the commencement of this thesis was to use population level data to illustrate the impact and course of frailty in community-dwelling older adults. My interest in this topic has its origins in my 20-plus years of clinical and allied health management experience in community-based aged care and rehabilitation as an occupational therapist. Working in this field has offered me opportunities to see individuals both decline physically and cognitively into advanced frailty and end-of-life care, but also to observe them recover from illness and frailty, and to make improvements in physical functioning, participation in daily life, and quality of life. Much of the heterogeneity of health, functioning, and survival across the ageing populations, and my clients, may be attributable to frailty (Rockwood & Howlett, 2018). An important focus of my clinical practice has been on recommending strategies for clients that can prevent, delay, or reverse frailty. Over recent years my clinical work has increasingly dealt with Aboriginal aged care, where social determinants of health play a noticeable part in the wellbeing of this population.

As the Australian and global population ages over coming decades, a clear understanding of frailty will be required in order to maximise the health outcomes of frail older people (World Health Organization, 2015). A challenge facing researchers in the field of frailty, as well as clinicians looking to apply research findings, is that a consensus on the method of frailty measurement is yet to be achieved (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). The research projects reported in this thesis examined two of the key approaches to frailty measurement with a view to the results being informative and useful to health policy makers and practitioners alike. Both population level planning and face-to-face clinical care are important in managing frailty and promoting healthy ageing (Hoogendijk et al., 2019).

The following paragraphs provide a summary of the research projects included in this thesis.

The study in **Chapter 4** described frailty prevalence in Australian older adults. Frailty was measured in DYNOPTA and North West Adelaide Health Study (NWAHS) using the frailty phenotype (FP). We identified 20.5% of participants as frail, while a further 47.9% were pre-frail. Frailty was significantly higher for women (approximately double that of men), increased significantly with advancing age for both sexes, and was significantly higher for women who were widowed, divorced or never married.

The study in **Chapter 5** reported the prevalence of frailty and associated factors in the NWAHS using the FP and frailty index (FI). Frailty prevalence was higher when assessed using the FI; the FP classified 18% of participants as frail, and the FI 48%. The measures were strongly correlated but had only a modest agreement for frailty classification, with 37% of participants classified as non-frail by the FP being classified as frail by the FI. Socioeconomic factors

and other health determinants contribute to higher frailty levels. Being older, a current smoker, and having multimorbidity and polypharmacy were associated with higher frailty levels by both tools. Female, low income, obesity, and living alone were associated with the FI. This difference in sensitivity of frailty measures has clinical implications, where the choice of tool may impact the accurate identification of frailty. The higher frailty prevalence of 20.5% reported in Chapter 4 compared to 18% in this chapter is likely attributable to the higher proportion of females and older age (DYNOPTA and NWAHS: 86% female and median age 80 years) compared with 55% female and mean age 74 years in NWAHS only.

The study in **Chapter 6** measured frailty state transitions and factors associated with improvement or worsening frailty status in the NWAHS. Frailty was measured using the frailty phenotype (FP) and the frailty index (FI) with repeated measures at 4.5 years follow-up. Improvement in frailty state was common for both tools, while the majority of participants remained stable, and many transitioned to a worse level of frailty. A number of characteristics were associated with worsening and improvement of frailty status. Multimorbidity, obesity, age and sex were associated with frailty transitions for both tools. Among the factors that were identified as associated with frailty transitions, age and sex are non-modifiable, but multimorbidity, obesity, polypharmacy and living status may be targeted. These factors pose different risks for frailty transition at different stages of the frailty process, as does frailty classification itself and, hence, suggests a tailored approach in targeting vulnerable individuals.

Chapter 7 was a systematic review with the aim of determining the diagnostic test accuracy of self-reported and/or self-administered frailty screening instruments against two frailty reference standards, the FP and FI, for community-dwelling older adults. There were 24 studies that met selection criteria. Four self-reported screening instruments (PRISMA-7, Groningen Frailty Indicator, Self-Reported Health, and Self-Reported Physical Activity) across three studies met minimum sensitivity and specificity thresholds (80% and 60% respectively). However, in most cases, study design considerations limited the reliability and generalisability of the results. The current evidence for the DTA of many screening instruments does not support their widespread use to identify frailty in community dwelling adults. Predictive validity, which was outside the scope of this review, may be an alternative outcome to inform health policy and decision making regarding instrument selection for different populations. Further well-designed DTA studies of self-reported screening instruments to identify frailty are required.

The study in **Chapter 8** examined the relationship between frailty status (at baseline and follow-up) and mortality in the NWAHS using both the FP and FI. For both measures, baseline frailty was a significant predictor of mortality up to 10 years, with initially good predictive ability decreasing over time. Repeated measurement at follow-up resulted in good prediction compared to lower discrimination of equivalent baseline frailty status. Frailty measurement at follow-up was a stronger predictor of mortality compared to baseline. Frailty change for the Continuous FI was a significant predictor of decreased or increased mortality risk based on corresponding improvement or worsening of score. This study found that recency of frailty measurement is important for predicting survival.

The study in **Chapter 9** examined the predictive ability of frailty and sarcopenia classification on mortality in the NWAHS. Frailty was measured using the FP and FI. Sarcopenia was measured using the revised European consensus definition. Classification as both frail and sarcopenic resulted in significantly elevated mortality risk for both the FP and FI measures. The risk or mortality was, in fact, over four times the risk for those neither frail nor sarcopenic. Frail-only was also a significant mortality predictor at double the rate of non-frail individuals, while sarcopenic-only approached significance for both frailty instruments.

The study in **Chapter 10** examined the predictive validity of the FRAIL Scale and diagnostic test accuracy (DTA) against the reference standards of the FP. The FRAIL Scale demonstrated significant predictive validity for mortality up to 10 years in an adjusted analysis, more than double that of non-frail participants, and was significantly correlated with the FP. The FRAIL Scale demonstrated acceptable DTA findings against the FP for Specificity (86.8%) and Youden index (0.50), but not Sensitivity (63.6%), or area under receiver operator curve (auROC) (0.75) for ≥ 3 characteristic cut-point. All DTA estimates were acceptable when a cut-point of ≥ 2 characteristics was used instead (Sensitivity: 95.6%, Specificity: 64.1%, Youden Index: 0.60, auROC: 0.80).

The study in **Chapter 11** examined the relationship between frailty status, for both the FP and FI, and utility (preference-based health state), and to determine a minimally important difference (MID) for both frailty measures. Utilities were calculated using the six-dimensional health survey (SF-6D) Health Survey, with Australian and UK weighting applied. For both the FP and FI, frailty was significantly associated with lower utility. Between-person MID for the FP was identified as 0.59 (anchor-based) and 0.59 (distribution-based), while for the FI, MID was 0.11 (anchor-based) and 0.07 (distribution-based).

12.2 Significance and contribution

This PhD research has generated new knowledge and contributed significantly to the scientific literature in the area of frailty.

A major contribution to the public health of Australian older adults to emerge from this PhD research is the reporting of Australian frailty prevalence data across multiple longitudinal studies, and a comparison of both forms of frailty measurement in the Australian context (Chapters 4 and 5). These findings, when published in the *Australasian Journal on Ageing*, were accompanied by an editorial by Vasi Naganathan (2018), highlighting the importance of these findings in the Australian setting.

Prevalence estimates (Chapter 4) were used as the basis for a publication by Taylor and colleagues (2019) which examined geospatial modelling of the prevalence and changing distribution of frailty in Australia, and was published in the *Journal of Experimental Gerontology*. This publication addressed the call from a Commonwealth funded report by Burgess and Hercus (2017) for geospatial data about the current and future distribution of Australia's frail and pre-frail population

in order to inform policy, resource allocation and planning initiatives that aim to treat and reverse frailty. The resulting interactive online frailty mapping resource, using data from Chapter 4, covers all of Australia is accessible at: http://www.spatialonline.com.au/frailtyestimates. (See Figure 12.1.)

Chapter 4 has four citations to date (Kojima, Walters, Iliffe, Taniguchi, & Tamiya, 2019; Naganathan, 2018; Taylor et al., 2019; Zucchelli et al., 2019). Data from Chapter 4 have been included in a systematic review by Kojima and colleagues (2019) examining marital status and frailty.
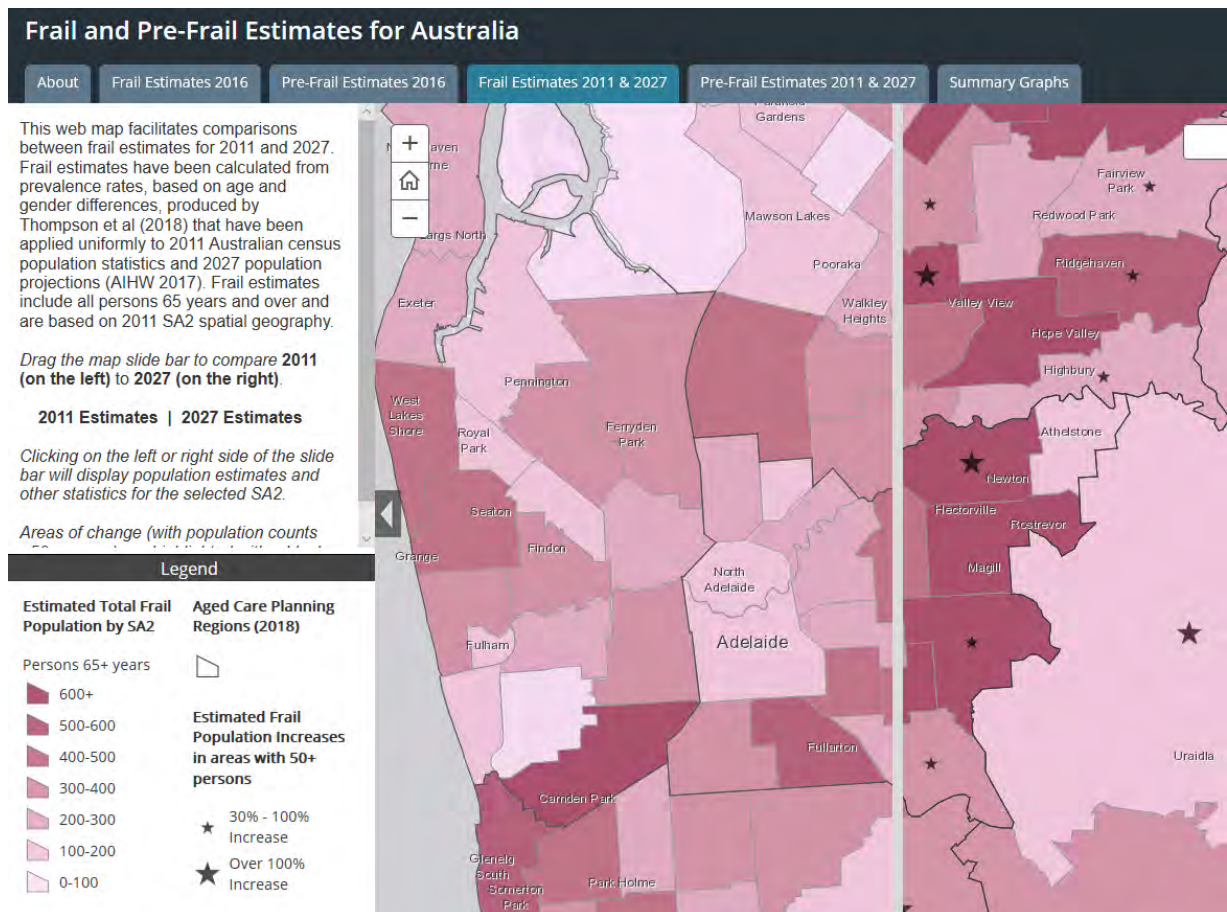
Figure 12.1. **Screen capture of frail estimates 2011 and 2027 for Adelaide from interactive online frailty mapping resource by Taylor et al (2019).**

Chapter 5 has had six citations (excluding self-citation) (Amiri & Behnezhad, 2019; Arakawa Martins et al., 2019; Ge, Liu, Tang, Lu, & Szanton, 2019; Ge, Liu, Liu, et al., 2019; Hale, Shah, & Clegg, 2019; Naganathan, 2018). Data from this chapter were included in a systematic review by Amiri and associates (2019) examining the relationship between smoking and frailty.

Chapter 6 has been cited six times by other authors (Brothers & Rockwood, 2019; Buto et al., 2019; Haji Ali Afzali et al., 2019; Kojima, Taniguchi, Iliffe, Urano, & Walters, 2019; Ofori-Asenso et al., 2019; Visvanathan et al., 2018). Data from this chapter were included in the systematic

reviews of Ofori-Aseno and colleagues (2019) on frailty incidence in community-dwelling older adults, and the review of Kojima et al. (2019) which examined factors associated with improvement in frailty status.

A number of chapters in this thesis have direct relevance for the identification and management of frailty in the primary care setting. In Chapter 6, we highlighted the fact that frailty is dynamic and that improvement and remaining stable are possible. This was further emphasised in the mortality findings in Chapter 8, which indicate that a regular review of frailty status is important to account for the changeability of frailty. The importance of investigating the presence of sarcopenia in combination with frailty is another factor which will contribute to clinical practice in terms of informing prognosis and management of individuals with both conditions (Chapter 9).

The reporting of diagnostic test accuracy (DTA) estimates (Chapter 7) for various screening instruments for frailty will be of value to clinicians and policy makers in identifying suitable instruments for consideration in primary care and for population level screening. Likewise, the DTA and predictive validity findings for the FRAIL Scale (Chapter 10) provide useful information on the performance of these instruments in an Australian context.

The findings on frailty state utility and minimally important difference (MID) have important clinical, health economic, and research implications. Chapter 11 reports the first known population-level data on frailty state utility, which is an important component of health economic evaluation. (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005; Neumann, Goldie, & Weinstein, 2000). Likewise, in Chapter 11 the reporting of MID findings for both frailty instruments provides a valuable patient perspective that informs clinical decision making regarding the effectiveness of frailty interventions, as well as being novel information to inform the design of clinical trials.

The message about frailty, its modifiability, and strategies for assessment and intervention, has been communicated to general practitioners (GPs) across Australia in an article published in *Australian Doctor* in the *Therapy Update* section. The *Therapy Update* is an important section of this magazine in terms of providing GPs with the latest information on the identification and management of different health conditions, and in this case frailty. Aspects of Chapter 2 were the basis of this publication.

Another contribution arising from this PhD has been to incorporate the findings about the dynamic and modifiable nature of frailty into a video: 'Frailty: Every step you take matters!' (Archibald et al., 2019). (See Figure 12.2.) This video was designed with a knowledge translation and consumer health literacy aim of providing the latest research on frailty and its management to consumers. The video is accessible to the public online and has had nearly 2,400 views to date. This video can be accessed at: https://www.youtube.com/watch?v=41cMkvsaOOM.

Figure 12.2.   Screen captures from the video: 'Frailty: Every step you take matters!'
(Archibald et al., 2019).

12.3 Future directions

As a result of the research presented in this thesis, a number of research priorities have been identified:

- Further examination of frailty prevalence and associated factors in Australian longitudinal population studies is required. Regularly re-examining population level prevalence is necessary to address differences in cohort groups with correspondingly different social composition and health status (Bell & Jones, 2015). Updated prevalence data has practical implications for policy development, health and social service planning, and predictive mapping. Population ageing studies are particularly important, where additional effort is focused on recruiting the oldest old and individuals with

physical limitations to provide a representative sample (Bonk, 2010; Stanziano, Whitehurst, Graham, & Roos, 2010).

- In addition to prevalence, routinely reviewing the trajectory of frailty in Australian cohorts is also important to provide a picture of the natural course of this condition. which provides policy planners and clinicians with a better understand of prognosis, and is necessary for health economic modelling of frailty interventions.

- Further research is required to refine the process of frailty screening, assessment and intervention, in particular:

  – Continued investigation of the properties of both the frailty phenotype (FP) and frailty index (FI), their shared characteristics, and the implications of using either in clinical practice or in planning for population ageing.

  – Does screening for frailty in the community and General Practice actually result in better outcomes?

  – What interventions are effective in treating and preventing frailty in primary care? If these interventions are effective, how can they be implemented in the real world and scaled up?

  – Further investigation is required into the DTA properties of frailty screening instruments, in particular the FRAIL Scale, and examination of DTA estimates using various cut-points of this instrument. Effective screening for frailty potentially leads to comprehensive assessment and the offering of timely intervention.

- As health-state utility and MID for frailty classification have been reported for the first time in this thesis, further research is required to compare these estimates with those of other population cohorts.

My career direction following the completion of the PhD candidature is that of a clinician researcher. In addition to continuing my current work as an occupational therapist, I have been successful in being appointed to a Research Fellow position with the NHMRC Centre for Research Excellence in Frailty and Health Ageing in 2020.

From a clinical perspective, the detailed understanding of frailty that I have developed over my PhD candidature has had a direct influence on the quality of clinical care that I deliver to my clients (who are primarily Aboriginal older adults in metropolitan Adelaide, as well as a rural outreach service in Port Lincoln). Identifying, discussing, and planning interventions for modifiable factors contributing to frailty are elements of a key strategy in delivering my clinical service. This role as a clinician researcher resulted in my invitation to participate in the planning and delivery of a System Wide Health and Wellbeing Strategy Workshop for South Australia Health. The Health and Wellbeing Strategy 2019-2024 is a State-wide, system-level strategy developed to meet future health challenges, specifically focused on South Australia's health priorities for the next five years (SA Health, 2019). In particular, my participation involved the interview of a health consumer to explore barriers and facilitators to personalised high quality care in the health system. This video can be accessed at: https://www.youtube.com/watch?v=7MNxpQ3dq2c

I have also delivered workshops and training on the identification and management of frailty and promotion of healthy ageing to service coordinators, managers, and direct care staff of Aboriginal Community Services.

One of the immediate research priorities when I commence as a research fellow in 2020 will be to analyse data from the Frailty In Residential Sector Over Time (FIRST) Study. FIRST is a three year prospective cohort study involving 12 residential aged care facilities of Resthaven Inc. across South Australia and including approximately 756 residents (Jadczak, 2019). Specifically, analysis will be of minimally important difference in the frailty status of residents. These findings will be important in order to understand the perceived effectiveness of interventions that aim to improve function and quality of life from the perspective of individuals living in residential care.

