Understanding frailty and its association with medicine use

by

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Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ADL	Activity of daily living
ADR	Adverse drug reaction
AFS	Albuquerque Falls Study
ALSA	Australian Longitudinal Study of Ageing (ALSA)
AUC	Area under the curve
BDES	Beaver Dam Eye Study
BMI	Body mass index
BPOMA	Balance Performance Oriented Mobility Assessment
BRIGHT	Brief Risk Identification of Geriatric Health Tool
CCB	Calcium channel blocker
CES-D	Center of Epidemiologic Studies-Depressions
CGA	Comprehensive Geriatric Assessment
CHS	Cardiovascular Health Study
CI	Confidence interval
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CSHA	Canadian Study of Health and Aging
DBI	Drug burden index
EMA	European Medicines Agency
EPIDOS	Epidemiologie de l'osteoporose
FCA	Federal Council on Aging
FEFA	Frail Elderly Functional Assessment
FI	Frailty index
FIM	Functional Independence Measure
FiND	Frail Non-Disabled
FOD-CC	Frailty Operative Definition-Consensus Conference
FP	Frailty phenotype
FRAIL	Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight
GP	General Practitioner
GUG	Get-Up-and-Go
HR	Hazard ratio
HRCA	Hebrew Rehabilitation Center for Aged
IADL	Instrumental activities of daily living
ICS	Inhaled corticosteroid
IQR	Interquartile range
LR	Likelihood ratio
MCPS	Marigliano-Cacciafest polypathological scale
MEDLINE	Medical Literature Analysis and Retrieval System Online (US National Library of Medicine's life science database)
MMSE	Mini mental state examination
MnSq	Mean square
MPPT	Modified Physical Performance Test
NSAID	Non-steroidal anti-inflammatory drug
NPV	Negative predictive value
OR	Odds ratio
PCAR	Principal component analysis of the residuals
PFS	Prognostic frailty score
PIM	Potentially inappropriate medicine

PPV	Positive predictive value
PRISMA	Program of Research to Integrate Services for the Maintenance of Autonomy
RR	Relative risk
SABA	Short-acting beta agonist
SD	Standard deviation
SFP	Simplified frailty phenotype
SHARE	Survey of Health, Ageing and Retirement in Europe
SPPB	Short Physical Performance Battery
SWILSO-O	The Swiss Interdisciplinary Longitudinal Study on the Oldest Old
TUG	Time-Up-and-Go
US	United States
VES	Vulnerable Elders Survey
YHAP-EPESE	Yale Health and Aging Project-Established Populations for Epidemiologic Study of the Elderly

Summary

The aim of this thesis was to understand frailty assessment and its association with medicine use in an older Australian population. Frailty is a condition that has been shown to be associated with an increased risk of adverse health outcomes among the older population. While there is consensus on a definition of frailty, to date, there is no consensus on how to measure frailty.

In Chapter 1, a review of the literature on frailty measures is presented. There were 52 different frailty measures examined. Only eleven measures had been assessed for their validity, with all of the eleven measures having been examined for predictive validity while construct validity was not commonly assessed. Comparison on the performance between different frailty measures was limited.

The need to identify the best frailty measure has been included in the geriatric medicine policy of the European Medicines Agency (EMA), as part of the agency's effort to improve the quality of medicine use in the older population. In Australia, prior to the work presented in this thesis, there had been no studies that examined the prevalence of frailty and compared the validity of different frailty measures in a community-dwelling older Australian population.

In Chapter 2, a review of the literature on the association between frailty and medicine use among community-dwelling older population is presented. There has been only a small number of studies previously undertaken in the community-dwelling population, with seven articles from five different studies included in the review. Limitations with the available studies, including some studies limited to a cross-sectional design, lack of

studies among older Australians as well as limited understanding of how frailty status influences medicine use over time.

The first study of this thesis examined the prevalence of frailty in an older Australian population, using data from the Australian Longitudinal Study of Ageing (ALSA). Four internationally validated frailty measures: Frailty Phenotype, Simplified Frailty Phenotype, Frailty Index and Prognostic Frailty Score were used to measure the prevalence of frailty. The study found that the prevalence estimates of frailty varied from 2% up to 49.4% depending on the measures used. Additionally, there was minimal overlap between the measures, meaning that each frailty measure was identifying different individuals as frail. To determine which of the four measures might be the most appropriate, the subsequent studies in the thesis aimed to assess the predictive and construct validity of each measure.

In the second study, the predictive validity of the four frailty measures was examined. The validity assessment showed that being identified as frail by any of the four measures was associated with an increased risk of a combination of adverse outcomes, including: death, hospitalisation, nursing home admission, and falls. Odds ratios (95% confidence interval) for the combined outcome were 1.9 (1.4-2.8) for Frailty Phenotype, 3.6 (1.5-8.8) for Simplified Frailty Phenotype, 3.4 (2.7-4.3) for Frailty Index and 2.3 (1.8-2.8) for Prognostic Frailty Score. However, in terms of predictive performance, only the Frailty Index had acceptable sensitivity and area under the curve (AUC) values.

The construct validity of the four frailty measures was examined using Rasch analysis. The study found that of the four measures, the Frailty Index had the best construct

validity. Based on these findings, the Frailty Index was selected to be used in the studies on medicine use. The Frailty Index included comorbidity variables to assess frailty; which may introduce bias in a study assessing medicine use, particularly when medicines are used to treat comorbidity. A modification of the Frailty Index without comorbidity variables was developed and its validity was also assessed. The modified Frailty Index showed an acceptable predictive and construct validity with a high correlation to the original Frailty Index (correlation coefficient: 0.848, p-value: <0.0001).

The last study of this thesis described the association between frailty and medicine use. Frailty scores at baseline were highest in participants who used opioids and lowest in those who used statins. There was a positive association between frailty score and number of medicines used; the median frailty score increased from 0.068 to 0.208 between participants with 0 and 9 medicines respectively. The study examined whether stopping medicines at follow-up had an influence on frailty scores. There was a significantly higher increase in frailty score changes in participants who stopped using any preventive medicines compared to those who continued using the preventive medicines (p-value: 0.01). However, further study is warranted to confirm this finding; as due to limited information on the reason of stopping medicines, it was difficult to determine whether preventive medicines contributed to the lower increase in frailty scores or the progression of frailty caused the discontinuation of medicines. Prior to this thesis, studies on frailty and medicines use had not assessed the association between stopping use of medicines and frailty.

This thesis has demonstrated that the Frailty Index had the best predictive and construct validity in identifying frailty among community-dwelling older Australians. The further development of a standard and valid frailty measure that is applicable across different settings is necessary to ensure consistency in the identification of frailty. Consistently identifying frailty is essential in translating research into clinical practice which can include development of prevention or intervention programs to improve health outcomes of the older population. The thesis also identified that increasing numbers of medicines use are associated with increasing frailty and there are differences in frailty score changes over time in relation to stopping or continuing medicines. These findings suggest that there is a need for further studies to determine the risks or benefits to frailty development in continuing or stopping medicines.

Declaration

This thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, are clearly acknowledged.

Imaina Sabella Widagdo

[Signature] 29 February 2016

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- Chapter 5:
  Predictive performance of four frailty measures in an older Australian population
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- Chapter 6.1:
  Construct validity of four frailty measures in an older Australian population: A Rasch analysis
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Publication plan:

- Chapter 1:
  Characteristic and criteria of frail older persons: A review of frailty measures
- Chapter 2:
  The association between frailty and medicine use in older people: A literature review
- Chapter 6.2:
  The validity of a modified Frailty Index
- Chapter 7:
  The association between frailty and medicine use changes over time

Presentations arising out of this thesis

Invited presentation

What about frail older people?

Presented at the Australian Association of Gerontology seminar "Cutting Edge Research: South Australia's Postgraduate Research", 24th March 2014, Adelaide

Oral presentations

Characteristics and criteria of the frail elderly: A review of frailty measures

Presented at the Australian Pharmaceutical Science Association Conference, 14th December 2011, Adelaide

Prevalence of frailty and number of medicines use in elderly Australian: A comparison of four frailty measures

Presented at the Australian Pharmaceutical Science Association Conference, 4th December 2012, Sydney

Medicine use among the frail and non-frail elderly

Presented at the 8th Asian Conference on Pharmacoepidemiology, 27h October 2013, Hong Kong

The effect of medicine use on frailty over time: A case of benzodiazepines

Presented at the National Medicines Symposium Conference, 22nd May 2014, Brisbane

Construct validity of four frailty measures in an older Australian population: A Rasch analysis

Presented at the 13th National Conference of Emerging Researchers in Ageing, 24th November 2014, Adelaide

Identifying frailty: in search of the best frailty measure

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Awards arising out of this thesis

- Schulz Veterans' MATES Travel Scholarship 2012
- 8th Asian Conference on Pharmacoepidemiology Scholarship 2013
- South Australian Gary Andrews Student Award at the 47th Australian Association of Gerontology National Conference 2014

Chapter 1: Introduction

This chapter provides the background to the thesis. It begins with an overview of the ageing population and presents the definition of frailty. A review of the measures used to assess frailty in the older population is then presented. The review includes a discussion of the characteristics of the various frailty measures and their strengths and weaknesses. The chapter concludes with a discussion on the challenges in assessing frailty and the importance of measuring frailty in older populations.

1.1 Background of thesis

The world population is steadily growing older. In 1950, 8% of people were aged over 60 years, with the percentage predicted to increase to 22% by 2050 [1]. In Australia the proportion of people aged 65 years and over in 2012 was 14% and by 2061, the proportion is predicted to be around 22% of the population [2].

The growth in the older population is of concern, particularly for the health care sector as older people use a significant amount of health care services [3]. In 2013-14, 40% of hospital separations were for people aged 65 years and over, even though they only make up 13% of the national population [4]. The high use of health care services among the older population is largely due to the increased prevalence of chronic diseases in this group. It has been estimated that 80% of older Australians report having three or more chronic diseases [5]. Chronic diseases such as diabetes, heart failure or lung disease require regular monitoring of symptoms and long-term management, usually involving medicines.

Management of multiple chronic diseases often requires the use of multiple medicines, which can potentially put older people at risk of developing medicine-related problems. Age-related decline of multiple organ functions, as well as the presence of diseases may affect the pharmacokinetics and pharmacodynamics of many medicines [6-8]. Pharmacokinetic changes can result in the accumulation of toxic concentrations of medicines in the blood, whereas pharmacodynamic changes generally result in increased sensitivity to the adverse effects of medicines. Thus, medicine-related problems are common in the older population and can lead to adverse health outcomes such as hospitalisation and mortality [9-12]. It has been estimated that approximately 30% of unplanned hospital admissions among Australians aged 75 years old and over are due to medicine-related problems [13].

The presence of diseases and the use of multiple medicines have been shown to predict adverse health outcomes among the older population [10, 14]. Polypharmacy, or the use of multiple medicines, has been found to be a significant predictor of hospitalisations, mortality, and nursing home admission [14, 15]. A large multicentre United States (US) study involving older persons (mean age of 70 years) found that multiple diseases (co-morbidities) were a significant predictor of serious adverse drug reactions (ADRs), with a 12% increased risk of an ADR for every additional disease [10]. In addition, older people are not well represented in clinical trials, despite the high prevalence of medicine use among the older population [16-18]. Because of the limited availability of evidence from clinical trials, prescribing medicines to the elderly is challenging and may result in unexpected harm [16-18]. Thus, there is a need for strategies to improve the understanding of the risks and benefits of medicine use among the older population.

The older population is a heterogeneous group, with the rate of declining health varying between individuals within the same age band [19, 20]. The term frailty has been used to classify older adults with an increased risk of failing health, as evidenced by an increased risk of death or adverse health outcomes [21-23]. Given that frailty and medicine use are both common among the older population and that both frailty and medicine use are commonly associated with adverse events, there is a need to understand the relationship between the presence of frailty and the use of medicines in older people. This thesis will examine the assessment of frailty and its association with medicine use. In the next section of this chapter, frailty is defined, as are methods for its assessment, and the potential significance of frailty to studies of medicine use.

1.2 What is frailty?

1.2.1 Frailty definition

The term frailty was originally used by the US Federal Council on Aging (FCA) in the 1970s to categorise a specific group within the older population that may require additional health care services [24]. In 1978 FCA defined the frail elderly as 'persons, usually but not always, over the age of 75 years, who because of an accumulation of various continuing problems often require one or several supportive services in order to cope with daily life' [24]. Since then research into frailty has been growing. The number of MEDLINE, publications with the medical subject heading (MeSH) 'frail elderly' increased from one in 1980 to just over 1000 by the year 2000 [24] and over 8000 publications by 2015. Across this time the definition of frailty has changed, with more than 20 different definitions being published [24-27]. Table 1.1 lists examples of frailty definitions over time. In 2011, a multinational team of experts from the Frailty Operative Definition-Consensus Conference (FOD-CC) agreed to the following standard definition of frailty: '*a multidimensional syndrome characterized by*

decreased reserve and diminished resistance to stressors' [23]. An important aspect of this standard definition is the recognition of the syndrome as multidimensional.

Table 1. 1 Examples of the earlier definitions of frailty

Definitions of frailty
Woodhouse 1988 [28]
'The frail elderly are individuals, over 65 years of age, dependent on others for activities of daily living, and often in institutional care. They are not independently mobile – whilst they do not have overt cardiac, respiratory, hepatic, renal or metabolic disease minor abnormalities may be revealed on laboratory investigation. They may require regular prescribed drug therapy.'
Rockwood et al 1994 [29]
'…those in whom the assets maintaining health and the deficits threatening it are in precarious balance.'
Gobbens et al 2010 [27]
'Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes"

1.2.2 Characteristics and criteria of frail older persons: A review of frailty measures

While the FOD-CC group agreed that identifying frailty should involve a multidimensional assessment, including assessment of a physical dimension (e.g. gait speed, mobility, and nutritional status) and a psychological dimension (e.g. mental health and cognition), they could not, agree on exactly how frailty should be measured [23]. Many frailty measures had been developed prior to the FOD-CC meeting, while others have been developed since then. In the next section of this chapter a review of the frailty measures developed to date is provided. This review of the literature aimed to identify measures that were developed with the purpose of assessing frailty in the older population.

1.2.2.1 Literature search strategy

This literature search was conducted to compile a comprehensive list of frailty measures identified by published systematic reviews and any articles published subsequently to the systematic reviews. The electronic databases MEDLINE, Embase, CINAHL, and Scopus were searched from the start date of each database until 18 October 2015. The search strategy used MeSH terms including: 'frail elderly', 'geriatric', and 'aging', as well as the keywords including: 'screening', 'assessment', 'evaluation', 'identification', 'diagnosis', 'tool,

'instrument', and 'systematic review'. A search was also made of the frailty.net website (http://www.frailty.net/frailty-toolkit/diagnostic-tools). The search was limited to publications in English. Studies that reviewed frailty measures were selected. The identified frailty measures were excluded if there was no classification or scoring of frailty. In addition, studies of frailty measures that were conducted in a restricted population with a particular morbidity (e.g. oncology or cardiac patients) were excluded.

Nine published reviews were identified and information from the frailty.net website was obtained (Table 1.2). Overall, 66 types of frailty measure were identified. No other studies published after the systematic reviews were identified. Of the 66 measures, 14 were not included in this review: nine measures did not have frailty classifications or a scoring of frailty [30-38] and five measures were developed in a restricted older population with a particular comorbidity [39-43].