Other future studies that combine both my research and clinical interests will be to examine frailty specifically in Aboriginal populations, and the effectiveness of strategies to address it. There has been only limited examination of frailty in this vulnerable population, and the need for further research has been described as urgent (Hyde et al., 2016). My well-established clinical connection with Aboriginal health and aged care services will help to facilitate this work.

12.4 Conclusion

The research for this thesis has demonstrated that frailty is common in community-dwelling older adults, however, a downward trajectory of decreased function and worsening health is not always inevitable. As frailty is a dynamic condition, a regular review of frailty status and offering targeted interventions as appropriate, are likely to result in improved quality of life. A range of simple screening tools for frailty is available for use in primary care as a first step in a process that may lead to comprehensive management.

The findings in this thesis have important clinical implications for both the identification and management of frail individuals, and for promoting healthy ageing by offering preventative strategies. A key message from this thesis for health practitioners and older adults is that, despite frailty being common, it can be either prevented, reversed, or delayed.

This thesis has generated new evidence and strengthened the evidence base relating to the frailty burden in Australia. As a result, there is increased awareness of frailty's dynamic nature, which has the potential to drive interest among policy makers and clinicians alike in intervening to improve the health outcomes of older adults.

12.5 References for Chapter 12

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Supplementary material

Supplementary Material Chapter 5

Chapter 5. Figure S1. Relationship between proportion classified as frail and age, stratified according to sex, using the frailty phenotype and frailty index.

Male
Female

Chapter 5. Table S1. Coding, frequency & histograms of included frailty variables for both the Frailty Phenotype and Frailty Index.

Frailty Phenotype

Variable	Coding	Frequency n (sample %, weighted sample %)	Histogram Characteristic present against age
10% Weight loss between phase 1 and 2	0: <10% weight loss 1: >10% weight loss	0 = 876 (92.7, 92.7) 1 = 69 (7.3, 7.3) Missing = 0	
Exhaustion 'everything was an effort' and 'could not get going'	Original Fried criteria used.	0 = 772 (81.7, 80.7) 1 = 131 (13.9, 14.3) Missing = 42 (4.4, 5.0)	

Weak Grip strength – mean of dominant hand	Original Fried criteria used (stratified by sex & BMI quartiles)	0 = 575 (60.8, 57.9) 1 = 360 (38.1, 40.9) Missing = 10 (1.1, 1.3)	
Walking 100m SF-36 – 11 Substitute for slow walk speed	0: not limited at all, limited a little 1: limited a lot	0 = 853 (90.3, 90.1) 1 = 73 (7.7, 7.7) Missing = 19 (2.0, 2.1)	
Low physical activity level Montgomerie et al [29] method: <100 METs (inactive) Walk = 3.5 METs Mod = 5.0 METs Vig = 7.5 METs	0: >100 METs per week (equates to 150 mins mod exercise) 1: <100 METs per week	0 = 529 (56.0, 54.4) 1 = 404 (42.8, 44.0) Missing = 12 (1.3, 1.6)	
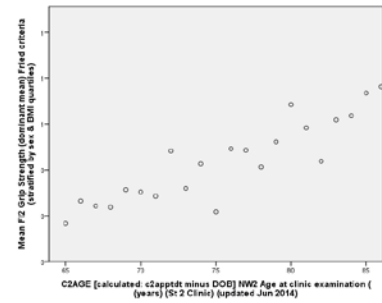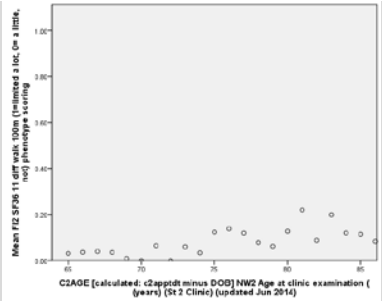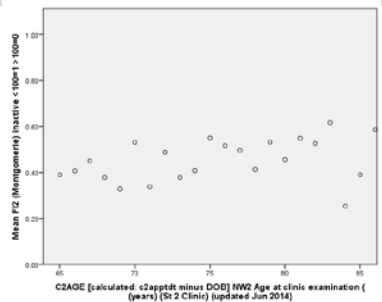
Frailty Index

Variable	Coding	Frequency n (sample %, weighted sample %)	Histogram Deficit present against age
10% Weight loss between phase 1 and 2	0: <10% weight loss 1: >10% weight loss	0 = 876 (92.7, 92.7) 1 = 69 (7.3, 7.3) Missing = 0	
Weak Grip strength – mean of dominant hand	Uses Fried criteria (stratified by sex & BMI quartiles)	0 = 575 (60.8, 57.9) 1 = 360 (38.1, 40.9) Missing = 10 (1.1, 1.3)	
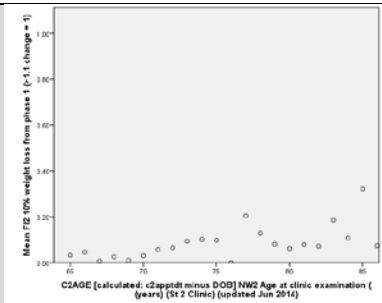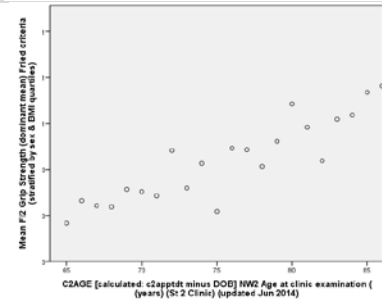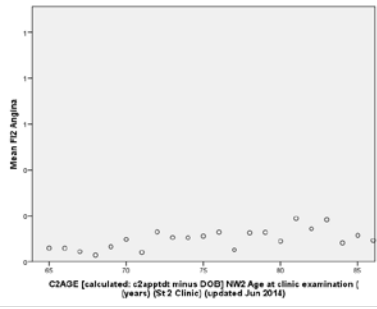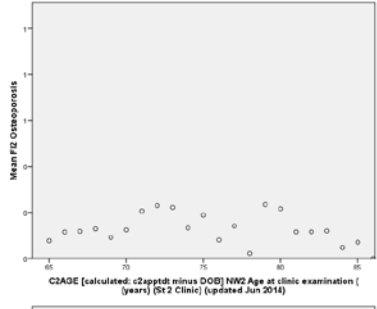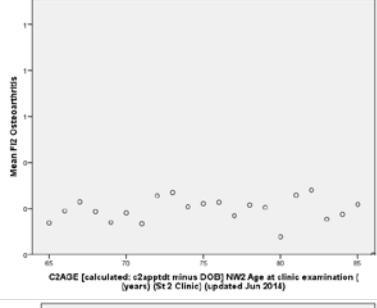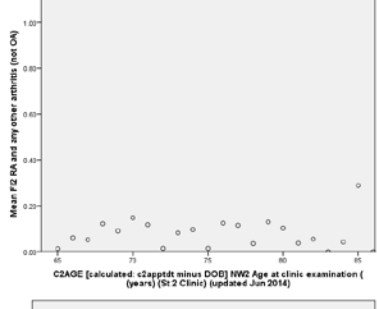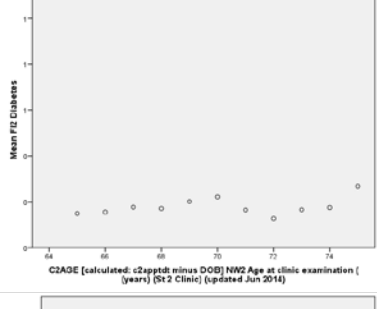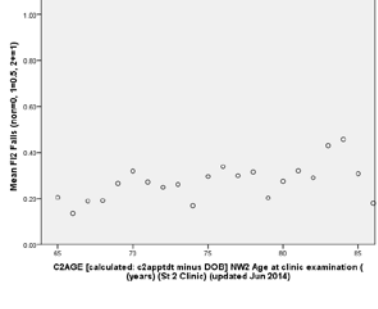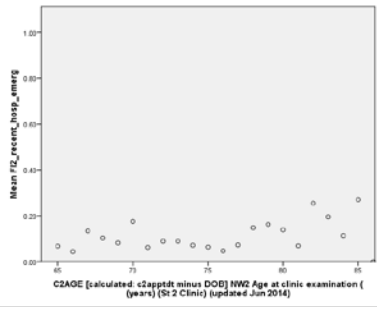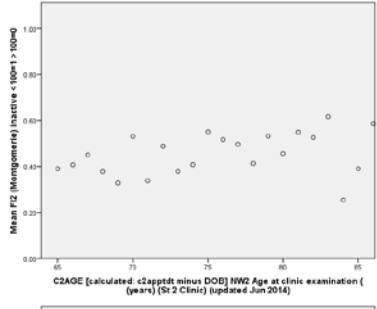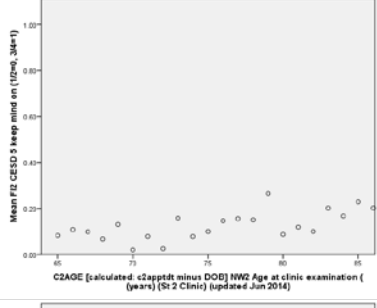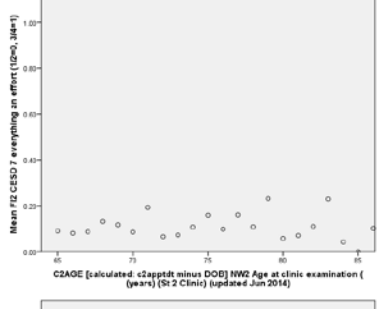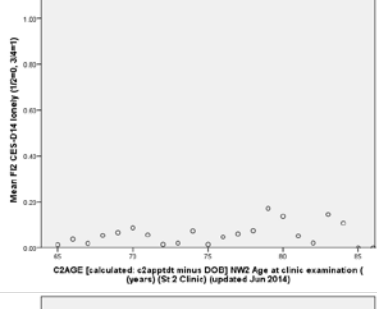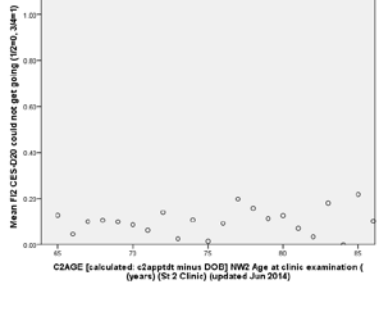
Spirometry post FEV1/FVC ratio	0: >70% 1: ≤70%	0 = 764 (80.8, 82.0) 1 = 153 (16.2, 14.8) Missing = 28 (3.0, 3.1)	
Systolic blood pressure mean	0: <160 mmHg 1: ≥160	0 = 828 (87.6, 86.9) 1 = 114 (12.1, 12.7) Missing = 3 (0.3, 0.4)	
Diastolic blood pressure mean	0: <90 mmHg 1: ≥90	0 = 831 (87.9, 87.7) 1 = 111 (11.7, 11.9) Missing = 3 (0.3, 0.4)	
Stroke and/or TIA	0: no 1: yes	0 = 831 (87.9, 86.7) 1 = 79 (8.4, 8.9) Missing = 35 (3.7, 4.4)	
Any Mental health problem (anxiety, depression, stress, other mental health)	0: no 1: yes	0 = 798 (84.4, 83.9) 1 = 112 (11.9, 11.8) Missing = 35 (3.7, 4.4)	
Heart Attack	0: no 1: yes	0 = 816 (86.3, 86.3) 1 = 94 (9.9, 9.4) Missing = 35 (3.7, 4.4)	

Angina	0: no 1: yes	0 = 822 (87.0, 86.5) 1 = 88 (9.3, 9.2) Missing = 35 (3.7, 4.4)	
Osteoporosis	0: no 1: yes	0 = 795 (84.1, 82.7) 1 = 115 (12.2, 13.0) Missing = 35 (3.7, 4.4)	
OA	0: no 1: yes	0 = 744 (78.7, 77.5) 1 = 166 (17.6, 18.2) Missing = 35 (3.7, 4.4)	
RA & any other arthritis	0: no 1: yes	0 = 847 (89.6, 88.5) 1 = 63 (6.7, 7.2) Missing = 35 (3.7, 4.4)	
Diabetes	0: no 1: yes	0 = 785 (83.1, 82.3) 1 = 157 (16.6, 17.4) Missing = 3 (0.3, 0.3)	
Falls	0: none 0.5: 1 fall 1: 2+ falls	0 = 598 (63.3, 61.1) 0.5 = 173 (18.3, 18.4) 1 = 134 (14.2, 15.8) Missing = 40 (4.2, 4.8)	

Recent hospital admission	0: none 1: 1+ hospital admission	0 = 809 (85.6, 84.8) 1 = 97 (10.3, 10.3) Missing = 35 (4.1, 4.8)	
Low physical activity level Montgomerie et al [29] method: <100 METs / week (inactive) Walk = 3.5 METs Mod = 5.0 METs Vig = 7.5 METs	0: >100 METs per week (equates to 150 mins mod exercise) 1: <100 METs per week	0 = 529 (56.0, 54.4) 1 = 404 (42.8, 44.0) Missing = 12 (1.3, 1.6)	
Keep mind on what you were doing CES-D 5	0: rarely & some/little, 1: occasional & most	0 = 797 (84.3, 83.3) 1 = 102 (10.8, 11.3) Missing = 46 (4.9, 5.4)	
Everything was an effort CES-D 7	0: rarely & some or a little 1: occasional or moderate & most or all (scoring matches phenotype)	0 = 801 (84.8, 84.2) 1 = 99 (10.5, 10.6) Missing = 45 (4.8, 5.2)	
Felt lonely CES-D 14	0: rarely & some/little, 1: occasional & most.	0 = 849 (89.8, 89.6) 1 = 54 (5.7, 5.5) Missing = 42 (4.4, 5.0)	
Could not get going CES-D 20	0: rarely & some or a little 1: occasional or moderate & most or all (phenotype coding)	0 = 821 (86.9, 85.7) 1 = 80 (8.5, 9.0) Missing = 44 (4.7, 5.3)	

Your health is SF-36 – 1	0: excellent, very good, good 1: fair, poor	0 = 692 (73.2, 72.0) 1 = 249 (26.3, 27.6) Missing = 4 (0.4, 0.4)	
Lifting or carrying groceries SF-36 - 5	0: not limited at all 0.5: limited a little 1: limited a lot	0 = 451 (47.7, 44.4) 0.5 = 365 (38.6, 40.4) 1 = 125 (13.2, 14.7) Missing = 4 (0.4, 0.5)	
Climbing several flights of stairs SF-36 - 6	0: not limited at all 0.5: limited a little 1: limited a lot	0 = 203 (21.5, 19.3) 0.5 = 416 (44.0, 42.8) 1 = 311 (32.9, 36.4) Missing = 15 (1.6, 1.5)	
Climbing one flight of stairs SF-36 7	0: not limited at all 0.5: limited a little 1: limited a lot	0 = 435 (46.0, 43.0) 0.5 = 341 (36.1, 37.5) 1 = 155 (16.4, 17.9) Missing = 14 (1.5, 1.5)	
Bending, kneeling or stooping SF-36 - 8	0: not limited at all 0.5: limited a little 1: limited a lot	0 = 236 (25.0, 23.0) 0.5 = 474 (50.2, 51.0) 1 = 231 (24.4, 25.6) Missing = 4 (0.4, 0.4)	
Walking more than 1km SF-36 - 9	0: not limited at all 0.5: limited a little 1: limited a lot	0 = 389 (41.2, 38.6) 0.5 = 299 (31.6, 31.1) 1 = 244 (25.8, 29.0) Missing = 13 (1.4, 1.3)	
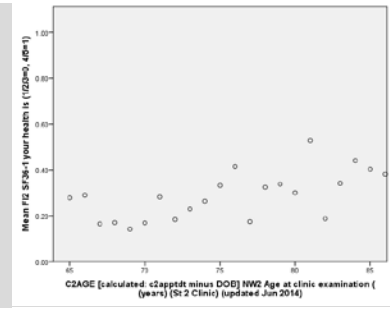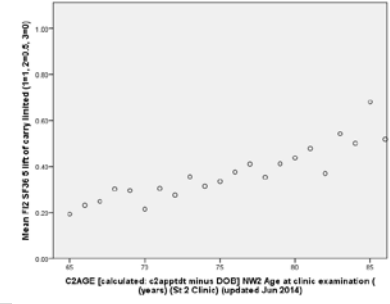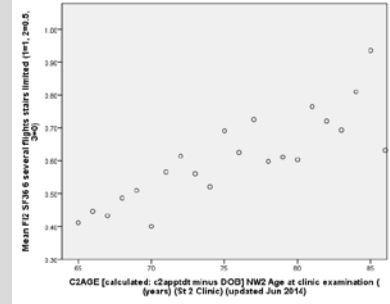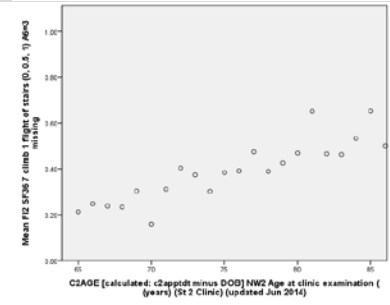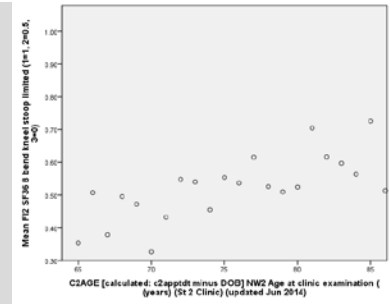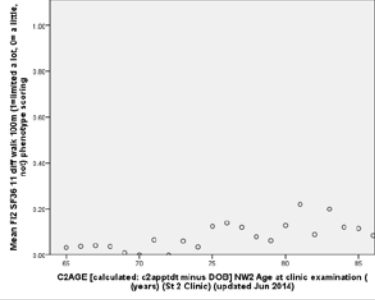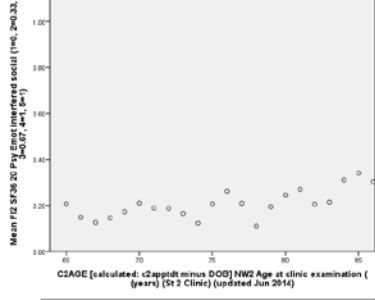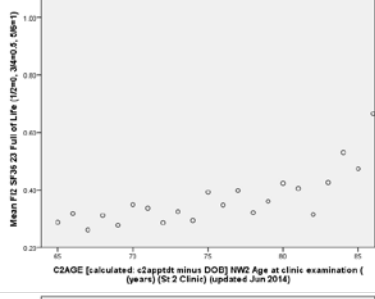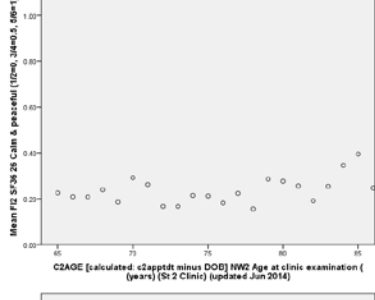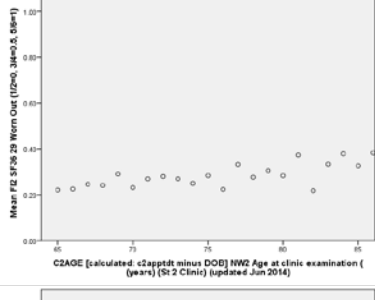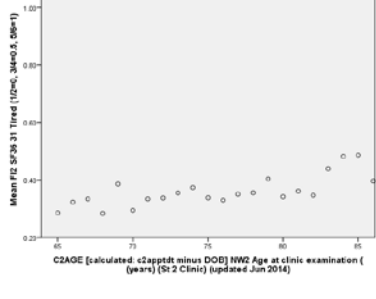
Walking 100m SF-36 – 11	0: not limited at all, limited a little 1: limited a lot (Phenotype – walk speed)	0 = 853 (90.3, 90.1) 1 = 73 (7.7, 7.7) Missing = 19 (2.0, 2.1)	
Extent physical & emotional probs interfered – social activities SF-36 – 20	0: not at all 0.33: slightly 0.67: moderately 1:quite a bit & extremely	0 = 633 (67.0, 65.6) 0.33 = 157 (16.6, 17.3) 0.67 = 84 (8.9, 9.7) 1 = 67 (7.1, 7.1) Missing = 4 (0.4, 0.3)	
full of life SF-36 – 23	0: all the time & most time 0.5: good bit & some 1: a little & none of the time	0 = 434 (45.9, 44.2) 0.5 = 370 (39.2, 40.8) 1 = 134 (14.2, 14.2) Missing = 7 (0.7, 0.7)	
calm & peaceful SF-36 – 26	0: all the time & most time 0.5: good bit & some 1: a little & none of the time	1 = 610 (64.6, 63.0) 0.5 = 259 (27.4, 28.1) 1 = 73 (7.7, 8.5) Missing = 3 (0.3, 0.4)	
worn out SF-36 – 29	0: a little & none of the time 0.5: some & good bit 1: all the time & most time	0 = 521 (55.1, 52.7) 0.5 = 348 (36.8, 39.1) 1 = 73 (7.7, 7.9) Missing = 3 (0.3, 0.4)	
tired SF-36 – 31	0: a little & none of the time 0.5: some & good bit 1: all the time & most time	0 = 394 (41.7, 39.7) 0.5 = 452 (47.8, 49.0) 1 = 96 (10.2, 10.9) Missing = 3 (0.3, 0.4)	