Table 1. 2 List of literature reviews on frailty measures

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
Theou and Kloseck, 2008 [44]	'To examine through a systematic review of the literature, the tools that can identify community-dwelling older adults in different stages of frailty'	Frail, classification, stage, typology, onset, pre-frail	January 1997 to March 2007	27	8 frailty measures: • YHAP-EPESE frailty measure (Speechley and Tinetti, 1991)[45] • 1994 Frailty Measure (Ho et al., 2002) [46] • CSHA rules based definition (Rockwood et al., 1999)[47] • MPPT frailty measure (Brown et al., 2000 [48], Villareal et al., 2003 [49]) • Frailty Phenotype (Fried et al., 2001) [21] • Frailty Index-CGA (Jones et al., 2004) [50] • CSHA Geriatric Status Scale (Rockwood et al., 2004) [51] • CSHA Clinical Frailty Scale (Rockwood et al., 2005) [52]	2 frailty measures: Restricted population • Frailty measure in patient with pressure ulcers (Donini et al., 2005) [39] • Palliative care frailty measure (Boockvar and Meier, 2006) [40]
Van Kan et al., 2008 [53]	'To perform a comprehensive review of the definitions and assessment tools on frailty in clinical practice and research, combining evidence derived from a systematic review of literature along with an expert opinion of a European, Canadian, and American Geriatric Advisory Panel (GAP), who met in Barcelona, Spain in May 2007.'	Frailty, frailty definition, frailty assessment, elderly older-people	n/a	41	7 frailty measures: • Frailty Phenotype (Fried et al., 2001) [21] • CSHA rules based definition (Rockwood et al., 1999) [47] • AFS frailty measure (Vellas et al., 1997) [54] • The Zutphen Study frailty measure (Chin A Paw et al., 1999) [55] • Short physical frailty measure (Gill et al., 2002) [56] • Frailty Index-CGA (Jones et al., 2004) [50] • Static and dynamic frailty index Puts et al., 2005) [57]	5 frailty measures: No frailty classification • IADL as potential frailty marker (Nourhashemi et al., 2001) [30] • SPPB frailty measure (Studenski et al., 2003 [58], Rolland et al., 2006 [59]) • Grip strength as frailty marker (Syddall et al., 2003) [32] • The Mini Nutritional Assessment (Vellas et al., 2006) [33] Restricted population • Gait speed as frailty measure in hospitalised coronary heart disease older patients (Purser et al., 2006) [41]

Table 1.2 List of literature reviews on frailty measures (cont.)

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
de Vries et al., 2011 [60]	'To assess frailty instruments on clinimetric properties and to search for the best available instrument that can be used as an evaluative outcome measure in clinical practice and that is useful in observational and experimental studies.''	Frail elderly, questionnaire, self-report, self-assessment, outcome measure, and outcome assessment.	Start date of databases until 23 February 2010	n/a	18 frailty measures: • Rapid clinical screening (Winograd et al., 1991) [61] • FEFA Questionnaire (Gloth et a.,l 1995) [62] • ADL/IADL scale as frailty measure (Gealy ,1997) [63] • Modified FIM (Carlson et al., 1998) [64] • 1994 Frailty Measure (Strawbridge et al., 1998) [65] • The Zutphen Study frailty measure (Chin A Paw et al., 1999) [55] • Frailty Phenotype (Fried et al., 2001) [21] • Frailty Index (Mitnitski et al., 2001) [66] • The VES frailty measure (Saliba et al., 2001) [67] • Frailty Index-CGA (Jones et a., 2004) [50] • Groningen Frailty Indicator (Schuurmans et al., 2004) [68] • CSHA Clinical Frailty Scale (Studenski et al., 2004) [69] • French EPIDOS study frailty measure (Carriere et al., 2005) [70] • Geriatric Functional Evaluation (Scarcella et al., 2005) [71] • Static and dynamic frailty index (Puts et al., 2005) [57] • The SWILSO-O frailty measure (Guilley et al., 2008) [72] • Prognostic frailty score (Ravaglia et al., 2008) [73] • Simplified Frailty Phenotype (Kiely et al., 2009) [74]	3 frailty measures: No frailty classification • Self-report screening instrument (Brody et al., 1997) [34] • Grip strength as frailty marker (Syddall et al., 2003) [32] • Potential frailty criteria (Rothman et al., 2008) [35]

Table 1.2 List of literature reviews on frailty measures (cont.)

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
Sternberg et al., 2011 [75]	'To systematically review the literature on the identification of frailty'	Aged, frail/frailty, vulnerable/vulnerability, healthy aging/successful aging, disability/disabled persons, geriatric (methods), risk assessment, risk factors, health status indicators, disability evaluation, forecasting, patient care planning, clinical markers, health surveys, and diagnosis	1 January 1997 to 31 December 2009	22 studies	18 frailty measures: • 1994 Frailty Measure (Strawbridge et al., 1998) [65] • The Zutphen Study frailty measure (Chin A Paw et al., 1999) [55] • CSHA rules based definition (Rockwood et al., 1999) [47] • MPPT frailty measure (Brown et al., 2000) [48] • Frailty Phenotype (Fried et al., 2001) [21] • The VES frailty measure (Saliba et al., 2001) [67] • Frailty Index – 20 items (Mitnistki et al., 2002) [76] • Frailty Index-CGA (Jones et al., 2004) [50] • CSHA Clinical Frailty Scale (Rockwood et al., 2005 [52]) • French EPIDOS study frailty measure (Carriere et al., 2005) [70] • Modified BDES frailty measure (Klein et al., 2005) [77] • Static and dynamic frailty index (Puts et al., 2005) [57] • The Edmonton Frail Scale (Rolfson et al., 2006) [78] • Simplified Frailty Phenotype (Ensrud et al., 2008) [79] • Prognostic frailty score (Ravaglia et al., 2008) [73] • MCPS frailty measure (Amici et al., 2008) [80] • Frailty Phenotype with cognitive impairment (Avila-Funes et al., 2009) [81] • Modified 5 indicators (Hubbard et al., 2009) [82]	3 frailty measures: No frailty classification • Self-report screening instrument (Brody et al., 1997) [34] • Clinical judgment algorithm (Brody et al., 2002) [36] • Potential frailty criteria (Rothman et al., 2008) [35]

Table 1.2 List of literature reviews on frailty measures (cont.)

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
Pialoux et al., 2012 [83]	'To review the different tools screening for frailty in the elderly in primary health care available in the literature, to determine which is today the best instrument to assist GPs in this task, and to explore perspectives for the future'	Frail elderly, screening instrument, tool, instrument, mass screening, questionnaire, and primary health care	Start date of databases until 25 June 2011	11	8 frailty measures: • Screening letter (Barber et al., 1980) [84] • 1994 Frailty Measure (Matthews et al., 2004 [85]) • 6-item Sherbrooke postal questionnaire (Hebert et al., 1996) [86] • PRISMA-7 (Raiche et al., 2008) [87] • The BRIGHT questionnaire (Kerse et al., 2008) [88] • The Tilburg Frailty Indicator (Gobbens et al., 2010) [89] • SHARE frailty index (Romero-Ortuno et al., 2010) [90] • MCPS frailty measure (Amici et al., 2011) [91]	2 frailty measures: No frailty classification • Functional assessment screening package (Moore et al., 1996) [37] • Screening instrument (Maly et al., 1997) [38]
Bouillon et al., 2013 [92]	'To provide a comprehensive catalogue of existing frailty measures; review evidence on the validity and reliability of these measures; and quantify the popularity of each frailty measure by investigators other than the originators'	Frailty	1948 to May 2011	27	24 frailty measures: • YHAP-EPESE frailty measure (Speechley and Tinetti, 1991) [45] • 1994 Frailty Measure (Strawbridge et al., 1998) [65] • ADL and self-reported health as frailty measure (Dayhoff et al., 1998) [93] • CSHA rules based definition (Rockwood et al., 1999) [47] • MPPT frailty measure (Brown et al., 2000) [48] • Groningen Frailty Indicator (Steverink et al., 2001) [94] • Frailty Phenotype (Fried et al., 2001) [21] • Physical frailty measure (Binder et al., 2002) [95]	2 frailty measures: Restricted population • Brief frailty index in patients with coronary artery disease (Freiheit et al., 2010) [42] • Comprehensive assessment of frailty in patients undergoing elective cardiac surgery (Sundermann et al., 2011) [43]

Table 1.2 List of literature reviews on frailty measures (cont.)

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
Bouillon et al., 2013 [92] (cont.)					• Frailty Index – 20 items (Mitnistki et al., 2002) [76] • Short physical frailty measure (Gill et al., 2002) [56] • BDES frailty measure (Klein et al., 2003) [96] • Subjective Frailty Score (Gerdhem et al., 2003) [97] • CSHA Clinical Frailty Scale (Studenski et al., 2004) [69] • Static and dynamic frailty index (Puts et al., 2005) [57] • Frailty Staging System (Cacciatore et al., 2005 [98]) • French EPIDOS study frailty measure (Carriere et al., 2005) [70] • The Edmonton Frail Scale (Rolfson et al., 2006) [78] • Modified SPPB frailty score (Bandinelli, 2006) [99] • MCPS frailty measure (Amici et al., 2008) [80] • Simplified Frailty Phenotype (Ensrud et al., 2008) [79] • The HRCA Vulnerability Index and The VES frailty measure (Kanauchi et al., 2008) [100] • The Tilburg Frailty Indicator (Gobbens et al., 2010) [89] • BPOMA and GUG test (Opasich et al., 2010) [101] • FRAIL scale (Hyde et al., 2010) [102]	

Table 1.2 List of literature reviews on frailty measures (cont.)

Study	Aim of review	Search terms	Search period	Number of studies	Number of frailty measures identified	
					Included	Excluded
Drubbel et al., 2014 [103]	'To perform a systematic review of the literature and assess the psychometric properties of the Frailty Index in identifying frailty among community-dwelling older people'	Frailty, index, deficit, cumulative, accumulation	8 August 2001 to 30 October 2012	20	1 frailty measure: • Frailty Index (Mitnitski et al., 2001) [66]	
Clegg et al., 2015 [104]	'To provide information on the diagnostic test accuracy of simple instruments for identifying frailty'	n/a	January 1990 to October 2013	3	7 frailty measures: • Comparison of 5 frailty measures (Hoogendijk et al., 2013) [105] • PRISMA-7 (Hebert et al., 2009) [106] • TUG test (Savva et al., 2013) [107]	
Craig et al., 2015 [108]	'To examine the evidence of validity, reliability, and acceptability of EASY-Care'	EASY-Care/ EASYCare	January 1994 to May 2014	29	1 frailty measure: • EASY-Care (Olde-Rikkert et al 2013) [109]	
Frailty.net (http://www.frailty.net/frailty-toolkit/diagnostic-tools)					3 frailty measures: • FiND questionnaire (Cesari et al., 2014) [110] • EASY-Care (Olde-Rikkert et al., 2013) [109] • Gerontopole Frailty Screening Tool (Vellas et al., 2013) [111]	1 frailty measure: No frailty classification • SPPB frailty measure (Guralnik et al., 1994) [31]

YHAP-EPESE: Yale Health and Aging Project-Established Populations for Epidemiologic Study of the Elderly, CSHA: Canadian Study on Health and Aging, MPPT: Modified Physical Performance Test, CGA: Comprehensive Geriatric Assessment, AFS: Albuquerque Falls Study, IADL: instrumental activities of daily living, ADL: activities of daily living, SPPB: Short Physical Performance Battery, FEFA: Frail Elderly Functional Assessment, FIM: Functional Independence Measure, VES: Vulnerable Elders Survey, EPIDOS: Epidemiologie de l'osteoporose, MCPS: Marigliano-Cacciafest polypathological scale, SWILSO-O: The Swiss Interdisciplinary Longitudinal Study on the Oldest Old, BDES: Beaver Dam Eye Study, PRISMA: Program of Research to Integrate Services for the Maintenance of Autonomy, BRIGHT: Brief Risk Identification of Geriatric Health Tool, SHARE: Survey of Health, Ageing and Retirement in Europe, HRCA: Hebrew Rehabilitation Center for Aged, BPOMA: Balance Performance Oriented Mobility Assessment, GUG: Get-Up-and-Go, FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, TUG: Time-Up-and-Go, FiND: Frail Non-Disabled

1.2.2.2 Overview of frailty measures identified from the review of the literature

In this review, 52 unique frailty measures were identified across the nine published reviews as well as on the frailty.net website (Table 1.3). The Frailty Phenotype [21] and the Frailty Index [66] were the two most commonly used measures. One published review identified that the Frailty Phenotype was used in 104 studies [92] and another published review found that the Frailty Index was used in 20 studies [103]. Physical and psychological dimensions were the two dimensions that the FOD-CC recommended for assessment in a frailty measure [23]. Other dimensions, however, have also been assessed among the 52 frailty measures. The frailty dimensions assessed among the 52 frailty measures can be categorised into: physical, psychological, medical, social, and environmental dimensions. While the frailty definition specifies that frailty is a multidimensional measure, 20 of the 52 measures were uni-dimensional measures. Of the 20 uni-dimensional measures, 19 assessed the physical dimension only and one measure assessed the medical dimension only. In each of the dimensions that were assessed by the 52 frailty measures, various characteristics were measured. For example, in the assessment of the physical dimension, several factors have been measured within this dimension by various measures including: nutrition, physical activity, mobility, strength, and energy [112]. The details of the criteria assessed by each frailty measure are presented in Appendix B.

The 52 measures that were identified could be classified into four broad categories based on their assessment methods: 1) self-report (16 measures), 2) physical examination (ten measures), 3) self-report and physical examination (21 measures), and 4) clinician's judgment (five measures). All of the self-report measures included questions related to difficulties in daily activities, except for one measure, where only self-reported health was assessed to determine frailty. Table 1.3 shows the frailty measures identified from the review

of the literature based on the type of assessment method and the type of frailty dimension assessed. The next section of this chapter discusses the individual factors assessed within each dimension of the 52 measures and examines whether validated tools were used to assess individual factors, as validated tools are likely to strengthen the internal validity of the measure.

Table 1. 3 List of frailty measures

Self – report	**Physical**	**Psychological**	**Medical**	**Social**	**Environmental**
Screening letter (Barber et al., 1980) [84]	✓		✓	✓	
FEFA Questionnaire (Gloth et al., 1995) [62]	✓				
Sherbrooke postal questionnaire (Hebert et al., 1996) [86]	✓	✓	✓	✓	
Ten-item questionnaire (Gealy, 1997) [63]	✓				
ADL and self-reported health as frailty measure (Dayhoff et al., 1998) [93]	✓	✓			
1994 Frailty Measure (Strawbridge et al., 1998 [65], Ho et al., 2002 [46], Matthews et al., 2004 [85])	✓	✓			
The VES frailty measure (Saliba et al., 2001) [67]	✓				
Groningen Frailty Indicator (Steverink et al., 2001 [94], Schuurmans et al., 2004 [68])	✓	✓	✓	✓	
Geriatric Functional Evaluation (Scarcella et al., 2005) [71]	✓	✓	✓	✓	✓
The SWILSO-O frailty measure (Guilley et al., 2008) [72]	✓	✓	✓		
The HRCA Vulnerability Index and the VES frailty measure (Kanauchi et al., 2008) [100]	✓	✓			
The BRIGHT questionnaire (Kerse et al., 2008) [88]	✓	✓			
PRISMA-7 (Raiche et al., 2008 [87], Hebert et al., 2009 [106])	✓		✓	✓	
The Tilburg Frailty Indicator (Gobbens et al., 2010) [89]	✓	✓		✓	
Self-rated health as frailty measure (Hoogendijk et al., 2013) [105]	✓				
FiND questionnaire (Cesari et al., 2014) [110]	✓	✓			
Physical assessment	**Physical**	**Psychological**	**Medical**	**Social**	**Environmental**
AFS frailty measure (Vellas et al., 1997) [54]	✓				
MPPT frailty measure (Brown et al., 2000 [48], Villareal et al., 2003 [49])	✓				
Short physical frailty measure (Gill et al., 2002) [56]	✓				
BDES frailty measure (Klein et al., 2003) [96]	✓				
Grip strength as frailty marker (Syddall et al., 2003) [32]	✓				
Modified BDES frailty measure (Klein et al., 2005) [77]	✓				
SPPB frailty score (Bandinelli et al., 2006) [99]	✓				
BPOMA and GUG test (Opasich et al., 2010) [99]	✓				
TUG test (Savva et al., 2013) [107]	✓				

Table 1.3 List of frailty measures (cont.)