I'm as healthy as anybody I know SF-36 - 34	0: def true 0.25: mostly true 0.5: don't know 0.75: mostly false 1: def false	0 = 226 (23.9, 23.1) 0.25 = 389 (41.2, 41.7) 0.5 = 188 (19.9, 20.1) 0.75 = 83 (8.8, 8.9) 1 = 51 (5.5, 5.5) Missing = 7 (0.7, 0.8)	
My health is excellent SF-36 - 36	0: def true, mostly true, 0.5: don't know 1: mostly false, def false	0 = 546 (57.8, 55.7) 0.5 = 134 (14.2, 15.0) 1 = 230 (24.3, 25.1) Missing = 35 (3.7, 4.2)	
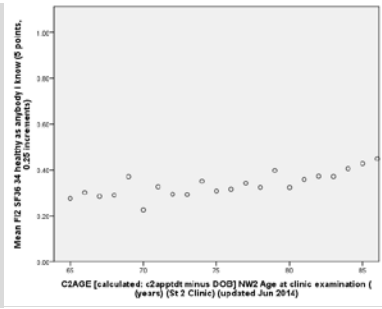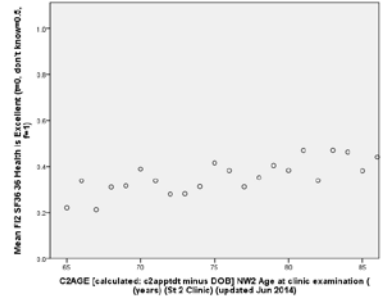
Supplementary Material Chapter 6

Chapter 6. Table S1. Frailty category and death status at 4.5 years mean follow up according to baseline frailty category. Percentage by baseline frailty status.

Baseline Frailty Status	Follow-up Frailty Status, n(%)				
	Non-frail	Pre-frail	Frail	Dead	Total
Phenotype					
Whole Sample					
Non-frail	120 (47.7)	78 (33.9)	13 (6.9)	22 (11.5)	233
Pre-frail	82 (23.1)	167 (44.7)	47 (15.4)	61 (16.8)	357
Frail	2 (1.8)	19 (19.8)	40 (36.9)	45 (41.4)	106
Total	204 (27.5)	264 (37.2)	100 (16.2)	128 (19.1)	696
Male					
Non-frail	64 (48.2)	43 (36.0)	4 (3.5)	16 (12.3)	127
Pre-frail	40 (23.6)	74 (39.1)	19 (11.2)	46 (26.1)	179
Frail	0 (0.0)	9 (20.5)	16 (34.1)	22 (45.5)	47
Total	104 (29.2)	126 (35.4)	39 (11.6)	84 (23.8)	353
Female					
Non-frail	56 (46.6)	35 (33.0)	9 (10.7)	6 (9.7)	106
Pre-frail	42 (22.5)	93 (49.7)	28 (18.8)	15 (8.9)	178
Frail	2 (3.0)	10 (19.4)	24 (38.8)	23 (38.8)	59
Total	100 (25.8)	138 (39.3)	61 (20.2)	44 (14.7)	343
Frailty Index					
Whole Sample					
Non-frail	94 (54.4)	50 (26.6)	20 (11.4)	11 (7.6)	175
Pre-frail	33 (13.6)	87 (38.0)	74 (37.1)	25 (11.3)	219
Frail	3 (1.0)	22 (7.4)	185 (61.5)	92 (30.1)	302
Total	130 (17.3)	159 (21.4)	279 (42.3)	128 (19.0)	696
Male					
Non-frail	60 (63.2)	19 (18.4)	11 (10.3)	8 (8.0)	98
Pre-frail	17 (12.3)	42 (34.9)	36 (34.9)	20 (17.9)	115
Frail	2 (0.8)	10 (8.0)	72 (51.2)	56 (40.0)	140
Total	79 (21.7)	71 (19.8)	119 (34.6)	84 (23.9)	353
Female					
Non-frail	34 (42.3)	31 (36.6)	9 (14.1)	3 (7.0)	77
Pre-frail	16 (15.0)	45 (41.1)	38 (39.3)	5 (4.7)	104
Frail	1 (0.5)	12 (7.0)	113 (68.8)	36 (23.8)	162
Total	51 (12.9)	88 (22.9)	160 (49.3)	44 (14.9)	343

Note: Frailty Phenotype cut points (number of deficits): 0 = Not Frail, 1-2 = pre-frail, 3+ = Frail; Frailty Index cut points (proportion of deficits): 0 to ≤.10 = not frail, >.10 to ≤.21 = vulnerable, and >.21 = frail.

Chapter 6. Table S2. Frailty category and death status at 4.5 years mean follow up according to baseline frailty category. Percentage of whole sample.

Baseline Frailty Status	Follow-up Frailty Status n (%)				
	Non-frail	Pre-frail	Frail	Dead	Total
Frailty Phenotype					
Non-frail	120 (15.3)	78 (10.9)	13 (2.2)	22 (3.7)	233 (32.1)
Pre-frail	82 (11.9)	167 (23.1)	47 (7.9)	61 (8.7)	357 (51.6)
Frail	2 (0.3)	19 (3.2)	40 (6.0)	45 (6.8)	106 (16.3)
Total	204 (27.5)	264 (37.2)	100 (16.2)	128 (19.1)	696 (100)
Frailty Index					
Non-frail	94 (12.6)	50 (6.1)	20 (2.6)	11 (1.8)	175 (23.1)
Pre-frail	33 (4.2)	87 (11.9)	74 (11.6)	25 (3.5)	219 (31.2)
Frail	3 (0.4)	22 (3.4)	185 (28.1)	92 (13.8)	302 (45.7)
Total	130 (17.3)	159 (21.4)	279 (42.3)	128 (19.0)	696 (100)

Note: Frailty Phenotype cut points (number of deficits): 0 = Not Frail, 1-2 = pre-frail, 3+ = Frail; Frailty Index cut points (proportion of deficits): 0 to ≤.10 = not frail, >.10 to ≤.21 = vulnerable, and >.21 = frail.

Chapter 6. Table S3. Frailty state transitions: Better, same, and worse (worse includes dead) at 4.5 years mean follow up according to baseline frailty category.

	Frailty Phenotype n (%)	Frailty Index n (%)
Whole Sample		
Better	103 (15.5)	58 (7.9)
Same	327 (44.4)	366 (52.6)
Worse or Dead	266 (40.1)	272 (39.5)

Worse = a more severe frailty state, including death, compared with baseline state; Improved = a less severe frailty state compared with baseline state

Chapter 6. Table S4. Univariate logistic regression for variables associated with frailty phenotype transitions in frailty states over 4.5 years, adjusted for time between clinic appointments. Reference category is 'same'.

	Odds Ratio (95% Confidence Interval) P-Value				
Baseline Frailty Status	Non-Frail	Pre-Frail	Pre-Frail	Frail	Frail
Follow up Status	Worse	Improved	Worse	Improved	Worse
Sex					
Male	1	1	1	1	1
Female	1.09 (.63, 1.89)	.83 (.47, 1.44)	.77 (.46, 1.29)	.88 (.29, 2.63)	.47 (.17, 1.34)
Age Group					
65-74 years	1	1	1	1	1
>75 years	.55 (.30, 1.02)	.32 (.19, .55)*	2.11 (1.09, 4.10)*	.13 (.04, .46)*	1.51 (.51, 4.48)
Education Level					
1 Up to secondary	2.41 (.56, 10.27)	.95 (.09, 9.91)	.35 (.06, 2.18)	1.49 (.45, 4.92)	-
2 Trade / Cert / Dip	1.77 (.41, 7.66)	1.02 (.09, 11.00)	.44 (.07, 2.86)	-	-
3 Bachelor degree+	1	1	1	1	1
Income Groups					
1 Up to $20k	2.44 (.62, 9.57)	.64 (.13, 3.12)	6.26 (.23, 170.12)	1.10 (.35, 3.46)	-
2 $20-$40k	1.58 (.41, 6.03)	.89 (.18, 4.40)	5.76 (.21, 158.60)	-	-
3 $40-$60k	1.65 (.35, 7.84)	1.76 (.29, 10.81)	7.09 (.22, 226.34)	-	-
4 More than $60k	1	1	1	1	1
Smoking Status†					
3 Never smoked	1	1	1	1	1
2 Former smoker	1.34 (.76, 2.35)	.63 (.35, 1.13)	.78 (.46, 1.33)	.55 (.18, 1.70)	.94 (.33, 2.66)
1 Current smoker	1.02 (.24, 4.22)	1.53 (.433, 5.40)	1.13 (.33, 3.88)	.94 (.14, 6.24)	.22 (.01, 3.69)
Alcohol Consumption†‡					
Not at risk	1	1	1	1	1
Excess	1.10 (.43, 2.82)	1.02 (.44, 2.36)	.70 (.31, 1.60)	2.70 (.43, 17.08)	1.22 (.17, 9.04)
Waist Circumference †§					
Normal	1	1	1	1	1
Obese	1.45 (.83, 2.53)	.45 (.26, .79)*	.53 (.31, .89)*	1.87 (.56, 6.22)	.98 (.34, 2.82)
Multimorbidity					
0-1 conditions	1	1	1	1	1
2+ conditions	3.94 (1.75, 8.89)*	.67 (.36, 1.25)	1.23 (.72, 2.10)	.52 (.18, 1.51)	.47 (.17, 1.32)
Polypharmacy					
0-4 medication	1	1	1	1	1
5+ medications	1.21 (.68, 2.14)	.44 (.24, .78)*	.91 (.55, 1.53)	.39 (.13, 1.18)	.37 (.13, 1.11)
Living Arrangements†					
Lives with others	1	1	1	1	1
Lives alone	1.13 (.60, 2.14)	.59 (.31, 1.14)	1.34 (.76, 2.38)	.50 (.14, 1.86)	2.89 (.96, 8.72)

OR = Odds Ratio; 95%CI = 95% Confidence Interval; – = unable to estimate; Improved = a less severe frailty state compared with baseline state; Worse = a more severe frailty state, including death, compared with baseline state; Obesity = Waist Circumference: male >102cm, female >88cm; Excess alcohol consumption = >14 drinks per week and/or >4 drinks per session.

* P < .05

Chapter 6. Table S5. Univariate logistic regression for variables associated with frailty index transitions in frailty states over 4.5 years, adjusted for time between clinic appointments. Reference category is 'same'

	Odds Ratio (95% Confidence Interval) P-Value				
Baseline Frailty Status	Non-Frail	Pre-Frail	Pre-Frail	Frail	Frail
Follow up Status	Worse	Improved	Worse	Improved	Worse
Whole Sample					
Sex					
Male	1	1	1	1	1
Female	1.52 (.78, 2.97)	1.86 (.72, 4.83)	1.13 (.57, 2.22)	.72 (.29, 1.79)	.46 (.25, .84)*
Age Group					
65-74 years	1	1	1	1	1
>75 years	.61 (.29, 1.29)	.27 (.13, .59)*	4.14 (.84, 20.40)	.14 (.07, .28)*	7.19 (1.52, 34.05)*
Education Level					
Up to secondary	.88 (.18, 4.36)	-	.80 (.12, 5.45)	-	.21 (.02, 1.90)
Trade / Cert / Dip	.43 (.08, 2.17)	-	.70 (.10, 4.91)	-	.29 (.03, 2.74)
Bachelor degree+	1	1	1	1	1
Income Groups					
Up to $20k	2.42 (.38, 15.39)	.88 (.16, 4.95)	3.03 (.68, 13.51)	-	.25 (.01, 5.95)
$20-$40k	1.57 (.25, 9.71)	1.19 (.22, 6.39)	2.51 (.56, 11.29)	-	.14 (.01, 3.51)
$40-$60k	1.37 (.18, 10.31)	.46 (.02, 10.00)	2.45 (.34, 17.85)	-	.18 (.01, 5.77)
More than $60k	1	1	1	1	1
Smoking Status†					
Never smoked	1	1	1	1	1
Former smoker	1.70 (.40, 7.15)	.36 (.02, 7.27)	2.07 (.37, 11.63)	-	.81 (.19, 3.52)
Current smoker	1.18 (.60, 2.34)	.33 (.11, .95)*	1.11 (.56, 2.20)	.52 (.20, 1.39)	1.37 (.73, 2.55)
Alcohol Consumption†‡					
Not at risk	1	1	1	1	1
Excess	1.03 (.37, 2.89)	.50 (.09, 2.84)	.90 (.33, 2.50)	.13 (.00, 4.39)	.51 (.17, 1.52)
Waist Circumference †§					
Normal	1	1	1	1	1
Obese	2.03 (1.03, 3.99)*	.30 (.11, .83)*	.58 (.29, 1.16)	.42 (.17, 1.05)	.76 (.41, 1.38)
Multimorbidity (FI24)					
0-1 conditions	1	1	1	1	1
2+ conditions	6.29 (1.45, 27.22)*	.88 (.27, 2.85)	1.46 (.67, 3.29)	.08 (.02, .46)*	.59 (.32, 1.10)
Polypharmacy					
0-4 medication	1	1	1	1	1
5+ medications	1.83 (.88, 3.80)	.87 (.32, 2.36)	1.44 (.72, 2.87)	.26 (.09, .74)*	1.09 (.60, 1.99)
Living Arrangements†					
Lives with others	1	1	1	1	1
Lives alone	.59 (.27, 1.29)	.60 (.18, 2.07)	1.40 (.64, 3.07)	.62 (.21, 1.87)	2.41 (1.25, 4.65)*

OR = Odds Ratio; 95%CI = 95% Confidence Interval; – = unable to estimate; Improved = a less severe frailty state compared with baseline state; Worse = a more severe frailty state, including death, compared with baseline state; Obesity = Waist Circumference: male >102cm, female >88cm; Excess alcohol consumption = >14 drinks per week and/or >4 drinks per session; FI24 = a 24 item FI that excludes all chronic conditions.
* P < .05
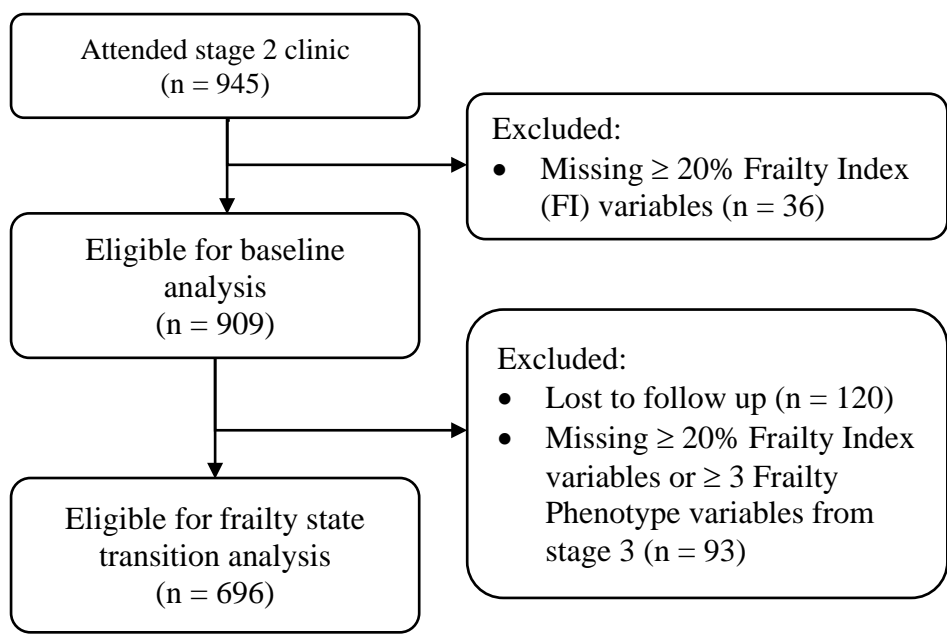
Supplementary Material Chapter 7

Chapter 7. Table S1: Search Syntax.
Diagnostic test accuracy of self-reported frailty screening instruments in identifying community-dwelling older people at risk of frailty and pre-frailty: A systematic review.