Mixed (Self report and physical assessment)	Physical	Psychological	Medical	Social	Environmental
YHAP-EPESE frailty measure (Speechley and Tinetti, 1991) [45]	✓	✓	✓		
Rapid clinical screening (Winograd et al., 1991) [61]	✓		✓	✓	
Modified FIM (Carlson et al., 1998) [64]	✓	✓			
The Zutphen Study frailty measure (Chin A Paw et al., 1999) [55]	✓				
CSHA rules based definition (Rockwood et al., 1999) [47]	✓	✓	✓		
Frailty Phenotype (Fried et al., 2001) [21]	✓				
Frailty Index (Mitnitski et al., 2001 [66], Mitnistki et al., 2002 [76])	✓	✓	✓		
Physical frailty measure (Binder et al., 2002) [95]	✓				
Frailty Index-CGA (Jones et al., 2004) [50]	✓	✓	✓	✓	
CSHA Geriatric Status Scale (Rockwood et al., 2004) [51]	✓	✓			
Frailty Staging System (Cacciatore et al., 2005) [98]	✓	✓	✓	✓	✓
French EPIDOS study frailty measure (Carriere et al., 2005) [70]	✓	✓		✓	
Static and dynamic frailty index (Puts et al., 2005) [57]	✓	✓	✓		
The Edmonton Frail Scale (Rolfson et al., 2006) [78]	✓	✓	✓	✓	
MCPS (Amici et al., 2008 [80], Amici et al., 2011 [91])	✓	✓	✓		
Simplified Frailty Phenotype (Ensrud et al., 2008 [79], Kiely et al., 2009 [74])	✓				
Prognostic Frailty Score (Ravaglia et al., 2008) [73]	✓	✓	✓		
Frailty Phenotype with cognitive impairment (Avila-Funes et al., 2009) [81]	✓	✓			
Modified 5 indicators (Hubbard et al., 2009) [82]	✓	✓			
FRAIL scale (Hyde et al., 2010) [102]	✓	✓	✓		
SHARE frailty index (Romero-Ortuno et al., 2010) [90]	✓				
EASY-Care (Olde-Rikkert et al., 2013) [109]	✓	✓	✓	✓	
Clinician's judgment					
Subjective Frailty Score (Gerdhem et al., 2003) [97]	✓				
CSHA Clinical Frailty Scale (Studenski et al., 2004 [69], Rockwood et al., 2005 [52])	✓	✓	✓	✓	
General Practitioner's clinical judgment (Hoogendijk et al., 2013) [105]	✓	✓		✓	
Polypharmacy as frailty measure (Hoogendijk et al., 2013) [105]			✓		
The Gerontopole Frailty Screening Tool (Vellas et al., 2013) [111]	✓	✓			

YHAP-EPESE: Yale Health and Aging Project-Established Populations for Epidemiologic Study of the Elderly, CSHA: Canadian Study on Health and Aging, MPPT: Modified Physical Performance Test, CGA: Comprehensive Geriatric Assessment, AFS: Albuquerque Falls Study, ADL: activities of daily living, SPPB: Short Physical Performance Battery, FEFA: Frail Elderly Functional Assessment, FIM: Functional Independence Measure, VES: Vulnerable Elders Survey, EPIDOS: Epidemiologie de l'osteoporose, MCPS: Marigliano-Cacciafest polypathological scale, SWILSO-O: The Swiss Interdisciplinary Longitudinal Study on the Oldest Old, BDES: Beaver Dam Eye Study, PRISMA: Program of Research to Integrate Services for the Maintenance of Autonomy, BRIGHT: Brief Risk Identification of Geriatric Health Tool, SHARE: Survey of Health, Ageing and Retirement in Europe, HRCA: Hebrew Rehabilitation Center for Aged, BPOMA: Balance Performance Oriented Mobility Assessment, GUG: Get-Up-and-Go, FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, TUG: Time-Up-and-Go, FiND: Frail Non-Disabled

1.2.3 Dimensions of frailty

1.2.3.1 Physical dimension

The physical dimension of frailty was assessed in 51 of the 52 measures (Table 1.3). Several different characteristics of the physical dimension were assessed across the different measures. The characteristics assessed within the physical dimension could be categorised as follows: mobility, nutrition, disability, physical activity, sensory ability, strength, and energy.

The frailty measures varied in regard to how physical characteristics were measured. Mobility was the most common characteristic measured within the physical dimension. In general, the purposes of the mobility assessment were to evaluate older individuals' ability to live independently and to assess their risk of falls. Sixteen frailty measures assessed mobility, but did so in a variety of ways: self-reported difficulty with walking [62, 63, 67, 72, 88, 89, 93, 94, 100, 110], direct examination of gait speed [48, 56], balance testing [54], or the use of mobility aids such as a walking stick or a wheelchair [21, 34, 35, 50, 61, 62, 64, 66, 67, 69-74, 113]. Of the criteria used to assess mobility in frailty measures, gait speed examination has been validated and widely used in the older population [114, 115]. In the older population, gait speed examination has been shown to be an important predictor of adverse events including: disability, nursing home admissions, falls, or mortality [116, 117]. Six of the reviewed frailty measures identified used a validated method of gait speed examination [56, 70, 77, 96, 99, 111]

The second most common characteristic measured within the physical dimension of frailty was disability. Of the 52 frailty measures considered, 26 considered disability. The criteria for disability assessed an individual's ability to perform daily activities. The standardised disability measures included activities of daily living (ADL) or instrumental activities of daily living (IADL) questionnaires [118]. ADL questionnaires examined the need for help in

bathing, dressing, toileting, transferring, continence, and feeding [119]. IADL measures include assessment of ability to use the telephone, shop, prepare food, do housekeeping or laundry, use public transport, take medications, and handle finances [120]. Some frailty measures used a combination of both ADL and IADL scores [34, 50, 62, 63, 67, 69, 71] and some used only ADL [61, 64, 66] or IADL [73]. Most ADL and IADL assessments included in the frailty measures did not use the complete questionnaires; only selected components of the ADL and IADL questionnaires were used. Therefore, the validity of the ADL and IADL scores included in the frailty measures when only components of the questionnaires are used is not known.

Nutrition was the third most commonly assessed physical characteristic; 18 of the 52 frailty measures included assessment of nutrition. Older people are at risk of inadequate nutrition or malnutrition due to several factors. These factors include the natural age-related reduction in appetite, the presence of chronic diseases, medicines-related weight loss, poor dentures, and inability to prepare meals [121, 122]. The prevalence of older people at risk of malnutrition was found to be as high as 46% in a multinational study that used a validated Mini Nutritional Assessment (MNA) and that was conducted among older population in variety of residential settings [123]. Malnutrition in older people has been associated with the following complications: illness, loss of muscle mass, weakness, anaemia, infection, or mortality [121, 122]. For this reason, the assessment criteria for nutrition in frailty measures are generally related to the examination of malnutrition. There is, however, no consistent standard. Several different assessment criteria, most of which are not validated, were used among the 18 frailty measures that assessed nutrition, including unintentional weight loss of three to five kg or more over a defined period of time, high or low body mass index (BMI), nutritional intake or laboratory results on protein, or plasma cholesterol levels [21, 35, 50, 55, 57, 61, 65, 66, 69-

71, 73, 74, 113]. Currently, there is no available standard to assess malnutrition in the older population.