- **Embase**

(kihon AND check* OR (reported AND edmonton AND frail AND ('scale'/exp OR scale)) OR ((frail* OR prefrail*) AND (screen* OR index* OR tool* OR instrument*) AND ((self NEXT/5 (evaluat* OR assess* OR diagnos* OR test* OR report* OR administ*)) OR survey* OR postal* OR questionnaire* OR reported*)))

- **PubMed**

((((((frail*[tw]) OR prefrail*[tw])) AND (((((((((Diagnostic Self Evaluation[mh]) OR Self-report*[tw]) OR Postal*[tw]) OR Self-diagnos*[tw]) OR Survey*[tw]) OR Questionnaire*[tw]) OR reported*[tw]) OR Self-assess*[tw]) OR Self-test*[tw]) OR Self-administ*[tw])) AND ((((screen*[tw]) OR instrument*[tw]) OR tool*[tw]) OR index*[tw]))) OR ((Kihon Check*[tw]) OR Reported Edmonton Frail Scale*[tw])

- **Scopus**

((TITLE-ABS-KEY (frail* OR prefrail*)) AND (TITLE-ABS-KEY ((screen* OR instrument* OR tool* OR index*))) AND ((TITLE-ABS-KEY (self PRE/5 (evaluat* OR assess* OR diagnos* OR test* OR report* OR administ*))) OR (TITLE-ABS-KEY (questionnaire* OR survey* OR postal OR reported)))) OR (TITLE-ABS-KEY ((kihon AND check*))) OR (TITLE-ABS-KEY ((reported AND edmonton AND frail AND scale*)))

- **Ovid Medline**
  - 1. frail$.mp.
  - 2. prefrail$.mp.
  - 3. 1 or 2
  - 4. screen$.mp.
  - 5. test$.mp.
  - 6. instrument$.mp.
  - 7. Reported Edmonton Frail Scale.mp.
  - 8. diagnostic self evaluation/
  - 9. Postal.mp.
  - 10. Self-diagnos$.mp.
  - 11. Survey$.mp.
  - 12. Questionnaire$.mp.
  - 13. Reported.mp.
  - 14. (Self adj5 report$).mp.
  - 15. (Self adj5 assess$).mp.
  - 16. (Self adj5 test$).mp.
  - 17. (Self adj5 administ$).mp.
  - 18. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
  - 19. index$.mp.
  - 20. 4 or 5 or 6 or 19
  - 21. Kihon Check$.mp.

- o   22. 7 or 21
- o   23. 3 and 18 and 20
- o   24. 22 or 23

- **CINAHL**

((TX ((Kihon AND Check*))) OR (TX ((Reported AND Edmonton AND Frail AND Scale)))) OR (((TX (frail*)) OR (TX (prefrail*))) AND ((TX (screen*)) OR (TX (tool*)) OR (TX (index*)) OR (TX (instrument*))) AND ((TX (self W5 (evaluat* OR assess* OR diagnos* OR test* OR adminst* OR report*))) OR (TX (questionnaire*)) OR (TX (survey*)) OR (TX (postal)) OR (TX (reported))))

- **Web of Science**

#9	#8 OR #4 OR #3 *DocType=All document types; Language=All languages;*
#8	#7 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#7	#6 OR #5 *DocType=All document types; Language=All languages;*
#6	TS=(self NEAR/5 (evaluat* OR assess* OR diagnos* OR test* OR report* OR administ*)) *DocType=All document types; Language=All languages;*
#5	TS=(questionnaire* OR survey* OR postal OR reported) *DocType=All document types; Language=All languages;*
#4	TS=(reported edmonton frail scale*) *DocType=All document types; Language=All languages;*
#3	TS=(kihon check*) *DocType=All document types; Language=All languages;*
#2	TS=(screen* OR instrument* OR tool* OR index*) *DocType=All document types; Language=All languages;*
#1	TS=(frail* OR prefrail*) *DocType=All document types; Language=All languages;*

- **PsycINFO**

1	(frail* or prefrail*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2	(screen* or instrument* or tool*OR index*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3	(questionnaire* or survey* or postal or reported).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
4	(self adj5 (evaluat* or assess* or diagnos* or test* or report* or administ*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5	(kihon and check*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
6	Reported Edmonton Frail Scale.mp.
7	3 or 4
8	1 and 2 and 7
9	5 or 6 or 8

- **Pedro**

Searched for frail* and prefrail* in abstract or title

- **ProQuest Dissertations & Theses Global**

(ab(frail* OR prefrail*) OR ti((frail* OR prefrail*))) AND screen* AND all((self PRE/5 (evaluat* OR assess* OR diagnos* OR test* OR report* OR administ*) OR questionnaire* OR survey* OR postal))

- **Open Grey**

frail AND (screening* OR instrument* OR tool* OR index*) lang:"en"

- **Grey Literature Report**

frail

Chapter 7. Table S2: 2 x 2 Data for Selected Studies

Study	A (TP) RS+/IT+ (n)	B (FP) RS-/IT+ (n)	C (FN) RS+/IT- (n)	D (TN) RS-/IT- (n)	Test+ IT+ (n)	Test- IT- (n)	D+ RS+ (n)	D- RS- (n)	(Ref Standard) Prevalence n (%)	Total
Aeyeung et al : Self-Reported Exhaustion	71	177	146	3606	248	3752	217	3783	217 (5.4)	4000
Aeyeung et al : Self-Reported Physical Activity	175	596	42	3187	771	3229	217	3783	217 (5.4)	4000
Braun et al: PRISMA-7/FP	2	10	0	40	12	40	2	50	2 (3.9)	52
Braun et al: FRAIL SCALE/FP	1	4	1	46	5	47	2	50	2 (3.9)	52
Braun et al: GFI/FP	2	10	0	40	12	40	2	50	2 (3.9)	52
Braun et al: PRISMA-7/FI	9	3	3	37	12	40	12	40	12 (23.1)	52
Braun et al: FRAIL SCALE/FI	4	1	8	39	5	47	12	40	12 (23.1)	52
Braun et al: GFI/FI	6	6	6	34	12	40	12	40	12 (23.1)	52
de Llano et al: SRH/FP**	72	20	283	439	92	722	355	459	355 (43.6)	814
Dong et al TFI/FP	31	119	11	666	150	677	42	785	42 (5.1)	827
Dong et al TFI/FI (>.35)	45	116	21	723	161	744	66	839	66 (8.0)	827
Drubbel et al	211	39	172	216	250	388	383	255	383 (60.0)	638
Hoogendijk et al: GFI	11	41	4	46	52	50	15	87	15 (11.6)	102
Hoogendijk et al: PRISMA-7	14	19	1	68	33	69	15	87	15 (11.6)	102
Hoogendijk et al: Self-Rated Health	n.a	n.a	n.a	n.a	n.a	n.a	15	n.a	15 (11.6)	n.a
McCaul et al (Wave 2)^	913	122	831	3173	1035	4004	1744	3295	1744 (24.4)	5039
McCaul et al (Wave 3)^	989	81	561	912	1070	1473	1550	993	1550 (33.8)	2543
Mijnarends et al	13	8	6	200	21	206	19	208	19 (8.4)	227
Mossello et al	284	202	96	455	489	548	380	657	380 (36.6)	1037
Ntanasi et al TFI/FP	58	400	18	1317	458	1335	76	1717	76 (4.2)	1793
Ntanasi et al TFI/FI	224	234	108	1227	458	1335	332	1461	332 (18.5)	1793
Orkaby et al	803	412	1618	3729	1215	10828	2421	9622	2421 (20.1)	12043
Qiao et al	160	180	85	777	340	862	245	957	245 (20.4)	1202
Roppolo et al	27	92	7	141	119	148	34	233	34 (12.7)	267
Theou et al: RS = SHARE-Fi (70)	1219	228	3667	21948	1447	25615	4886	22176	4886 (18.1)*	27062
Theou et al: RS = SHARE-Fi-CGA (44)	1231	215	3569	22031	1446	25600	4800	22246	4800 (21.6)*	27046

*^ Frailty Index >0.21 *Unweighted percentage ** Self-reported FP*

Chapter 7. Table S3: Diagnostic Test Accuracy Statistics for Selected Studies

Study	Index Test (Reference Standard)	Sensitivity % (95%CI)	Specificity % (95%CI)	Youden Index	Positive Predictive Value % (95%CI)	Negative Predictive Value % (95%CI)	Likelihood Ratio: Positive Test LR+ (95%CI)	Likelihood Ratio: Negative Test LR- (95%CI)
Aeyeung et al (1)	SREx (FP)	33.0 [0.27 - 0.40]	95.3 [0.95 - 0.96]	28.3	28.9 [0.24 - 0.35]	96.1 [0.95 - 0.97]	7.02 [5.57 - 8.95]	0.70 [0.64 - 0.77]
Aeyeung et al (2)	SRPA (FP)	80.6 [0.75 - 0.85]	84.2 [0.83 - 0.85]	64.8	22.7 [0.20 - 0.26]	98.7 [0.98 - 0.99]	5.10 [4.64 - 5.65]	0.23 [0.18 - 0.30]
Braun et al (1)	PRISMA-7 (FP)	100.0 [0.34 - 1.00]	80.0 [0.67 - 0.89]	80.0	16.7 [0.05 - 0.45]	100.0 [0.91 – 1.00]	5.00 [2.87 - 8.70]	0.00 [0.00 - NaN]
Braun et al (2)	FRAIL (FP)	50.0 [0.10 - 0.91]	92.0 [0.81 - 0.97]	42.0	20.0 [0.04 - 0.62]	97.9 [0.89 – 1.00]	6.25 [1.17 - 33.35]	0.54 [0.14 - 2.18]
Braun et al (3)	GFI (FP)	100.0 [0.34 - 1.00]	80.0 [0.67 - 0.89]	80.0	16.7 [0.05 - 0.45]	100.0 [0.91 – 1.00]	5.00 [2.87 - 8.70]	0.00 [0.00 - NaN]
Braun et al (4)	PRISMA-7 (FI)	75.0 [0.47 - 0.91]	92.5 [0.80 - 0.97]	67.5	75.0 [0.47 - 0.91]	92.5 [0.80 - 0.97]	10.00 [3.21 - 31.15]	0.27 [0.10 - 0.72]
Braun et al (5)	FRAIL (FI)	33.3 [0.14 - 0.61]	97.5 [0.87 - 1.00]	30.8	80.0 [0.38 - 0.96]	83.0 [0.70 - 0.91]	13.32 [1.64 - 108.25]	0.68 [0.46 - 1.02]
Braun et al (6)	GFI (FI)	50.0 [0.25 - 0.75]	85.0 [0.71 - 0.93]	35.0	50.0 [0.25 - 0.75]	85.0 [0.71 - 0.93]	3.33 [1.32 - 8.45]	0.59 [0.33 - 1.05]
de Llano et al	SRH (FP)	20.3 [0.16 - 0.25]	95.6 [0.93 - 0.97]	15.9	78.3 [0.69 - 0.86]	60.8 [0.57 - 0.64]	4.61 [2.89 - 7.49]	0.83 [0.79 - 0.88]
Dong et al (1)	TFI (FP)	73.8 [0.59 - 0.85]	84.8 [0.82 - 0.87]	58.6	20.7 [0.15 - 0.28]	98.4 [0.97 - 0.99]	4.86 [3.81 - 6.22]	0.31 [0.19 - 0.51]
Dong et al (2)	TFI (FI)	68.2 [0.56 - 0.78]	86.2 [0.84 - 0.88]	54.4	28.0 [0.22 - 0.35]	97.2 [0.96 - 0.98]	4.94 [3.90 - 6.24]	0.37 [0.26 - 0.53]
Drubbel et al	GFI (FI)	55.1 [0.50 - 0.60]	84.7 [0.79 - 0.89]	39.8	84.4 [0.79 - 0.88]	55.7 [0.51 - 0.61]	3.60 [2.66 - 4.88]	0.53 [0.47 - 0.60]
Hoogendijk et al (1)	PRISMA-7 (FP)	93.3 [0.70 - 0.99]	78.2 [0.68 - 0.86]	71.5	42.4 [0.27 - 0.59]	98.6 [0.92 – 1.00]	4.28 [2.81 - 6.50]	0.09 [0.01 - 0.57]
Hoogendijk et al (2)	GFI (FP)	73.3 [0.48 - 0.89]	52.9 [0.43 - 0.63]	26.2	21.2 [0.12 - 0.34]	92.0 [0.81 - 0.97]	1.56 [1.07 - 2.27]	0.51 [0.21 - 1.19]
Hoogendijk et al (3)	SRH (FP)	85	73	58.0	n.a.	n.a.	n.a.	n.a.
McCaul et al: W2	FRAIL (FI)	52.4 [0.50 - 0.55]	96.3 [0.96 - 0.97]	48.7	88.2 [0.86 - 0.90]	79.2 [0.78 - 0.81]	14.16 [11.81 - 16.92]	0.49 [0.47 - 0.52]
McCaul et al: W3	FRAIL (FI)	63.8 [0.61 - 0.66]	91.8 [0.90 - 0.93]	55.6	92.4 [0.91 - 0.94]	61.9 [0.59 - 0.64]	7.78 [6.33 - 9.67]	0.39 [0.37 - 0.42]
Mijnarends et al	FRAIL (FP)	68.4 [0.46 - 0.85]	96.2 [0.93 - 0.98]	64.6	61.9 [0.41 - 0.79]	97.1 [0.94 - 0.99]	18.00 [8.45 - 37.47]	0.33 [0.17 - 0.64]
Mossello et al	FPQ (FP)	74.7 [0.70 - 0.79]	69.3 [0.66 - 0.73]	44.0	58.4 [0.54 - 0.63]	82.6 [0.79 - 0.86]	2.43 [2.14 - 2.77]	0.37 [0.30 - 0.44]
Ntanasi et al (1)	TFI (FP)	76.3 [0.66 - 0.85]	76.7 [0.75 - 0.79]	53.0	12.7 [0.10 - 0.16]	98.7 [0.98 - 0.99]	3.28 [2.81 - 3.81]	0.31 [0.21 - 0.46]
Ntanasi et al (2)	TFI (FI)	67.5 [0.62 - 0.72]	84.0 [0.82 - 0.86]	51.5	48.9 [0.44 - 0.54]	91.9 [0.90 - 0.93]	4.22 [3.67 - 4.84]	0.38 [0.33 - 0.45]
Orkaby et al	MSOF (FI)	33.2 [0.31 - 0.35]	95.7 [0.95 - 0.96]	28.9	66.1 [0.63 - 0.69]	85.1 [0.84 - 0.86]	7.72 [6.94 - 8.65]	0.70 [0.68 - 0.72]
Qiao et al	CFAI (FI)	65.3 [0.59 - 0.71]	81.2 [0.79 - 0.84]	46.5	47.1 [0.42 - 0.52]	90.1 [0.88 - 0.92]	3.47 [2.96 - 4.08]	0.43 [0.36 - 0.51]
Roppolo et al	TFI (FP)	79.4 [0.63 - 0.90]	60.5 [0.54 - 0.67]	39.9	22.7 [0.16 - 0.31]	95.3 [0.91 - 0.98]	2.01 [1.59 - 2.54]	0.34 [0.17 - 0.66]
Theou et al: RS = SHARE-FI (70 item)	FRAIL (FI)	25.9 [0.24 - 0.26]	99.0 [0.99 - 0.99]	24.9	84.2 [0.82 - 0.86]	85.7 [0.85 - 0.86]	24.90 [21.14 - 27.86]	0.76 [0.75 -0.77]
Theou et al: RS = SHARE-FI-CGA (44 item)	FRAIL (FI)	25.6 [0.24 - 0.27]	99.0 [0.99 - 0.99]	24.6	85.1 [0.83 - 0.87]	86.0 [0.86 - 0.87]	25.60 [23.04 - 30.57]	0.75 [0.74 -0.76]

aCGA, abbreviated Comprehensive Geriatric Assessment. CI, 95% Confidence Interval. CFVI, Clinical Functional Vulnerability Index. CGA, Comprehensive Geriatric Assessment. CFAI, Comprehensive Frailty Assessment Instrument. FI, Frailty Index. FP, Frailty Phenotype. FPQ, Frailty Postal Questionnaire. FRAIL, FRAIL Scale. GFI, Groningen Frailty Index. G8, Geriatric 8. MSOF, Modified Study of Osteoporotic Fracture Frailty Score. PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument. SREx, Self-Reported Exhaustion. SRH, Self-Rated Health. SRPA, Self-Reported Physical Activity. TFI, Tilburg Frailty Index, VES-13, Vulnerable Elders Survey.

a) Sensitivity Forest Plot (Reference Standard = Frailty Phenotype)
Note: Forest plots were generated only for index tests with more than one study comparing sensitivity and specificity against the reference standard.

FI, Frailty Index. FP, Frailty Phenotype. FRAIL, FRAIL Scale. GFI, Groningen Frailty Indicator. PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument. TP, True Positive, FP False Positive, FN False Negative, TN True Negative

b) Sensitivity Forest Plot (Reference Standard = Frailty Index)#

#FI threshold: ≥ 0.08 Drubbel et al 2013. > 0.21: McCaul et al 2015. > 0.25: Ntanasi et al 2018.   ≥ 0.25: Braun et al 2017, Theou et al 2013. > 0.35: Dong et al 2017.