Self-rated health was assessed in eleven frailty measures (Appendix B). Studies have shown that poor self-rated health is an important predictor of mortality among the older population [124-126]. There has, however, been limited research into the associations between self-rated health and other adverse health outcomes such as falls, hospitalisations, or nursing home admissions. The assessment criteria for self-rated health varied across the eleven measures (Appendix B). Only five of the eleven frailty measures used the version of self-rated health known to be predictive of mortality. This version contains suggested responses of "excellent, very good, good, fair, or poor". The use of different versions of self-rated health has been shown to have varying association with mortality [127]. Frailty measures that used versions of self-rated health assessment that have not been shown to be predictive of mortality are likely to be limited compared to those that use versions of self-rated health assessment known to be predictive of mortality.

1.2.3.2 Psychological dimension

Twenty-eight frailty measures included a psychological assessment (Table 1.3). The presence of a decline in cognition or low mood was the general assessment criteria. Cognition was measured using either a validated method such as the Mini Mental State Examination (MMSE) [35, 50, 57] or questionnaires on the presence of memory problems [65, 66, 71, 72, 113]. Mood was assessed using a validated depression scale including the Center of Epidemiologic Studies Depressions Scale (CES-D) [57] or the Geriatric Depression Scale [50]. The use of validated assessment tools to measure the psychological dimension of frailty is considered strength of these measures.

Differing from the physical dimension assessment, in which eleven frailty measures included the use of self-rated health, none of the 28 frailty measures that examined the psychological dimension used self-rated mental health. This could be due to the limited evidence of the validity of self-rated mental health. Only four studies were found to have examined the correlation between self-rated mental health and other measures of mental health condition, while no known studies have examined the validity of self-rated mental health in predicting mortality or other adverse health outcomes [128].

1.2.3.3 Medical dimension

Nineteen of the 52 frailty measures included a medical dimension in their assessment of frailty (Table 1.3). The assessment criteria for this dimension varied across the measures, however, the presence of one or more diseases was the most commonly used criterion [34, 50, 61, 66, 69, 71-73]. Other criteria included the use of multiple medicines [61, 69, 113] and hospital or nursing home admissions [34, 61, 69]. Examples of diseases which were considered in the frailty measures are urinary incontinence, cardiovascular diseases, and respiratory diseases. Laboratory markers of disease were used in some frailty measures [66], as were diagnostic tests including lung function tests [57] or neurological examinations [66].

An Australian study found that the burden of disease as measured using years life lost (YLL) was shown to increase with age among those with cardiovascular, neurological, and infectious disease [129]. In addition, chronic respiratory diseases were found to be one of the leading burdens of fatal disease worldwide [129]. Despite the significance of comorbidity in the quality of life among the older population, not all frailty measures included an assessment of comorbidity to measure frailty. The term frailty has been used to describe older people with multiple comorbidities [25, 130, 131]. There is an overlap between the concept of frailty

and comorbidity, in the literature [132, 133]. Further discussion of the relationship between frailty and comorbidity will be presented in the section 1.3.1.

1.2.3.4 Social dimension

The social dimension was considered in eleven frailty measures (Table 1.3). The measures assessed several characteristics of the social dimension of frailty, including availability of support services to the elderly [50, 71], social interaction [69, 71], feelings of loneliness [113], educational level [70], or financial status [61, 71]. Participation in social activities has been increasingly recognised as a component of successful ageing [134, 135], however, valid measures for assessing these characteristics are uncommon. Further research is needed to determine the indicators for social participations and their impact on health outcomes among the older population.

1.2.3.5 Environmental dimension

Two frailty measures included the assessment of an environmental dimension [71, 98], which mainly assessed criteria that related to home environmental hazards. One measure considered whether stairs or elevators were available to access the house [71] and the other measure considered potential safety issues around the house including slippery bathroom floors, lighting problems, or the positioning of rugs [98]. Environmental hazard is a potential cause of falls, with environment-related or accidental fall the most common documented reason for falls in older people. Environment-related or accidental fall was, on average, 31% across 12 large retrospective studies [136]. The cause of a fall is often multifactorial. Factors can include medical conditions, medicine use, mobility issues, as well as the presence of environmental hazards [136-138]. A systematic review found that addressing the multifactorial causes of fall has been shown to contribute to falls prevention as well as

improve physical functioning in an older population [139]. In terms of frailty assessment, most frailty measures did not consider the assessment of the environmental dimension in their measures, which may be due to environmental factor being considered as an external factor. Further research that examines whether the inclusion of environmental factors improves the performance of frailty measures is warranted.

In summary, among the 52 frailty measures reviewed, the assessment of frailty was found to include up to five dimensions: physical, psychological, medical, social, and environmental. The assessment of the physical dimension was found in 51 measures, with 20 of the 51 measures assessing the physical dimension only (Table 1.3). The criteria included in the assessment of each dimension varied between different frailty measures. In general, the criteria were included with the purpose to identify indicators of declining health as well risk factors for adverse health outcomes.

1.2.4 Methods of frailty assessment

Four types of assessment method were identified among the 52 frailty measures, with the majority of frailty measures using self-report or a combination of self-report and physical examination. Self-report as a method is susceptible to recall bias and the subjective nature of the reported outcome may make it less reliable and may affect the validity of the assessment. Self-report was used in 32 frailty measures to assess physical function and one measure used only self-rated health to assess frailty. Studies have shown that self-reported physical function was only moderately correlated to physical examination assessment [140-142] demonstrating that the two methods do not always produce the same result. Further, there is a difference in the way that men and women report difficulties in physical function. Studies have shown that women are more likely than men to report physical difficulties or limitations [143, 144]. These findings suggest that there is a higher prevalence of disability among

women than in men; however it may also reflect that men may be more reluctant to admit that they have difficulties.

In terms of measurement method, there was often an underlying difference in the purpose of self-report questions and physical examinations. Self-report questions of physical function were often used to determine the need for care or service, while physical examination was often used to obtain an objective measure of a person's physical condition [141]. In general, the use of self-report in combination with physical assessment is preferable when the tool is used for clinical assessment in a frailty measure.

The advantage of physical assessment, if undertaken using validated assessment tools, such as gait speed, is that a more reliable and comparable assessment across the population is likely to be achieved. The practicality of frailty measures that only use physical assessment may, however, be limited; because they may require significant resources to be implemented and the specialist equipment is required for assessment, they may not be able to be implemented in all locations.

Five frailty measures were based solely on the clinician's judgment (Table 1.3). Two measures assessed frailty based only on the clinician's impression of an older person [97, 105], which, similarly to self-reported measures, may result in biased subjective assessments. This is because different clinicians may have different interpretations on the impression of a frail older person. Two measures included a validated questionnaire for clinicians to use [69, 111].

1.2.5 Determination of frailty

As shown in the previous section, variations exist in both the dimensions included in the frailty measures and the actual components measure within those dimensions. Differences were also found in the way that each measure actually categorised subjects as frail or not frail. In general, there were two different methods used among the 52 frailty measures: criteria-based definitions [21, 34, 35, 50, 55, 57, 61, 62, 65, 69, 72-74, 145] or score-based definitions [63, 64, 66, 67, 70, 71, 113]. A criteria-based definition determined frailty as the presence of one or more factors of interest. For example, the Frailty Phenotype classifies individuals as frail if they meet three or more of the following five criteria: weight loss, low grip strength, exhaustion, slow walking time, and low physical activity [21]. For the score-based definitions, individuals are considered frail based on the scores obtained from the assessed factors [63, 64, 66, 67, 70, 71, 113]. The Frailty Index is an example of a score-based frailty measure; where an individual with a calculated score of 0.25 or greater is considered frail [146]. Another example is a measure that included 32 items with negative and positive scores that makes up a total score that ranged from -118 to +91, older persons are considered severely frail if they have a total score of <10, frail if they have a total score of 10-20, moderately frail if they have a total score of 21-40, and robust if they have a score >40 [71].