FI, Frailty Index. FP, Frailty Phenotype. FRAIL, FRAIL Scale. GFI, Groningen Frailty Indicator. PRISMA-7, Program of Research on Integration of Services for the Maintenance of Autonomy 7 Instrument. TP, True Positive, FP False Positive, FN False Negative, TN True Negative

Supplementary Material Chapter 8

Chapter 8. Table S1. Frailty Phenotype and Frailty Index Variables

Frailty Phenotype	Frailty Index (34-item)	
Weight Loss: > 10% weight loss over four years (clinic measurement)	Angina	Health limits lifting or carrying groceries
	Heart attack	Health limits climbing several flights of stairs
	Osteoporosis	Health limits climbing one flight of stairs
Weakness: original method	Osteoarthritis	Health limits bending, kneeling or stooping
Exhaustion: original method	Rheumatoid and any other arthritis	Health limits walking more than 1km
Slowness: Self-report 'a lot' to health limits walking 100m (SF36 q11)	Stroke or TIA	Health limits walking 100m
	Diabetes	Felt lonely
	Any mental health problem	Felt that could not get going
Low Activity Level: Australian Bureau of Statistics National Health Survey (< 100 METs per week)	Systolic blood pressure	Difficulty keeping mind on what you were doing
	Diastolic blood pressure	
	10% weight loss over 4 years	Felt everything was an effort
	FEV1/FVC post ratio	Physical & emotional problems interfered with social activities
	Weak grip strength	
	Falls	Felt full of life
	Hospital emergency admission	Felt calm and peaceful
	Low activity level (<100 METs per week)	Felt worn out
	Healthy as anybody I know	Felt tired
	Health is excellent	
	Self-reported health	

METs, metabolic equivalent of task; SF36, 36-Item Short Form Health Survey; TIA, transient ischaemic attack; FEV1/FVC, forced expiratory volume/forced vital capacity

Chapter 8. Table S2 Baseline descriptive characteristics and frailty classification of participants who died before 31/07/2018 or who were lost to follow-up.

	Died before 31/07/2018 n (%)	Lost to follow-up n (%)
Total	147	213
Sex		
Male	101 (62.4)	99 (39.5)
Female	46 (37.6)	114 (60.5)
Age Groups		
65-74 years	44 (27.7)	113 (47.0)
≥75 years	103 (72.3)	100 (53.0)
Education Level [a]		
Up to secondary	87 (61.2)	141 (71.5)
Trade / Cert / Dip	48 (35.1)	60 (26.0)
≥Bachelor degree	6 (3.8)	6 (2.4)
Income Groups [a]		
Up to $20k	84 (61.1)	118 (58.1)
$20-$40k	318 (60.8)	57 (32.8)
$40-$60k	8 (6.5)	11 (6.9)
>$60k	2 (1.6)	3 (2.2)
5-Category FP		
0 characteristics	27 (20.1)	55 (23.8)
1 characteristic	33 (19.7)	68 (30.9)
2 characteristics	35 (24.1)	46 (20.8)
3 characteristics	34 (25.2)	29 (17.6)
≥4 characteristics	18 (10.9)	15 (6.9)
3-Category FP		
Non-frail	27 (20.1)	55 (23.8)
Pre-frail	68 (43.8)	114 (51.7)
Frail	52 (36.1)	44 (24.5)
10% Increment FI		
0-10%	15 (10.3)	36 (16.3)
10-20%	26 (15.8)	63 (26.6)
20-30%	30 (22.1)	46 (21.4)
30-40%	39 (24.1)	31 (16.6)
40-50%	22 (17.2)	22 (12.3)
>50%	15 (10.5)	15 (6.7)
3-Category FI		
Non-frail	15 (10.3)	36 (16.3)
Pre-frail	29 (19.0)	65 (27.5)
Frail	103 (70.8)	112 (56.2)

n unweighted. % reported using cohort case weights. 5-Category FP (number of characteristics): 0, 1, 2, 3, 4-5. 3-Category FP (number of characteristics): 0, non-frail; 1-2, pre-frail, ≥ 3, frail. 10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%. 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
[a] missing nor included.

Chapter 8. Table S3 Mortality rates by baseline descriptive characteristics, frailty status for the frailty phenotype (FP) and frailty index (FI).

	n (%)	1 year	2 years	4 years	6 years	8 years	10 years
		**n (%) dead within**					
Whole sample	909	19 (2.0)	37 (4.1)	86 (9.5)	153 (17.5)	214 (24.8)	292 (33.8)
Sex							
Male	453 (45.2)	8 (1.6)	22 (4.8)	54 (11.2)	104 (23.1)*	140 (31.5)*	180 (40.1)*
Female	456 (54.8)	11 (2.4)	15 (3.5)	32 (8.1)	49 (13.0)	74 (19.2)	112 (28.6)
Age Groups							
65-74 years	554 (56.3)	4 (0.7)*	13 (2.2)*	30 (5.4)*	46 (8.5)*	63 (12.2)*	96 (17.8)*
≥75 years	355 (43.7)	15 (3.7)	24 (6.5)	56 (14.7)	107 (29.1)	151 (40.9)	196 (54.3)
Education Level [a]							
Up to secondary	569 (63.5)	15 (2.6)	28 (4.7)	57 (9.6)	93 (17.0)	128 (23.6)	181 (33.2)
Trade / Cert / Dip	288 (30.6)	3 (1.0)	7 (3.0)	22 (8.6)	49 (18.0)	72 (26.9)	93 (34.1)
≥Bachelor degree	25 (2.5)	1 (3.6)	1 (3.6)	3 (10.8)	5 (19.4)	7 (29.5)	9 (35.4)
Income Groups [a]							
Up to $20k	462 (46.5)	13 (2.8)	24 (5.1)	54 (10.9)	86 (18.3)	115 (25.9)	157 (35.5)*
$20-$40k	281 (33.5)	3 (1.3)	5 (2.0)	17 (7.6)	34 (14.3)	51 (20.3)	76 (28.9)
$40-$60k	59 (6.8)	1 (1.3)	3 (6.5)	5 (9.8)	8 (13.0)	13 (21.3)	19 (31.8)
>$60k	26 (2.6)	0 (0)	0 (0)	0 (0)	2 (8.3)	2 (8.3)	3 (11.6)
5-Category FP							
0 characteristics	289 (30.1)	0 (0)*	1 (0.4)*	12 (5.3)*	27 (10.8)*	45 (177)*	68 (26.3)*
1 characteristic	289 (30.8)	3 (1.0)	10 (3.2)	18 (5.4)	36 (11.3)	49 (15.9)	69 (22.1)
2 characteristics	181 (20.8)	5 (2.3)	10 (5.0)	24 (12.4)	36 (20.3)	51 (29.1)	68 (38.5)
3 characteristics	108 (13.8)	6 (5.5)	9 (8.5)	18 (15.3)	35 (32.8)	44 (41.9)	59 (58.0)
≥4 characteristics	42 (4.5)	5 (10.8)	7 (16.5)	14 (33.4)	19 (44.9)	25 (59.9)	28 (67.0)
3-Category FP							
Non-Frail	289 (30.1)	0 (0)*	1 (0.4)*	12 (5.3)*	27 (10.8)*	45 (17.7)*	68 (26.3)*
Pre-frail	470 (51.6)	8 (1.5)	20 (3.9)	42 (8.3)	72 (15.0)	100 (21.2)	137 (28.7)
Frail	150 (18.3)	11 (6.8)	16 (10.5)	32 (19.8)	54 (35.8)	69 (46.4)	87 (60.2)
10% Increment FI							
0-10%	211 (21.5)	0 (0)*	0 (0)*	6 (2.9)*	16 (8.1)*	28 (13.1)*	44 (21.4)*
10-20%	266 (28.1)	5 (1.8)	10 (3.7)	17 (6.1)	27 (9.4)	43 (16.2)	65 (24.6)
20-30%	182 (21.0)	2 (1.0)	5 (2.3)	13 (7.1)	31 (18.7)	46 (27.5)	63 (35.3)
30-40%	129 (14.7)	3 (2.7)	8 (6.6)	22 (15.7)	39 (26.6)	49 (37.2)	59 (45.7)
40-50%	80 (10.0)	5 (5.5)	6 (7.5)	17 (20.6)	24 (33.5)	27 (37.2)	35 (50.7)
>50%	41 (4.7)	4 (7.8)	8 (17.9)	11 (27.0)	16 (42.2)	21 (51.7)	26 (65.2)
3-Category FI							
Non-Frail	211 (21.5)	0 (0)*	0 (0)	6 (2.9)*	16 (8.1)*	28 (13.1)*	44 (21.4)*
Pre-frail	285 (30.4)	5 (1.7)	10 (3.4)	18 (6.1)	30 (10.4)	47 (16.9)	69 (24.6)
Frail	413 (48.1)	14 (3.2)	27 (6.3)	62 (14.5)	107 (26.3)	139 (35.0)	179 (45.1)

n unweighted. % reported using cohort case weights. 5-Category FP (number of characteristics): 0, 1, 2, 3, 4-5. 3-Category FP (number of characteristics): 0, non-frail; 1-2, pre-frail, ≥ 3, frail. 10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%. 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
[a] missing nor included.
* p < 0.05 (main effects reported)

Chapter 8. Table S4 Frailty status at baseline and follow-up status for the 3-Category Frailty Phenotype and Frailty Index

Baseline Frailty Status	Follow-up Frailty Status, n (%)					
	Non-Frail	Pre-frail	Frail	Dead [a]	Missing [b]	Total
Frailty Phenotype						
Non-Frail	118 (37.5)	77 (27.2)	12 (5.1)	27 (10.7)	55 (19.5)	289 (100)
Pre-frail	78 (16.6)	163 (33.2)	47 (11.6)	68 (13.8)	114 (24.8)	470 (100)
Frail	2 (1.2)	18 (12.7)	34 (20.6)	52 (32.1)	44 (33.3)	150 (100)
Total	198 (20.1)	258 (27.6)	93 (11.3)	147 (16.2)	213 (24.8)	909 (100)
Frailty Index						
Non-Frail	93 (44.0)	47 (20.2)	20 (9.3)	15 (7.8)	36 (18.7)	211 (100)
Pre-frail	33 (10.5)	87 (29.5)	71 (27.6)	29 (10.2)	65 (22.2)	285 (100)
Frail	3 (0.7)	19 (4.6)	176 (42.1)	103 (23.9)	112 (28.7)	413 (100)
Total	129 (13.0)	153 (15.5)	267 (30.7)	147 (16.3)	213 (24.6)	909 (100)

n unweighted. % reported using cohort case weights. Frailty Phenotype (number of characteristics): 0, non-frail; 1-2, pre-frail, $\geq$ 3, frail. Frailty Index (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
[a] Died before 31/07/2018
[b] Participants who were either lost to follow-up or who had insufficient valid FP or FI variables at follow-up.

Chapter 8. Table S5 Mortality rates by baseline descriptive characteristics, frailty status (frailty phenotype (FP) and frailty index (FI)) for the returning sample (n = 549).

| | n (%) | n (%) dead years from baseline | | |
		6 years	8 years	10 years
Returning sample	549	3 (0.7)	26 (5.0)	70 (13.1)
Sex				
Male	253 (43.0)	2 (1.0)	13 (5.5)	39 (15.8)
Female	296 (57.0)	1 (0.4)	12 (4.3)	30 (10.8)
Age Groups				
65-74 years	397 (67.8)	1 (0.4)	8 (2.7)*	28 (7.6)*
≥75 years	152 (32.2)	2 (1.2)	17 (9.1)	41 (24.3)
Education Level [a]				
Up to secondary	341 (61.9)	2 (0.9)	13 (4.4)	42 (13.0)
Trade / Cert / Dip	180 (32.7)	1 (0.4)	11 (5.8)	25 (14.2)
≥Bachelor degree	13 (2.3)	0 (0)	0 (0)	1 (4.6)
Income Groups [a]				
Up to $20k	260 (43.6)	2 (1.2)	15 (6.8)	39 (17.0)
$20-$40k	193 (38.2)	1 (0.3)	8 (4.3)	24 (12.80
$40-$60k	40 (7.5)	0 (0)	1 (2.2)	4 (7.1)
>$60k	21 (3.0)	0 (0)	0 (0)	1 (4.5)
5-Category FP				
0 characteristics	207 (34.9)	0 (0)	8 (3.7)*	24 (11.9)*
1 characteristic	188 (34.4)	1 (0.4)	5 (1.8)	18 (8.2)
2 characteristics	100 (19.7)	1 (1.3)	7 (8.4)	16 (17.5)
3 characteristics	45 (9.2)	1 (3.1)	4 (11.2)	10 (25.7)
≥4 characteristics	9 (1.7)	0 (0)	1 (10.6)	1 (10.6)
3-Category FP				
Non-frail	207 (34.9)	0 (0)	8 (3.7)	24 (11.9)*
Pre-frail	288 (54.1)	2 (0.7)	12 (4.2)	34 (11.5)
Frail	54 (10.9)	1 (2.6)	5 (11.1)	11 (23.3)
10% Increment FI				
0-10%	160 (26.3)	1 (0.5)	7 (3.1)	17 (9.4)
10-20%	177 (32.7)	0 (0)	8 (5.5)	21 (12.9)
20-30%	106 (20.1)	1 (1.5)	4 (4.3)	16 (14.4)
30-40%	59 (11.5)	0 (0)	3 (5.3)	10 (18.0)
40-50%	36 (7.0)	1 (3.5)	2 (7.0)	3 (11.8)
>50%	11 (2.4)	0 (0)	1 (7.6)	2 (21.8)
3-Category FI				
Non-frail	160 (26.3)	1 (0.5)	7 (3.1)	17 (9.4)
Pre-frail	191 (35.5)	0 (0)	8 (5.1)	21 (11.8)
Frail	198 (38.1)	2 (0.7)	10 (5.6)	31 (16.6)

n unweighted. % reported using cohort case weights. 5-Category FP (number of characteristics): 0, 1, 2, 3, 4-5. 3-Category FP (number of characteristics): 0, non-frail; 1-2, pre-frail; ≥ 3, frail. 10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%. 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.
[a] missing nor included.
* p < 0.05 (main effects reported)

Chapter 8. Table S6. Frailty classification (frailty phenotype and frailty index) at baseline and follow up and mortality risk (Hazard Ratio) for the returning sample (n = 549). Baseline and Follow-up frailty classification are considered separately. Weighted multivariable analysis adjusted for age, sex, education and income.

Returning Sample (n = 549)	Baseline		Follow up	
Frailty Phenotype (FP)	Adj HR (95%CI)	p-value	Adj HR (95%CI)	p-value
Model 1: Continuous FP per 1 score	1.26 (1.02-1.57)	.035*	1.57 (1.27-1.92)	< .001*
Model 2: 5-Category FP				
0 characteristics (n = 207)	-	-	-	-
1 characteristic (n = 188)	1.05 (.60-1.84)	.874	.88 (.44-1.77)	.720
2 characteristics (n = 100)	1.31 (.68-2.52)	.421	1.83 (.94-3.55)	.073
3 characteristics (n = 45)	2.27 (1.06-4.84)	.035*	2.80 (1.41-5.58)	.003*
4-5 characteristics (n = 9)	1.71 (.43-6.77)	.445	5.43 (2.25-13.09)	< .001*
Model 3: 3-Category FP				
Non-frail (n = 207)	-	-	-	-
Pre-frail (n = 288)	1.14 (.68-1.89)	.626	1.27 (.71-2.29)	.417
Frail (n = 54)	2.16 (1.06-4.40)	.033*	3.49 (1.83-6.64)	< .001*
Frailty Index (FI)				
Model 4: Continuous FI per .01 score	1.02 (1.00-1.03)	.061	1.04 (1.02-1.06)	< .001*
Model 5: 10% Increment FI				
0-10% (n = 160)	-	-	-	-
10-20% (n = 177)	1.20 (.62-2.31)	.591	2.07 (.81-5.32)	.129
20-30% (n = 106)	1.84 (.93-3.65)	.080	3.44 (1.37-8.65)	.009*
30-40% (n = 59)	2.21 (1.05-4.63)	.036*	3.60 (1.35-9.62)	.011*
40-50% (n = 36)	1.58 (.62-4.00)	.338	5.09 (1.98-13.08)	.001*
> 50% (n = 11)	2.43 (.56-10.51)	.235	9.73 (3.32-28.50)	< .001*
Model 6: 3-Category FI				
Non-frail (n = 160)	-	-	-	-
Pre-frail (n = 191)	1.23 (.64-2.36)	.530	2.01 (.79-5.10)	.143
Frail (n = 198)	1.98 (1.10-3.56)	.023*	4.80 (2.07-11.16)	< .001*

Adj HR, Adjusted Hazard Ratio. 5-Category FP (number of characteristics): 0, 1, 2, 3, 4-5. 3-Category FP (number of characteristics): 0, non-frail; 1-2, pre-frail; $\geq$ 3, frail. 10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%. 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.

The follow up window for mortality was from study entry to a censoring date of 30/9/2016. (Minimum of 10 years of mortality data for all participants).

* p < 0.05

Chapter 8. Table S7. Frailty classification (frailty phenotype and frailty index) at baseline and mortality risk (Hazard Ratio) for the whole sample (n = 909). Weighted multivariable analysis adjusted for age, sex, education and income.

Whole Sample (n = 909)	Baseline	
Frailty Phenotype (FP)	Adj HR (95%CI)	p-value
Model 1: Continuous FP per 1 score	1.34 (1.19-1.52)	< .001*
Model 2: 5-Category FP		
0 characteristics (n = 289)	-	-
1 characteristic (n = 289)	.80 (.56-1.15)	.222
2 characteristics (n = 181)	1.34 (.90-1.99)	.152
3 characteristics (n = 108)	1.97 (1.29-3.01)	.002*
4-5 characteristics (n = 42)	3.14 (1.81-5.45)	< .001*
Model 3: 3-Category FP		
Non-frail (n = 289)	-	-
Pre-frail (n = 470)	.97 (.70-1.34)	.847
Frail (n = 150)	2.15 (1.46-3.15)	< .001*
Frailty Index (FI)		
Model 4: Continuous FI per .01 score	1.03 (1.02-1.03)	< .001*
Model 5: 10% Increment FI		
0-10% (n = 211)	-	-
10-20% (n =266)	1.36 (.89-2.07)	.159
20-30% (n =182)	1.99 (1.27-3.12)	.003*
30-40% (n = 129	2.86 (1.80-4.55)	< .001*
40-50% (n = 80)	2.66 (1.54-4.59)	< .001*
> 50% (n = 41)	3.98 (2.09-7.59)	< .001*
Model 6: 3-Category FI		
Non-frail (n = 211)	-	-
Pre-frail (n = 285)	1.36 (.89-2.06)	.153
Frail (n = 413)	2.63 (1.77-3.90)	< .001*

Adj HR, Adjusted Hazard Ratio. 5-Category FP (number of characteristics): 0, 1, 2, 3, 4-5. 3-Category FP (number of characteristics): 0, non-frail; 1-2, pre-frail, ≥ 3, frail. 10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%. 3-Category FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail.

The follow up window for mortality was from study entry to a censoring date of 30/9/2016. (Minimum of 10 years of mortality data for all participants).

* p < 0.05

Supplementary Material Chapter 9

Chapter 9. Table S1. Frailty Phenotype, Frailty Index, and Sarcopenia Variables

Variable	Description
Frailty Phenotype Variables	
Weight loss	>10% weight loss over 4 years (clinic measurement: Phase 1 and Phase 2)
Weakness	Grip strength (kg) measured using dynamometer in the lowest 20% at baseline stratified by sex and body mass index (BMI) quartiles:
	Male: $\quad$ BMI $\leq$ 24, Grip $\leq$ 29 $\quad$ BMI 24.1-26, Grip $\leq$ 30 $\quad$ BMI 26.1-28, Grip $\leq$ 30 $\quad$ BMI > 28, Grip $\leq$ 32
	Female: $\quad$ BMI $\leq$ 23, Grip $\leq$ 17 $\quad$ BMI 23.1-26, Grip $\leq$ 17.3 $\quad$ BMI 26.1-29, Grip $\leq$ 18 $\quad$ BMI > 29, Grip $\leq$ 21
Exhaustion	Two questions used from the CES–D Depression Scale. How often in the last week did you feel: a) I felt that everything I did was an effort, b) I could not get going. Scoring: rarely or none (0), some or a little (1), moderate (2), most (3). Characteristic present when answering "2" or "3" to either question.
Slowness	Self-report to the question: Health limits you a lot walking 100m. (SF36 q11)
Low Activity	Australian Bureau of Statistics National Health Survey. <100 Metabolic Equivalents (METs) per week.

Frailty Index Variables

Angina	Diastolic blood pressure	Health limits lifting or carrying groceries	Could not get going (FP)
Heart attack	FEV1/FVC post ratio		Difficulty keeping mind on what you were doing
Osteoporosis	Weak grip strength (FP cut points used)	Health limits climbing several flights of stairs	
Osteoarthritis			Felt everything was an effort (FP)
Rheumatoid and any other arthritis	Falls	Health limits climbing one flight of stairs	Physical & emotional problems interfered with social activities
Stroke or TIA	Hospital emergency admission	Health limits bending, kneeling or stooping	
Diabetes	Low activity level (<100 METs per week) (FP)		Felt full of life
Any mental health problem	Healthy as anybody I know	Health limits walking more than 1km	Felt calm and peaceful
10% weight loss over 4 years (FP)	Health is excellent		Felt worn out
	Self-reported health	Health limits walking 100m (FP)	Felt tired
Systolic blood pressure		Felt lonely	

Sarcopenia Variables

Variable	Description
Low Skeletal Muscle Index (SMI)	Low SMI (Male: < 7.36 kg/m2, Female: < 5.81 kg/m2) was based on DEXA measured appendicular skeletal muscle mass (ASM).
Weakness	Grip strength measured using dynamometer. Cut points: Male: < 30kg, Female: < 20kg.

Chapter 9. Table S2. Descriptive characteristics of sample and relationship with frailty and sarcopenia classification.

	Whole sample n (%)	Frailty Phenotype				Frailty Index			
		Frailty & Sarcopenia Status				Frailty & Sarcopenia Status			
		Neither Frail or Sarcopenic n (%)	Frail Only n (%)	Sarcopenic Only n (%)	Both Frail & Sarcopenic n (%)	Neither Frail or Sarcopenic n (%)	Frail Only n (%)	Sarcopenic Only n (%)	Both Frail & Sarcopenic n (%)
Total	716								
Sex									
Male	352 (44.5)	284 (81.2)	31 (8.3)	21 (5.3)	16 (5.3)	198 (56.4)	117 (33.1)	13 (3.6)	24 (6.9)
Female	364 (55.5)	274 (72.6)	57 (18.2)	19 (5.3)	14 (3.9)	164 (40.3)	167 (50.6)	12 (3.1)	21 (6.1)
Age Groups									
65-74 years	449 (58.3)	390 (86.7)	37 (8.5)	15 (2.7)	7 (2.1)	264 (57.0)	163 (38.2)	9 (1.9)	13 (2.9)
>75 years	267 (41.7)	168 (62.0)	51 (21.3)	25 (8.8)	23 (7.9)	98 (34.0)	121 (49.2)	16 (5.3)	32 (11.4)
Education Level†									
Up to secondary	454 (64.3)	344 (74.0)	61 (15.4)	29 (5.8)	20 (4.8)	213 (45.4)	192 (44.0)	20 (4.1)	29 (6.6)
Trade / Cert / Dip	220 (29.8)	180 (81.6)	21 (9.4)	10 (4.8)	9 (4.1)	127 (51.6)	74 (39.4)	4 (2.0)	15 (7.0)
Bachelor degree+	23 (2.9)	21 (90.2)	1 (3.9)	0 (0)	1 (5.9)	18 (78.2)	4 (16.0)	0 (0)	1 (5.9)
Income Groups†									
Up to $20k	365 (46.9)	275 (73.9)	50 (14.0)	21 (6.0)	19 (6.1)	162 (40.8)	163 (47.0)	14 (4.4)	26 (7.8)
$20-$40k	232 (35.5)	194 (81.9)	22 (11.5)	8 (3.1)	8 (3.5)	140 (56.7)	76 (36.8)	6 (2.2)	10 (4.3)
$40-$60k	42 (5.9)	34 (79.1)	5 (12.1)	3 (8.8)	0 (0)	26 (60.8)	13 (30.3)	0 (0)	3 (8.8)
More than $60k	20 (2.4)	18 (92.2)	0 (0)	1 (3.1)	1 (4.8)	14 (64.1)	4 (28.0)	1 (3.1)	1 (4.8)
Multimorbidity†									
0-1 health conditions	494 (67.0)	409 (81.6)	37 (8.3)	31 (6.0)	17 (4.1)	317 (60.7)	129 (29.2)	24 (4.7)	24 (5.4)
2+ health conditions	222 (33.0)	149 (65.8)	51 (25.1)	9 (3.8)	13 (5.3)	45 (20.4)	155 (70.5)	1 (0.5)	21 (8.7)
Living Arrangements†									
Lives with others	434 (68.6)	355 (79.8)	47 (12.3)	16 (3.8)	16 (4.2)	233 (50.3)	169 (41.8)	12 (2.6)	20 (5.4)
Lives alone	265 (29.2)	190 (68.8)	38 (16.6)	23 (8.9)	14 (5.7)	122 (40.8)	106 (44.6)	12 (5.1)	25 (9.5)

Frailty Phenotype categories: 0-2 characteristics = non-frail, ≥3 characteristics = frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics = not sarcopenic, 2 characteristics = sarcopenic.

† Not stated or missing not included. § Obesity Waist Circumference: male >102cm, female >88cm.

Chapter 9. Table S3. ANOVA mean number of FP frailty characteristics or FI proportion of deficits, based on classification as frail only, or both frail and sarcopenic.

	n (%)	Mean (SD) p-value
Total		-
FP Frailty & Sarcopenia Status		
Frail only	88 (13.8)	3.2 (0.8) p = .729
Both frail and sarcopenic	30 (4.5)	3.4 (0.6)
FI Frailty & Sarcopenia Status		
Frail only	284 (42.8)	0.34 (0.1) p = .016*
Both frail and sarcopenic	45 (6.5)	0.38 (0.1)

FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic.
* p < 0.05

Chapter 9. Table S4. Relationship of frailty classification (Frailty Phenotype and Frailty Index) and Sarcopenia with survival (over 10 years), with FP frailty, FI frailty, and sarcopenia analysed individually, stratified by sex. Complex samples Cox regression, adjusted for: age, income, education.

	n (%)	Adjusted HR (95%CI) p-value	Male HR (95%CI) p-value	Female HR (95%CI) p-value
Total	716	-	-	
FP Frailty				
Non-Frail	598 (81.7)	1	1	1
Frail	118 (18.3)	2.23 (1.55,3.22) p < .001*	2.02*	2.52*
FI Frailty				
Non-Frail	387 (50.7)	1	1	1
Frail	329 (49.3)	2.18 (1.55, 3.07) p < .001*	2.22*	2.18*
Sarcopenia				
Non-Sarcopenic	646 (90.2)	1	1	1
Sarcopenic	70 (9.8)	2.45 (1.57, 3.81) p < .001*	2.23*	2.52*

HR, Hazard Ratio; 95%CI, 95% Confidence Interval. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants.
* p < 0.05

Chapter 9. Table S5. Relationship of frailty and sarcopenia status with survival (over 10 years) stratified by sex. Complex samples Cox regression. Adjusted for: age, income, education.

	n (%)	Adjusted HR (95%CI) p-value	Male HR (95%CI) p-value	Female HR (95%CI) p-value
Total	716	-	-	-
FP Frailty & Sarcopenia Status				
Neither frail nor sarcopenic	558 (76.4)	1		
Frail only	88 (13.8)	1.78 (2.79, 8.19) p = .010*	1.48	2.17*
Sarcopenic only	40 (5.3)	1.71 (.90, 3.23) p = .100	1.49	1.88
Both frail and sarcopenic	30 (4.5)	4.78 (1.15, 2.76) p < .001*	3.51*	6.43*
FI Frailty & Sarcopenia Status				
Neither frail nor sarcopenic	362 (47.4)	1		
Frail only	284 (42.8)	2.05 (1.42, 2.96) p < .001*	2.08*	2.13*
Sarcopenic only	25 (3.3)	2.01 (.91, 4.83) p = .081	1.90	2.11
Both frail and sarcopenic	45 (6.5)	4.90 (2.84, 8.47) p < .001*	4.11*	6.22*

HR, Hazard Ratio; 95%CI, 95% Confidence Interval. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants.
* p < 0.05

Chapter 9. Table S6. Relationship of frailty (grip strength excluded from frailty measures) and sarcopenia status with survival (over 10 years). Complex samples Cox regression.

	Unadjusted HR (95% CI) p-value	Adjusted – Model 1 HR (95%CI) p-value	Adjusted – Model 2 HR (95%CI) p-value
Total	-	-	-
FP Frailty[a] & Sarcopenia Status			
Neither frail nor sarcopenic	1	1	1
Frail only	2.70 (1.60, 4.58) p < .001*	1.86 (1.05, 3.27) p = .032*	1.78 (1.02, 3.12) p = .043*
Sarcopenic only	3.45 (2.25, 5.29) p < .001*	2.36 (1.45, 3.85) p = .001*	2.41 (1.47, 3.96) p = .001*
Both frail and sarcopenic	6.89 (3.20, 14.87) p < .001*	3.60 (1.36, 9.57) p = .010*	3.57 (1.43, 8.94) p = .007*
FI Frailty[a] & Sarcopenia Status			
Neither frail nor sarcopenic	1	1	-
Frail only	2.22 (1.60, 3.09) p < .001*	2.06 (1.43, 2.96) p < .001*	-
Sarcopenic only	3.60 (1.87, 6.94) P < .001*	2.10 (0.91, 4.83) p = .081	-
Both frail and sarcopenic	7.04 (4.29, 11.53) p < .001*	4.91 (2.84, 8.48) p < .001*	-

HR, Hazard Ratio; 95%CI, 95% Confidence Interval. FP categories: 0-2 characteristics, non-frail; ≥3 characteristics, frail. FI categories: 0 to ≤ 0.21 deficits, non-frail; > 0.21 deficits, frail. Sarcopenia categories: 0-1 characteristics, not sarcopenic; 2 characteristics, sarcopenic. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016, with a minimum of 10 years of mortality data for all participants.
Model 1 - Adjusted for: age, sex, income, education.
Model 2 - Adjusted for: age, sex, income, education and multimorbidity.
[a] Weak grip strength is excluded from frailty measure.
* p < 0.05

Supplementary Material Chapter 10

Chapter 10. Table S1. FRAIL Scale and Frailty Phenotype variables.

Variable	Description
FRAIL Scale	
Fatigue	During the past 4 weeks did you feel tired? (SF36, q31) A good bit, some, a little, or none of the time = 0; all, or most of the time = 1.
Resistance	Health limits you in climbing one flight of stairs? (SF36, q7) Not limited = 0; a little or a lot = 1.
Ambulation	Health limits you walking half a kilometre? (SF36, q10) Not limited = 0; a little, or a lot, = 1.
Illnesses	of the following 11 chronic conditions: Angina, Heart attack, Osteoporosis, Osteoarthritis, Hypertension, Rheumatoid/osteo/other arthritis, Stroke or TIA, Diabetes, Any mental health problem, emphysema, asthma. 0-4 conditions = 0 and 5-11 conditions = 1
Loss of weight	>10% weight loss over 4 years (clinic measurement: Phase 1 and Phase 2)
Frailty Phenotype	
Weight loss	>10% weight loss over 4 years (clinic measurement: Phase 1 and Phase 2)
Weakness	Grip strength (kg) measured using dynamometer in the lowest 20% at baseline stratified by sex and body mass index (BMI) quartiles. Male $BMI \leq 24$, Grip ≤ 29 BMI 24.1-26, Grip ≤ 30 BMI 26.1-28, Grip ≤ 30 BMI > 28, Grip ≤ 32 Female $BMI \leq 23$, Grip ≤ 17 BMI 23.1-26, Grip ≤ 17.3 BMI 26.1-29, Grip ≤ 18 BMI > 29, Grip ≤ 21
Exhaustion	Two questions used from the CES–D Depression Scale. How often in the last week did you feel: a) I felt that everything I did was an effort, b) I could not get going. Scoring: rarely or none (0), some or a little (1), moderate (2), most (3). Characteristic present when answering "2" or "3" to either question.
Slowness	Self-report to the question: Health limits you a lot walking 100m. (SF36 q11)
Low Activity	Australian Bureau of Statistics National Health Survey. <100 Metabolic Equivalents (METs) per week.[30]

Chapter 10. Table S2. Cross tabulation of FRAIL Scale (number of characteristics present) against Frailty Phenotype.

Index Test	Reference Standard Frailty Phenotype		
FRAIL Scale ≥3	Condition +ve	Condition -ve	Total
Test +ve	100	91	191
Test -ve	58	597	655
Total	158	688	846
FRAIL Scale ≥2	Condition +ve	Condition -ve	Total
Test +ve	151	247	398
Test -ve	7	441	448
Total	158	688	846
FRAIL Scale ≥1	Condition +ve	Condition -ve	Total
Test +ve	156	405	561
Test -ve	2	283	285
Total	158	688	846

n reported using cohort case weights. Frailty Phenotype (number of characteristics):
0, non-frail; 1-2, pre-frail; ≥3, frail.

Supplementary Material Chapter 11

Chapter 11. Table S1. Frailty Phenotype and Frailty Index Variables

Frailty Phenotype	Frailty Index (34-item)	
Weight Loss: > 10% weight loss over four years (clinic measurement)	Angina	Health limits lifting or carrying groceries
	Heart attack	Health limits climbing several flights of stairs
	Osteoporosis	
Weakness: original method	Osteoarthritis	Health limits climbing one flight of stairs
Exhaustion: original method	Rheumatoid and any other arthritis	Health limits bending, kneeling or stooping
Slowness: Self-report 'a lot' to health limits walking 100m (SF36 q11)	Stroke or TIA	
	Diabetes	Health limits walking more than 1km
	Any mental health problem	Health limits walking 100m
Low Activity Level: Australian Bureau of Statistics National Health Survey (< 100 METs per week)	Systolic blood pressure	Felt lonely
	Diastolic blood pressure	Felt that could not get going
	10% weight loss over 4 years	Difficulty keeping mind on what you were doing
	FEV1/FVC post ratio	
	Weak grip strength	Felt everything was an effort
	Falls	Physical & emotional problems interfered with social activities
	Hospital emergency admission	
	Low activity level (<100 METs per week)	Felt full of life
	Healthy as anybody I know	Felt calm and peaceful
	Health is excellent	Felt worn out
	Self-reported health	Felt tired

METs, metabolic equivalent of task; SF36, 36-Item Short Form Health Survey; TIA, transient ischaemic attack; FEV1/FVC, forced expiratory volume/forced vital capacity

Appendices

Appendix A: Article published in *Australian Doctor*

Thompson, M. Q., Bollen, C., & Visvanathan, R. (2019). A strategy for frailty. *Australian Doctor* (22 March 2019), 23-24.

Appendix B: Systematic review protocol

Ambagtsheer, R. C., Thompson, M. Q., Archibald, M. M., Casey, M. G., & Schultz, T. J. (2017). Diagnostic test accuracy of self-reported frailty screening instruments in identifying community-dwelling older people at risk of frailty and pre-frailty: a systematic review protocol. *JBI Database System Rev Implement Rep*, 15(10), 2464-2468. doi:10.11124/jbisrir-2017-003363

Appendix C: Poster – Frailty state transitions

Thompson, M. Q., Theou O., Yu, S., Tucker, G., Adams, R., Visvanathan, R. (2018) *Frailty state transitions and associated factors in South Australian older adult.* Poster presented at the Australian & New Zealand Society for Geriatric Medicine Annual Scientific Meeting. Sydney, Australia.

Appendix D: Poster – Frailty recurrent measurement

Thompson, M. Q., Theou O., Yu, S., Tucker, G., Adams, R., Visvanathan, R. (2019) *Recurrent measurement of frailty is important for mortality prediction: Findings from NWAHS.* Poster presentation at Australia and New Zealand Society for Sarcopenia and Frailty Research annual meeting. Sydney, Australia.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Mark Q Thompson	
Contribution to the Paper	Literature review, wrote manuscript, coordinated review / feedback by co-authors, updated manuscript drafts.	
Overall percentage (%)	65%	
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.	
Signature		Date 25/1/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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A strategy for frailty

Geriatrics

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There are a number of strategies to minimise and mitigate frailty in the older population. Here's a good approach for GPs to adopt for this cohort.

AUSTRALIA'S population is ageing, with the proportion of individuals aged 65 and older expected to increase from a current 16% to an estimated 19% of the population by 2031, and to a possible 25% in 2061.[1] The largest proportional growth expected is in those aged over 85.[1]

Understanding frailty is a key priority in maximising the health of this demographic.[2] GPs play a crucial role in the recognition and management of frailty, as well as promoting healthy ageing through integrated and patient-centred care.[2] This article gives an overview of the often unrecognised health issue of frailty, its trajectory and complications, and describes strategies for identification and management.