1.3 Challenges in the assessment of frailty

1.3.1 The relationship between frailty, comorbidity, and disability

Frailty, comorbidity, and disability have been used interchangeably to categorise vulnerable older patients; some frailty measures have included comorbidity or disability as criteria of frailty whilst others have not [24, 147-149]. In 2012, the FOD-CC experts agreed that frailty and disability are not interchangeable, however, no consensus was reached on the association between frailty and comorbidity [23].

Two studies have assessed the relationship between frailty, comorbidity, and disability [21, 133]. An analysis of data from the Cardiovascular Health Study (CHS) examined the overlap between frailty, comorbidity (defined as having two or more comorbid disease), and disability (defined as having one or more difficulties with ADLs [21]. The Frailty Phenotype was used as the frailty measure in the study and there was no disability criteria included in the Frailty Phenotype. The findings were that 22% of frail older people also had comorbidity and disability; 46.2% of participants had both frailty and comorbidity, 6% had both frailty and disability, and 27% were frail without comorbidity or disability [21]. Another study from the Canadian Study of Health and Aging (CSHA), using a modified Frailty Index that excluded comorbidity and disability variables [133], found a higher overlap between frailty, comorbidity (defined as having two or more chronic diseases) and disability (defined as having at least one difficulty with ADLs); 48% of frail participants had both comorbidity and disability; 25% had frailty and comorbidity, 19% had frailty and disability, and 9% had frailty only [133]. The CSHA study did not report the overall proportion of frail participants. The extent of overlap between frailty, comorbidity, and disability as shown in the two studies suggests that the three concepts are interrelated but not interchangeable. To date, there has been no agreement as to whether to include comorbidity and disability as criteria in assessing frailty [23, 92]

1.3.2 Association between frailty scores and adverse health outcomes

The association between frailty scores and adverse health outcomes has been examined for eleven of the 52 frailty measures identified in the review of literature (Table 1.4). Mortality was the most common outcome assessed, with 10 frailty measures examining the association between frailty and mortality. The findings were that the rate of death within three to five years in the frail group was around twice the rate in the non-frail group, with hazard ratios (HR) ranging across the studies between 1.9 and 2.37 [21, 71, 73] (Table 1.4). Disability was

the second most common outcome assessed, the findings were that frail older people were more likely to have disability at the follow-up time than those who were non-frail, with odds ratios (OR) ranging from 2.76-5.2 [55, 73]. As shown in Table 1.4, when comparing the association between different frailty measures and adverse health outcomes, in general, the studies showed that there was a positive association between frailty and adverse health outcomes (Table 1.4). This review found only two measures that examined the association between frailty and hospitalisations or nursing home admission.

In terms of confounding factors, eight studies (Table 1.4) adjusted the association between frailty and adverse outcomes for a number of different confounders, including age, gender, comorbidity, and disability. Selection of confounders should be based on prior understanding of the causal relationship between the studied variables. Frailty, comorbidity, and disability are interrelated but not interchangeable [21, 133]. In addition, there has been no agreement between the FOD-CC experts on the association between frailty and comorbidity. Thus, it is difficult to determine whether comorbidity and disability are confounders, which should be adjusted or, intermediary factors on the causal pathway, which should not be adjusted for. While these studies show there is an association between the frailty measures and the adverse outcomes and in some papers have been described as validity assessments, they are not validity assessments but have only assessed associations. In the next section, studies assessing the validity of the measures are reviewed

Table 1. 4 The list of studies on the association between frailty and adverse health outcomes including: mortality, disability, and hospitalisation

Frailty measure	Study population	Follow-up period	Mortality (95%CI)	Hospitalisation (95%CI)	Nursing home admission (95%CI)	Falls (95%CI)	Disability (95%CI)	Adjustment variable
The Zutphen Study frailty measure (Chin A Paw et al., 1999) [55]	N= 450 Age ≥65 Male only Community Netherlands	3 years	OR: 4.1 (1.8-9.4)	-	-	-	ADL/IADL disability OR: 5.2† (1.04-25.8)	age
CSHA rules based definition (Rockwood et al., 1999) [47]	N= 9008 Age ≥65 Community Canada	18 months	Scale 1: RR: 1.2 (1.0-1.4) Scale 2: RR: 2.0 (1.8-2.2) Scale 3: RR 3.1 (2.7-3.6)	-	Scale 1: RR: 1.7 (1.3-2.1) Scale 2: RR: 3.6 (3.1-4.3) Scale 3: RR 9.4 (7.7-11.5)	-	-	age, gender
Frailty Phenotype (Fried et al., 2001) [21]	N= 5317 Age ≥65 Community United States	3 years	HR: 2.24 † (1.51-3.33)	-	-	-	ADL disability HR: 1.98† (1.54-2.55)	age, gender, race, income, smoking status, blood pressure, blood glucose level, albumin level, creatinine level, carotid stenosis, history of congestive heart failure, cognitive function, electrocardiogram abnormality, diuretics use, IADL problems, self-report health measure, depression
The VES frailty measure (Saliba et al., 2001) [67]	N= 6205 Age ≥65 Community United States	2 years	RR:4.2	-	-	-	-	-
Frailty Index-70 items (Rockwood et al., 2005) [52]	N= not reported Age ≥65 Community Canada	70 months	HR: 1.26 (1.24-1.29)	-	HR: 1.56 (1.48-1.65)	-	-	age, gender, and number of years of education

Table 1.4. The list of studies on the association between frailty and adverse health outcomes including: mortality, disability, and hospitalisation (cont.)

Frailty measure	Study population	Follow-up period	Mortality (95%CI)	Hospitalisation (95%CI)	Nursing home admission (95%CI)	Falls (95%CI)	Disability (95%CI)	Adjustment variable
Geriatric Functional Evaluation (Scarcella et al., 2005) [71]	N= 3060 Age ≥65 Community Italy	5 years	HR: 1.9 (1.58 – 2.50)	-	-	-	-	age, gender, and number of diseases
Prognostic Frailty Score (Ravaglia et al., 2008) [73]	N= 1007 Age ≥65 Community Italy	4 years	HR: 2.37 (1.34-4.19)	-	-	-	ADL disability OR: 2.76 (1.82-4.19)	-
The SWILSO-O frailty measure (Guilley et al., 2008) [72]	N= 339 Age ≥80 Female only Community Switzerland	5 years	RR: 3.42 (1.23-9.49)	-	-	-	ADL disability RR: 3.95 (1.14-13.66)	-
Simplified Frailty Phenotype (Kiely et al., 2009) [74]	N= 765 Age ≥70 Community United States	18 months	-	OR: 3.49† (1.53 – 7.98)	-	recurrent falls OR 2.19† (1.19 – 4.03)	IADL disability OR: 5.38† (2.34 – 12.35)	age, gender, race, diabetes, stroke hypertension, hyperlipidaemia, education, and income
Edmonton Frail Scale (Armstrong et al., 2010) [150]	N= 23952 Age ≥65 Home-care & long-term care clients Canada	1 year	Mortality/ institutional-isation Medium frail: HR: 1.71 (1.60-1.83) Frailest: HR: 2.49 (2.32-2.68)	-	-	-	-	age and gender
FRAIL scale (Hyde et al., 2010)	N= 3616 Age ≥65years Community Men only Australia	7 years	Score ≥4 HR: 3.97 (2.89-5.45)	-	-	-	-	age, body mass index, hypertension, dyslipidaemia, diabetes, Charlson's index, and smoking

OR: odds ratio, RR: relative risk, HR: hazard ratio, †non-frail as reference group
CSHA: Canadian Study on Health and Aging, ADL: activities of daily living, IADL: instrumental activities of daily living, VES: Vulnerable Elders Survey, SWILSO-O: The Swiss Interdisciplinary Longitudinal Study on the Oldest Old, FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight.