What is frailty?

Frailty represents a vulnerability arising from a decline across a range of physiological systems resulting in decreased physiological reserve, putting the older person at risk of adverse health outcomes when faced with stressors such as illness.[3,4]

Frailty is a useful concept for explaining the diversity of ageing, where some individuals of the same age remain robust and active while others experience substantial deterioration in their health with loss of independence. Frailty is distinct from multimorbidity and disability, but all three may present concurrently in some older adults.[5]

Why look for frailty?

The timely identification and management of frailty in the primary care setting is important as this condition is associated with a range of adverse health outcomes including geriatric syndromes such as falls and delirium, hospitalisation, decreased quality of life, cognitive impairment, disability, admission to residential aged care, and mortality.[2,4]

Trajectory of frailty

Frailty is a dynamic process where a majority of individuals are likely to remain stable, but the most common change is to a worse state.[6] Not everyone declines, however, and there are interventions available to reverse

or delay frailty.[7] A number of factors are associated with worsening frailty trajectory including increased age, cognitive impairment, obesity, and the presence of chronic conditions.[6,8,9]

Frailty assessment methods

There are two main approaches to describing frailty: the phenotype model and the cumulative deficit model.[10,11]

The phenotype model defines individuals as frail where three or more deficits are identified from among five physical criteria: unintentional weight loss; exhaustion; low physical activity level; slow walking speed; and weak grip strength.[10] The physical function variables assessed through this method are similar to those assessed for sarcopenia.[12]

The cumulative deficit model counts the proportion of deficits present in an individual across a range of physical and psychological variables, which can be evaluated through a comprehensive assessment (for example, the 75+ Health Assessment), and is represented in a frailty index (FI).[11] For example, if an individual is found to have 25 deficits out of 100 evaluated, then their FI is 0.25. A higher FI represents a higher level of frailty, and those with a score above 0.21 can be classified as frail.[13]

Prevalence and associated factors

Frailty prevalence varies depending on the method of measurement used, with the cumulative deficit model typically classifying more individuals as frail than the phenotype approach.[14] Among Australian community-dwelling adults 65 and over, frailty prevalence ranges between 9% and 21% based on phenotypic measurement.[15,16] Using a cumulative deficit approach reveals a prevalence of between 18% and 48%.[14,15]

The true prevalence of frailty is likely

to be higher because residents of aged care facilities are excluded from these figures.

Comprehensive assessments

While the phenotype method has been popular for its brevity, the FI is increasingly being used in population groups where frailty is common and where an electronic health record system exists.[17]

The annual MBS-funded 75+ health assessment is an ideal framework in which to comprehensively assess an individual, confirm their frailty level, identify remediable factors, undertake investigations and then institute an appropriate management plan (for example, a chronic disease management or mental health care plan) in collaboration with the patient and their carers.

Some components can be assessed through self-report or other healthcare professionals, such as a practice nurse. Aspects of these assessments can be computed to produce an FI score.[18] Domains that could be regularly assessed include:

- Medications;
- Continence;
- Falls, osteoporosis and fractures;
- Syncope or dizziness;
- Gait, walk speed, balance and Activities of Daily Living (ADL);
- Cognition (via MMSE, RUDAS, or GPCOG);
- Mood (Geriatric Depression Scale);
- Oral health, anorexia and nutritional status (via Mini Nutritional Assessment Short Form);
- Sensory ability (vision and hearing);
- Presence of pain (via FACES or PAINAD);
- Physical activity level;
- Presence of chronic diseases;
- Blood pressure (postural hypotension or hypertension), heart rate and rhythm (atrial fibrillation);
- Immunisation status;

- Social support and transport; and
- Advance care directives.[19-25]

There are a number of potential approaches to identifying frailty in the primary care setting. One strategy is to undertake a comprehensive review, such as the 75+ health assessment in all patients aged 75 and older.

Another method is to implement a frailty screening tool. There are many to choose from, with research underway to determine the best tool for Australian general practice.[26,27] The third potential method to identify cases is to target the comprehensive assessment to older people who present with symptoms consistent with geriatric syndromes, such as falls, functional decline, weight loss, polypharmacy or cognitive decline. While some screening instruments are useful to identify frailty risk, they are perhaps less helpful in guiding intervention to reverse or delay frailty.[28]

A number of short and easy-to-administer tools have been identified as practical for use in identifying frailty in the general practice setting.[28] These include:

- The Clinical Frailty Scale (see figure 1).[29]
- The Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight (FRAIL) Scale (see box 1).[30]
- For the residential aged care setting, the FRAIL-NH has been developed and validated in Australia (see table).[31]

Intervening or preventing frailty

Patients should be engaged in setting goals based on the needs that are most important to them.[32] As most frailty interventions require some form of behaviour change, using the principles of motivational interviewing and working collaboratively with patients is critical for success.[33]

Exercise and nutritional strategies (especially increasing protein intake) are core strategies in the prevention and treatment of frailty.[7] Older people are keen to know more about exercise and, importantly, have expressed a desire to be kept informed and encouraged by their GP.[34]

Exercise interventions also have positive effects on falls reduction, balance, mobility, mood and functional ability.[35] Group exercise programs can provide opportunities for socialisation, which has its own beneficial effects and contributes to adherence.[36]

Exercise programs should be multicomponent, involving a combination of resistance, balance, and flexibility.[37] Strength training is emphasised as a key component of exercise.[7] Online exercise prescribing resources are available to aid decision-making.[38]

There is evidence to recommend protein supplements in combination with exercise to improve frailty status, muscle strength and mobility of older adults.[39] The optimal daily protein intake for older people should be at least 1.0-1.2g/kg/day with an increase to 1.2-1.5g/kg/day in those who are unwell or with chronic disease (including dialysis).[40]

For those with severe kidney disease (GFR less than 30mL/min/1.73m^2), protein intake should be less than 0.8g/kg/day. For those with moderate kidney disease, the protein intake can be higher than this, but regular monitoring is required for those with GFR above 30 but less than 60mL/min/1.73m^2.

Additionally, strategies to minimise polypharmacy are an important component of the medical management of older adults who are both frail or at risk of becoming frail.

Medications with an anticholinergic effect (for example, antihistamines, tricyclic antidepressants, major tranquillisers, old and atypical antipsychotics, and antimuscarinics for urinary incontinence) are highlighted as being associated with frailty after adjusting for polypharmacy in general.[41]

The 2015 updated Beers Criteria (which identifies medications noted by an expert panel to have potential risks that outweigh potential benefits) is a useful reference for

identifying inappropriate medication for older adults.[42]

When reviewing medications, it is important to optimise vitamin D. Low vitamin D is a modifiable factor associated with frailty, through the dysregulation of proinflammatory cytokines.[43] Older adults with low vitamin D levels (below 30ng/mL) are, therefore, likely to benefit from supplementation, especially where osteoporosis is present.[3]

A tailored approach to monitoring and intervention is recommended depending on the stage of frailty progression.[44] Robust individuals would benefit from primary prevention strategies focused on minimising risk factors such as hypertension, smoking, cholesterol, and ensuring vaccinations are up-to-date.

Meanwhile, pre-frail individuals may require secondary prevention strategies such as chronic disease management, geriatric assessment and falls prevention. Frail individuals could benefit from rehabilitation, geriatric management, symptom management,

and strategies to maintain function and quality of life including rehabilitation.[44]

This approach will involve linking patients to relevant support services via Medicare (allied health), My Aged Care (allied health and support services), local gyms, pharmacy, geriatricians, and geriatric outpatient services. GPs or practice nurses co-ordinating these referrals can find information through primary healthcare networks frailty referral pathways under HealthPathways. For frail patients approaching end of life, a discussion on the goals of care is also required, considering advanced care directives, supportive and palliative care, and a transition from active treatment to comfort care.[45] ●

Conflicts

Figure 1. The Clinical Frailty Score is used to rate a patient's presentation after a usual consultation. Administration time: several minutes.

Clinical Frailty Scale*

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

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

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

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

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

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

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

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

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

Scoring frailty in people with dementia

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

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

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

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

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Table. FRAIL-NH Scale

	0	1	2
Energy	Good/Excellent	Fair	Poor
Transferring	Moves in and out of bed or chair unassisted; mechanical transferring aides are acceptable	Needs help moving from bed to chair or requires complete transfer	Needs help in moving from bed to chair or requires complete transfer and *Katz score <3
Continence	Exercises complete self-control over urination and defecation	Partially or totally incontinent of bowel or bladder	Partially or totally incontinent of bowel or bladder and *Katz score <3
Weight loss (past three months)	No weight loss	1–3 kg or does not know	>3 kg
Feeding	Gets food from plate into mouth without help; preparation of food may be done by another person	Needs partial or total help with feeding or requires parental feeding	Needs partial or total help with feeding or requires parental feeding and *Katz score <3
Dressing	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners; may have help tying shoes	Needs help with dressing or needs to be completely dressed	Needs help with dressing self or needs to be completely dressed and *Katz score <3

Non-Frail: 0–1, Frail: 2–5, most frail: 6–14.
Administration time: several minutes.
*The Katz Index assesses independence in performing activities of daily living.

Source: Journal of the American Geriatrics Society 2016; 64:e207-e212.[31]

Box 1. FRAIL Scale

- **Fatigue:** Do you feel tired all or most of the time?
- **Resistance:** Do you have any difficulty walking up 10 steps without resting?
- **Ambulation:** Do you have any difficulty walking several hundred metres?
- **Illnesses:** More than five illnesses from the following: hypertension, diabetes, cancer (not minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease.
- **Loss of weight:** Unintentional weight loss of more than 5% over the past 12 months

Individuals with three or more of the above are classified as frail.
Administration time: several minutes
Source: Journal of Nutrition, Health and Aging 2012; 16:601-608.[30]

Key messages

- As Australia's population ages, the primary care setting has a key role to play in the promotion of healthy ageing and the prevention and treatment of frailty.
- A range of frailty screening and assessment instruments are available that are quick to administer and can be self-reported by patients.
- Utilising the annual MBS 75+ health assessment makes the routine identification and management of frailty a feasible objective.
- Key frailty interventions include management of chronic conditions, minimising polypharmacy, addressing vitamin D deficiency, promoting multi-component exercise, nutritional interventions, and addressing any issues identified during a comprehensive geriatric assessment.

Statement of Authorship

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Contribution to the Paper	Contributed to protocol development, co-authored manuscript.
Overall percentage (%)	50%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

   i.   the candidate's stated contribution to the publication is accurate (as detailed above);

   ii.   permission is granted for the candidate in include the publication in the thesis; and

   iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author (Candidate)	Mark Q Thompson
Contribution to the Paper	Contributed to protocol development, co-authored manuscript.
Overall percentage (%)	40%
Signature	Date 3 ? /10 / 2017

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the secondary author of this paper.

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Signature	Date 31/10/1

Diagnostic test accuracy of self-reported frailty screening instruments in identifying community-dwelling older people at risk of frailty and pre-frailty: a systematic review protocol

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Review question/objective: The question of this systematic review is: What is the diagnostic test accuracy of self-reported frailty screening instruments among community-dwelling older people against any of the following reference standard tests: the frailty phenotype, frailty index and comprehensive geriatric assessment?

Keywords Community-dwelling older people; frailty; pre-frailty; self-reported frailty screening instruments

JBI Database System Rev Implement Rep 2017; 15(10):2464–2468.

Background

Aging is universal and inevitable, however, there is considerable variability in the health and functional abilities of individuals of the same age due to factors such as frailty, disability and chronic disease.[1] Frailty results from a cumulative decline over multiple body systems and is commonly described as a state of decreased functional reserve and reduced resistance to stressor events.[2] This increased vulnerability results in higher rates of morbidity, health service utilization and mortality.[3] Frailty is commonly observed amongst older people, and while there is currently no broad consensus on its prevalence, a meta-analysis conducted by Collard *et al.* suggested a weighted prevalence of 10.7% among those aged 65 years and over, increasing commensurately with age.[4,5]

There are currently two main approaches to defining frailty. The first is the frailty phenotype, which describes frailty as a biologic syndrome that is present when three or more of the following five physical signs are present: unintentional weight loss, self-reported exhaustion, weakness, slow walk speed and low physical activity.[6] The alternate approach is the cumulative deficits model which incorporates both physical and psychosocial variables and defines frailty as the proportion of deficits present in the individual, represented as a frailty index.[7] Despite the differences between the methods for defining and measuring frailty, the two approaches are moderately correlated.[8]

Regardless of how it is defined, frailty is a dynamic state in which individuals may move between non-frail and at-risk states, and a number of interventions have been identified which may potentially reverse or prevent frailty.[3,9] Screening for frailty in the primary care setting has been highlighted as an important component in the management of older adults to ensure that they receive timely and appropriate interventions.[9] Despite calls for widespread frailty screening of persons within the study age group, and the existence of a range of frailty measures, there is not yet a standard approach to screening for frailty.[10] One of the key challenges in frailty screening is to identify tools with high sensitivity to ensure frail individuals are correctly identified, and with high specificity to correctly diagnose non-frail individuals, so as to avoid unnecessary assessment and potential stress to patients.[11]

A number of studies have investigated the suitability of frailty screening measures and have highlighted that the different conceptual approaches and methods affect prevalence and accuracy, making comparison between instruments difficult.[12,13] Furthermore, high false positive rates, limited discriminative capability, and the limited quality of psychometric properties of different instruments mean that frailty screening is an emerging area of clinical practice.[14-16]

The use of self-report measures is another important element in frailty screening as physical measurement of frailty in the clinical setting is potentially time-consuming, and it is difficult to incorporate a comprehensive geriatric assessment into routine primary care.[12,13] Identification of a suitable, simple, self-report screening tool that reliably identifies frailty and allows referral for a more detailed assessment may avoid costs and unnecessary assessment.[10,13] The potential value of self-report measures of frailty in the primary care setting is strengthened by the finding that self-report and test-based measurement identify similar frailty characteristics.[17]

A number of systematic reviews have investigated the suitability of a variety of frailty screening measures for use in the primary care setting, however, these have focused on the performance of a combination of self-report and test-based measures.[13-15,18] A preliminary search of *JBI Database of Systematic Reviews and Implementation Reports*, The Cochrane Library, PROSPERO, PEDro, PubMed, PsycINFO, CINAHL, Scopus, Web of Science and Embase identified no listed systematic reviews either published or currently in progress investigating the diagnostic test accuracy of frailty self-report measures.

Inclusion criteria
Types of participants
Participants will be community-dwelling older people, defined as either being of a mean age in a study population of 65 years and over, or at least half of the study participants being aged 65 years and over. Studies in which participants have been recruited from hospitals but self-report measures have been used in a community setting will be included. Studies including participants who have been resident in a residential care facility (long-term care or nursing home) will be excluded.

Index test
The index tests for this review will be all currently available, diagnostic tests intended to identify frailty using self-report measures. Some examples of these self-report frailty instruments include the Reported Edmonton Frail Scale[19] and the Kihon Checklist.[20]

Reference standards
The reference standards for this review will be the Frailty Phenotype,[6] the Frailty Index[7] and/or Comprehensive Geriatric Assessment.[21]

Diagnosis of interest
The diagnosis of interest is presence of frailty or pre-frailty.

Types of studies
This review will consider all observational, cross-sectional studies assessing the diagnostic test accuracy of self-reported frailty screening instruments against one or more of the specified reference standards. It will include studies in which the self-report frailty instrument has been completed by a family member or nominated person on behalf of the older person as well as studies where the older person has completed the instrument himself/herself.

Search strategy
The search strategy aims to find both published and unpublished studies. The search strategy will use MeSH (Medical Subject Headings) terms and relevant keywords and will be adapted as appropriate to each database.

A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken, followed by analysis of the key text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Only studies published in English will be considered for inclusion in this review. In terms of timeframe, only studies published from 1 January 2000 to the present will be considered for inclusion in this review. This date has been selected as both the physical phenotype and accumulated deficits models of frailty were first published in 2001.

The databases to be searched will include MEDLINE/PubMed, PEDro, Embase, PsycINFO, CINAHL, Scopus and Web of Science.

Searches for unpublished studies will be performed using ProQuest (Dissertations), Open Grey and The Grey Literature Report database. Research centres with a focus on gerontology will also be identified via a keyword search and expert consultation, and their websites examined for additional studies of interest.

Initial keywords to be used will be:

1. Search for frailty: frail* OR prefrail*
2. Search for self-report: self-report*, diagnostic self-evaluation, postal, self-diagnos*, survey*, questionnaire*, reported, self-assess*, self-test*, OR self-admin*
3. Search for screening tools: screen*, instrument*, tool*, OR index
4. Search for specific screening tools: eg Kihon Checklist OR Reported Edmonton Frail Scale

Items 1, 2 and 3 will be joined with search operator AND item 4 to be joined to 1–3 with OR.

Assessment of methodological quality

Quantitative papers selected for retrieval will be assessed by two independent reviewers (RA and MT) for methodological validity prior to inclusion in the review using the JBI Critical Appraisal Checklist for Diagnostic Test Accuracy Studies[22] in association with the QUADAS 2 (Quality Assessment of Diagnostic Accuracy Studies) tool.[23] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (TS).

Data extraction
Data management

Initial literature search results will be compiled by one reviewer (RA) and uploaded to Mendeley Reference Manager (Mendeley Ltd., Elsevier, Netherlands) to aid in the process of removing duplicates. A final unique list of studies, along with abstracts, will be exported to Microsoft Excel, where the first stage of the selection and screening of studies will take place.

Selection process

In order to select studies for inclusion, two reviewers (RA and MT) will review the literature search results independently in a two-step process. In the first step, the titles and abstracts will be reviewed for eligibility against the inclusion criteria. In the second, the full text of the articles will be obtained and reviewed for consideration of inclusion. A record will be kept of the reason for exclusion against each study. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (MC) where appropriate. Study authors will be contacted should additional information be required.

Data items

Quantitative data will be extracted from papers included in the review by two independent reviewers (RA and MT) using the standardized data extraction tool from the Joanna Briggs Institute (JBI),[22] which incorporates most elements of the STARD (Standards for Reporting of Diagnostic Accuracy) checklist, and entered into a standardized template within Microsoft Excel. Calibration exercises will be conducted prior to commencement of the extraction to ensure a consistent approach across reviewers. The data extracted from each eligible study will include specific details about the populations, index and reference tests, study methods, index test results and outcomes of significance to the review question. Study authors will be contacted for additional information where necessary to resolve any outstanding issues or ambiguities.

Data synthesis

Graphic representation of the results of the systematic review will take the form of forest plots showing sensitivity and specificity for the primary studies included in the review. We will report the number of true positives, false positives, true negatives and false negatives in tabular format.

A sub-group analysis will be used to compare the diagnostic capabilities of the tests, diagnostic capabilities based on significant covariates identified in the included studies. For example, a study may report results separately for different patient age groups, gender or testing conditions.

With regard to meta-analysis, the study will adopt this basic approach as outlined in the relevant JBI literature:[22] if the same threshold is used through the primary studies, then we will estimate the summary sensitivity/specificity. If it is determined that different thresholds have been used, then we will produce a summary receiver operating

characteristic (SROC) curve and estimate the summary sensitivity/specificity for the different thresholds used in the articles.

The model used to perform the meta-analysis will be the Bivariate Model,[24] a hierarchical model recommended by the Cochrane Handbook.[25] The review team will follow the approach reported in Romano et al.[26] and use the Stata "metandi" command to compute the summarized data.

Heterogeneity between studies will be initially assessed with reference to the graphical representation of results outlined above and explored using subgroup analyses based on the different quantitative study designs included in this review. Where the extent of heterogeneity cannot be explained, the findings will be presented in a narrative form including tables and figures to aid in data presentation where appropriate.

Acknowledgements

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Frailty State Transitions and Associated Factors in South Australian Older Adults

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Background

Frailty represents a decline across multiple physiological systems, making individuals more vulnerable to stressor events and at a greater risk of adverse health outcomes.[1] Frailty is a dynamic process where improvement is possible.[2-5] Even so, transition to a worse frailty level is more common than improvement,[2,4,5] and remaining in a stable frailty state is the most common outcome.[2,3] Understanding the natural course of frailty and the characteristics of those most at risk of worsening or likely to improve their frailty status may be considered key elements in maximising the health, functioning, and wellbeing of individuals in our ageing populations.[1]

Aims

The aims of this study were to examine the transitions between frailty states for a cohort of older Australian adults using both the Frailty Phenotype and Frailty Index and to describe the characteristics associated with frailty status improving, remaining stable, or worsening.

Methods

Sample and Study Design

This study was a secondary analysis for data from the North West Adelaide Health Study (NWAHS), a population-based longitudinal study of community dwelling adults aged ≥18 years living in the North West of Adelaide, South Australia.[6] Stage 2 (2004-06) was used as the baseline for this study and only participants aged ≥ 65 years at the time of attending clinic stage 2 were included. Follow-up of participants for stage 3 occurred in 2008-10, with 4.5 (.45) years mean follow up.

Frailty Measurement

Both the Frailty Phenotype[7] and Frailty Index[8] were used to measure frailty status at baseline and follow-up.

Frailty Phenotype	Frailty Index
Variables: Weight loss, Weakness, Exhaustion, Slowness, Low Activity. **Cut Points:** Robust, 0; Vulnerable, 1-2; Frail, ≥3.	**Variables:** a combination of 34 clinic-based and self-report variables were used. Each variable scored 0-1. **Cut Points:** Robust, 0 to ≤.10; Vulnerable, >.10 to ≤.21; Frail, >.21

Statistical Analysis

Multivariate logistic regression was performed to examine the relationship between frailty state transitions and covariates. Covariates included in the analysis: Sex; age group (65-74 years, and ≥75 years); Multimorbidity (≥2 chronic conditions); Obesity (waist circumference male >102cm, female >88cm); Polypharmacy (≥5 medications); Living arrangements (alone or with others).

Results

Study Participants
Baseline Descriptive Characteristics and Frailty Classification

Mean age 73.4 (6.1) years; 53.1% female; n = 93 excluded due to insufficient variables; n = 120 lost to follow-up.

Frailty State Transitions

A number of participants **improved** their frailty state. Remaining **stable** was the most common frailty state transition for both the FP and the FI. The next most likely state transition was to a **worse** frailty state which also included death. When participants transitioned to a different frailty state (improved, worsened, or dead) this was most typically to a state adjacent their baseline classification.

|	Whole sample n (%)	Frailty Phenotype Categories			Frailty Index Categories		
		Robust n (%)	Vulnerable n (%)	Frail n (%)	Robust n (%)	Vulnerable n (%)	Frail n (%)
Total	696	233 (32.0)	357 (51.7)	106 (16.3)	175 (23.2)	219 (31.2)	302 (45.6)
Sex							
Male	353 (46.9)	127 (35.7)	179 (50.5)	47 (13.8)	98 (27.3)	115 (33.2)	140 (39.5)
Female	343 (53.1)	106 (28.5)	178 (52.9)	59 (18.6)	77 (19.4)	104 (29.4)	162 (51.2)
Age Groups							
65-74 years	442 (59.9)	171 (37.3)	234 (53.3)	37 (9.4)	129 (28.6)	152 (33.7)	161 (37.7)
≥75 years	254 (40.5)	62 (24.0)	123 (49.5)	69 (26.5)	46 (15.2)	67 (27.5)	141 (57.2)

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Key Findings

- Frailty is a dynamic process where improvement was possible.
- Multimorbidity, obesity, age and sex were associated with frailty transitions for both tools.
- Improvement in frailty state was common for both tools (FP 15.5%; FI 7.9%).
- The majority of participants remained stable (FP 44.4%; FI 52.6%), and many transitioned to a worse level of frailty (FP 40.1%; FI 39.5%).
- Among robust participants, multimorbidity was associated with worsening frailty for both measures.
- Among vulnerable participants, normal waist circumference was associated with improvement, whereas older age was associated with worsening of frailty status.
- Among frail individuals, younger age was associated with improvement, and male sex and older age were associated with worsening frailty status.
- These factors pose different risks for frailty transition at different stages of the frailty process, as does frailty classification itself and, hence, suggests a tailored approach in targeting vulnerable individuals.

Frailty State Transitions between Baseline and Follow-up
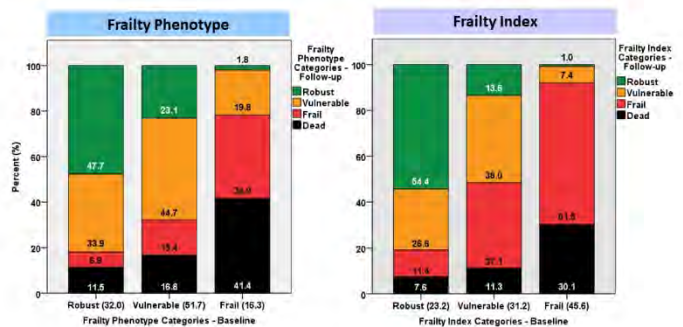
Covariates associated with IMPROVEMENT in frailty status at follow up

Baseline frailty status	Frailty Phenotype	Frailty Index
Vulnerable	less likely to improve... **Obesity** OR = .37 (.20, .68)* **Polypharmacy** OR = .42 (.22, .81)*	less likely to improve... **Obesity** OR = .25 (.09, .74)*
Frail	-	less likely to improve... **Older age** OR = .13 (.03, .65)* **Multimorbidity** OR = .11 (.02, .67)*

Covariates associated with WORSENING in frailty status at follow up

Baseline frailty status	Frailty Phenotype	Frailty Index
Robust	more likely to worsen... **Multimorbidity** OR = 4.20 (1.78, 9.89)*	more likely to worsen **Multimorbidity** OR = 5.74 (1.21, 27.09)* **Obesity** OR = 2.24 (1.06, 4.76)* less likely to worsen... **Living Alone** OR = .37 (.15, .93)*
Vulnerable	more likely to worsen... **Older Age** OR = 3.06 (1.72, 5.47)* less likely to worsen... **Obesity** OR = .54 (.30, .97)*	more likely to worsen **Older Age** OR = 3.55 (1.56, 8.05)*
Frail	more likely to worsen... **Male** OR = 3.91 (1.01, 15.14)* **Older Age** OR = 6.74 (1.66, 27.33)*	more likely to worsen... **Male** OR = 3.22 (1.50, 6.92)* **Older Age** OR = 6.40 (2.95, 13.86)* **Living Alone** OR = 2.70 (1.23, 5.92)*

Odds Ratio (95% Confidence Interval), * P < 0.05

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Recurrent Measurement of Frailty is Important for Mortality Prediction: Findings from NWAHS

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Background

Frailty represents a state of decreased physiological reserve which places individuals at a greater risk of adverse outcomes.[1] Despite the negative perceptions associated with frailty, it is possible for frailty status to improve or to remain stable over time.[2] This is pertinent as interventions exist that may slow or reverse the frailty process.[3] Frailty has been identified as a significant long-term predictor of mortality, with predictive strength best over a shorter follow-up,[1] potentially due to the dynamic nature of frailty where change is likely over time.[4] Whilst clinicians increasingly recognise the need for assessing frailty status,[5] review of frailty status following intervention requires just as much attention..

Aims

The aims of this study were to examine the predictive ability of frailty classification for mortality over 10 years, and the effect of recency of frailty measurement (at follow-up 4.5 years later) on mortality prediction for the FP and FI.

Methods

Sample and Study Design

This study was a secondary analysis for data from the North West Adelaide Health Study (NWAHS), a longitudinal study of community dwelling adults living in the North West of Adelaide, South Australia.[6] Stage 2 (2004-06) was used as the baseline for this study and only participants aged ≥ 65 years at the time of attending clinic stage 2 were included. Follow-up of participants for stage 3 occurred in 2008-10, with 4.5 (SD 0.45) years mean follow up.

Statistical Analysis

Survival modelling used complex samples cox regression, with hazard ratio (HR) reported. Multivariable analysis was performed combining frailty classification at baseline and follow-up, and adjusted for sex, age group, education, & income. Logistic regression was performed to estimate predictive probability of surviving 1, 2, 4, 6, 8 and 10 years to generate area under the curve (AUC) values, for frailty classification at baseline and at follow-up.

Frailty Measurement

Both the Frailty Phenotype(FP) [7] and Frailty Index (FI)[8] were used to measure frailty status at baseline and follow-up.

Frailty Phenotype (FP)

Variables: Weight loss, Weakness, Exhaustion, Slowness, Low Activity.
Continuous FP: per 1 characteristic increase
5-Category FP: 0, 1, 2, 3, 4-5 characteristics
3-Category FP: Non-frail, 0; Pre-Frail, 1-2; Frail, ≥3.

Frailty Index (FI)

Variables: 34 clinic-based and self-report variables were used. Each scored 0-1.
Continuous FI: per 0.01 proportion increase
10% Increment FI: 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, > 50%.
3-Category FI: Non-frail, 0 to ≤.10; pre-frail, >.10 to ≤.21; Frail, >.21

Results

Cohort Characteristics and Frailty Classification

Baseline: n=909 participants, mean age 74.4 (SD 6.2) years; 55% female.
Follow-up: n=549 participants had measurement at two timepoints. The 360 excluded from the returning cohort were significantly older, lower income, and had higher baseline frailty prevalence.
Baseline frailty prevalence is reported in Table 1.

Survival

Over 10 years, 34% of participants died (Figure 1).
Frailty classification was a significant long-term predictor of mortality (up to 10 years) for both the FP and FI, with **predictive strength best immediately after measurement** and predictive strength **gradually decreased over time** (Table 2). **Repeated frailty measurement at follow-up resulted in improved prediction**, compared to baseline prediction.
In a multivariable model that included frailty measurement at baseline and follow-up, **measurement at follow-up was associated with greater predictive strength**. Only follow-up measurement was a significant predictor for FP (Table 3), while both baseline and follow-up were significant predictors for the continuous FI and the 10% increment FI (the masked coefficient at baseline was dominated by follow-up coefficient).
Controlling for this in a model that included **frailty change**, each 1% increase or decrease in the FI was associated with a corresponding 4% change in mortality risk.

Figure 1. Mortality rates (proportion dead) over 10 years by baseline frailty status for the FP and FI.

Frailty Phenotype
a) 3-Category Frailty Phenotype
b) 5-Category Frailty Phenotype

Frailty Index
c) 3-Category Frailty Index
d) 10% Increment Frailty Index

Table 3. Frailty classification (FP and FI) at baseline and follow-up and mortality risk (hazard ratio) for the returning sample.

Returning Sample (n = 549)	Baseline Adj HR (95%CI)	Follow up Adj HR (95%CI)
Frailty Phenotype (FP)		
Continuous FP per 1 score	.96 (.76-1.21)	1.59 (1.27-2.00)*
5-Category FP		
0 characteristics (n = 207)	1	1
1 characteristic (n = 188)	.86 (.47-1.58)	.91(.45-1.86)
2 characteristics (n = 100)	.68 (.33-1.40)	1.98 (.96-4.07)
3 characteristics (n = 45)	1.05 (.47-2.37)	2.97 (1.33-6.63)*
4-5 characteristics (n = 9)	.62 (.14-2.66)	6.24 (2.47-15.81)*
3-Category FP		
Non-Frail (n = 207)	1	1
Pre-frail (n = 288)	.90 (.53-1.55)	1.28 (.69-2.37)
Frail (n = 54)	1.16 (.55-2.43)	3.35 (1.65-6.79)*
Frailty Index (FI)		
Continuous FI per .01 score	.96 (.94-.98)*	1.07 (1.04-1.09)*
10% Increment FI		
0-10% (n = 160)	1	1
10-20% (n = 177)	.62 (.31-1.24)	2.55 (1.00-6.46)*
20-30% (n = 106)	.63 (.29-1.40)	4.82 (1.83-12.69)*
30-40% (n = 59)	.46 (.18-1.18)	5.53 (1.92-15.95)*
40-50% (n = 36)	.31 (.10-.98)*	9.52 (3.16-28.69)*
> 50% (n = 11)	.30 (.06-1.51)	21.62 (6.11-76.47)*
3-Category FI		
Non-Frail (n = 160)	1	1
Pre-frail (n = 191)	.67 (.34-1.33)	2.42 (.95-6.15)
Frail (n = 198)	.72 (.35-1.49)	6.08 (2.38-15.57)*

Weighted multivariable analysis adjusted for frailty at both time points, age, sex, education and income. The follow-up window for mortality was from study entry over the period 2004-2006 to a censoring date of 30/9/2016. (Minimum of 10 years of mortality data for all participants). * p < 0.05

Clinical Implications

Recurrent assessment of frailty is important as predictive ability for mortality is improved by more recent frailty classification which takes into account the dynamic nature of frailty.

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Table 1. Baseline frailty status for the Frailty Phenotype (FP) and Frailty Index (FI).

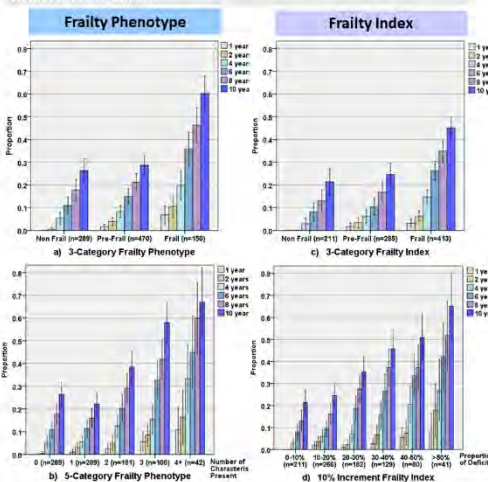| Whole Sample (n= 909)	Non-Frail n (%)	Pre-Frail n (%)	Frail n (%)
Frailty Phenotype	289 (30.1)	470 (51.6)	150 (18.3)
Frailty Index	211 (21.5)	285 (30.4)	413 (48.1)

Table 2. Discriminative ability of the Frailty Phenotype (FP) and Frailty Index (FI) at baseline and at follow-up for predicting mortality: Area Under the Curve for years survived from baseline. (adjusted for age, sex, education and income)

	Area Under Curve (95%CI)					
Whole Sample (n = 909)	1-year	2-years	4-years	6-years	8-years	10-years
FP at Baseline						
Continuous FP	.87 (.81-.94)*	.78 (.71-.85)*	.73 (.68-.79)*	.68 (.63-.73)*	.66 (.62-.71)*	.67 (.62-.71)*
5-Category FP	.87 (.80-.93)*	.78 (.71-.85)*	.73 (.68-.80)*	.69 (.64-.74)*	.67 (.63-.72)*	.67 (.63-.71)*
3-Category FP	.85 (.77-.93)*	.77 (.69-.84)*	.71 (.66-.78)*	.68 (.63-.73)*	.67 (.62-.71)*	.66 (.62-.71)*
FI at Baseline						
Continuous FI	.83 (.74-.92)*	.76 (.69-.84)*	.73 (.67-.79)*	.68 (.63-.73)*	.65 (.61-.70)*	.66 (.62-.70)*
10% Increment FI	.82 (.73-.92)*	.79 (.72-86)*	.76 (.71-.81)*	.71 (.66-.76)*	.68 (.64-.73)*	.68 (.64-.72)*
3-Category FI	.80 (.70-.90)*	.75 (.68-.83)*	.73 (.68-.79)*	.70 (.65-.74)*	.68 (.64-.72)*	.68 (.64-.72)*
Returning sample (n = 549) [a]						
FP at Follow-up			1.6-years [b]	3.6-years [b]	5.6-years [b]	
Continuous FP	-	-	.85 (.80-.91)*	.82 (.76-.88)*	.80 (.74-.85)*	
5-Category FP	-	-	.88 (.83-.94)*	.84 (.78-.90)*	.80 (.75-.85)*	
3-Category FP	-	-	.87 (.83-.91)*	.83 (.77-.88)*	.79 (.73-.84)*	
FI at Follow-up						
Continuous FI	-	-	.87 (.82-.92)*	.82 (.77-.87)*	.80 (.75-.85)*	
10% Increment FI	-	-	.87 (.82-.92)*	.85 (.80-.89)*	.81 (.76-.86)*	
3-Category FI	-	-	.85 (.80-.89)*	.83 (.78-.87)*	.80 (.75-.85)*	

AUC Discriminative Ability	
Good: 0.8 to 0.9	Acceptable: 0.7 to 0.8	Fair: 0.6 to 0.7

[a] AUC for the returning sample at follow-up (survival years from baseline).
[b] Mean years between follow-up measurement and survival years from baseline.
* p < 0.001

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