1.3.3 The assessment of validity

There is variation with the use and the application of the term validity in the literature [151]. As the purpose of frailty assessment is to identify older people with an increased risk of adverse health outcomes, the focus of this section is to discuss the predictive validity of frailty measures. The literature in terms of the validity of frailty measures for predicting adverse outcomes is reviewed. Predictive validity is used to examine the future correlation between criteria that are known to be associated with the measure [152, 153]. The literature on the construct validity of frailty measures is also reviewed. Construct validity assessment is undertaken to ensure that the measure assesses the concept it is intended to measure [152, 153].

1.3.3.1 Predictive validity

Assessing the predictive validity of a frailty measure is challenging; there are no available clinical or laboratory markers of frailty that can be used as a gold standard. A gold standard reference is preferable in evaluating the predictive validity [60]. Adverse outcomes have been used as a reference standard to assess the predictive validity of frailty measures [154, 155]. However, there is no agreement yet as to which adverse outcomes representing frailty are important to assess [156]. Since the purpose of a frailty measure is to identify older persons who are at an increased risk of adverse health outcomes, the prognostic value of a measure can be used as a reference standard [157, 158]. Therefore, the presence of adverse outcomes has been commonly used as a reference standard in assessing the validity of a frailty measure [154].

Six studies have examined the predictive validity of eleven different frailty measures (Table 1.5). Frailty Index (FI), Frailty Phenotype (FP), and FRAIL scale were the most common

measures assessed; with four studies having examined their predictive validity. The studies reported the predictive validity of frailty measures in predicting a range of adverse outcomes including, mortality, IADL disability, falls, and hip fracture. Table 1.5 presents the predictive validity of the eleven frailty measures in predicting mortality, the assessment includes: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). Across the six studies, there was variation in the type of assessments that were reported; all six studies reported AUC values. In addition to the AUC values, three studies reported sensitivity and specificity values. Only two studies reported PPV and NPV. Of the six studies, one study compared the predictive validity of frailty measures between older men and older women, however the study did not report the sensitivity, specificity, PPV, and NPV for the FRAIL scale among older men; this could be due to the small sample size of older men participants who were considered frail, thus, the value was unable to be calculated [159].

The findings showed that of the nine frailty measures that reported sensitivity values in predicting mortality, the values varied from 0.05 to 0.78 (Table 1.5). The Prognostic Frailty Score (PFS) had the highest sensitivity in predicting mortality within four years, which illustrates that 78% of participants who died were identified as frail. The CSHA Clinical Frailty Scale had the lowest sensitivity, only 5% of participants who died were identified as frail. In terms of PPV, the study that examined the Prognostic Frailty Score did not report PPV and NPV values. The PPV of the other six frailty measures was varied from 0.03 to 0.47 (Table 1.5); this means that among participants who were identified as frail between 3% and 47% of them had died at the end of the study period. These PPVs are considered low, indicating that the measures do not have good predictive value.

The AUC values were reported in all of the studies. The AUC values were used to examine the ability of each measure to differentiate between the frail and non-frail participants. The acceptable AUC values for a prognostic measure are between 0.6 – 0.85 [160]. As shown in Table 1.5, the Prognostic Frailty Score had the highest AUC value for predicting mortality compared to the other ten frailty measures; however, the majority of frailty measures all had AUC values for mortality within the acceptable range. There were variations in the AUC values of the same frailty measures when used in a different population. The Groningen Frailty Indicator, the Tilburg Frailty Indicator, and the CSHA Clinical Frailty Scale were found to have better AUC value when assessed in a larger multinational population (Table 1.5). The Frailty Index was shown to have acceptable AUC values in all four studies, except when used in a group of older women in Hong Kong.

Similar findings were reported when assessing predictive validity of frailty measures for other adverse health outcomes. Three frailty measures (Groningen Frailty Indicator, Tilburg Frailty Indicator, and Sherbrook Postal Questionnaire), were found to have better predictive when predicting the development of disabilities compared to predicting mortality [161].

In general, the studies showed that the accuracy of frailty measures varied depending on the type of adverse outcomes used in the assessment, demonstrating frailty does not predict all adverse outcomes equally. However, all but one of the measures were considered to have acceptable predictive validity based on AUC values, where scores above 0.6 were reported in at least one study for all measures. However, some measures had scores of less than 0.6 in some populations. Comparing the predictive validity of frailty measures is challenging; an agreement on the selection of adverse outcomes as the reference standard, as well as the length of time needed to assess the adverse outcomes related to frailty is needed to improve

the comparability of assessment of frailty measures. The predictive validity of existing frailty measures in older community-dwelling Australians has not been assessed. It is unknown if predictive validity of frailty measures from other countries corresponds to the Australian setting.

Table 1. 5 Predictive validity of frailty measures in predicting mortality

Frailty measure	Sensitivity	Specificity	PPV	NPV	AUC (full model)
Community-dwelling (Netherland), ≥70 years old, N= 687, follow up - 1 year [161]					
GFI	0.73	0.54	0.04	0.98	0.64
TFI	0.67	0.61	0.05	0.98	0.64
SPQ	0.71	0.41	0.03	0.98	0.56
Community-dwelling (Hong Kong), ≥65 years old, N= 4000, follow up - 4 years [159]					
FP					
Men	0.16	0.95	0.42	0.84	0.64
Women	0.14	0.94	0.14	0.94	0.60
FI (cut-off ≥0.25)					
Men	0.08	0.96	0.33	0.83	0.63
Women	0.10	0.94	0.11	0.93	0.56
FRAIL scale (cut-off ≥3)					
Men	-	-	-	-	0.54
Women	0	0.99	0	0.93	0.54
CSHA-CFS (cut-off ≥5)					
Men	0.05	0.99	0.47	0.83	0.53
Women	0.09	0.96	0.15	0.94	0.54
Community-dwelling (Italy), ≥65 years old, N= 1353, follow up - 4 years [162]					
SFP	0.36	0.93	-	-	0.75
PFS	0.78	0.69	-	-	0.83
Community-dwelling (Italy), ≥65 years old, N= 1353, follow up - 7 years [162]					
SFP	0.26	0.94	-	-	0.67
PFS	0.70	0.76	-	-	0.79
Community-dwelling (8 European countries), 40-79 years old, N= 3369, follow up - median: 4.3 years [163]					
FI	-	-	-	-	0.78
FP	-	-	-	-	0.68
FRAIL scale	-	-	-	-	0.66
Community-dwelling (11 European countries), ≥50 years old, N= 27527, follow up - 2 years [164]					
GFI	-	-	-	-	0.72
TFI	-	-	-	-	0.74
FI	-	-	-	-	0.77
FI-CGA	-	-	-	-	0.75
CSHA-CFS	-	-	-	-	0.73
FP	-	-	-	-	0.73
FRAIL scale	-	-	-	-	0.76
EFS	-	-	-	-	0.70
Community-dwelling (11 European countries), ≥50 years old, N= 27527, follow up - 7 years [164]					
GFI	-	-	-	-	0.70
TFI	-	-	-	-	0.73
FI	-	-	-	-	0.75
FI-CGA	-	-	-	-	0.74
CSHA-CFS	-	-	-	-	0.70
FP	-	-	-	-	0.70
FRAIL scale	-	-	-	-	0.75
EFS	-	-	-	-	0.67
Community-dwelling (United States), ≥49 years old, N= 779, follow up - 9 years [165]					
FRAIL scale	-	-	-	-	0.57
SFP	-	-	-	-	0.53
FP	-	-	-	-	0.53
FI	-	-	-	-	0.64

GFI: Groningen Frailty Indicator, TFI: Tilburg Frailty Indicator, SPQ: Sherbrook Postal Questionnaire, FP: Frailty Phenotype, FI: Frailty Index, CSHA-CFS: CSHA Clinical Frailty Scale, SFP: Simplified Frailty Phenotype, PFS: Prognostic Frailty Score, EFS: Edmonton Frail Scale, Sensitivity: probability of persons with outcome who are classified as frail; specificity: probability of persons without outcome who are classified as non-frail; PPV: probability that a person has the outcome if he/she was identified as frail; NPV: probability that a person has no outcome if he/she was identified as non-frail

1.3.2.2 Construct validity

In the previous section the predictive validity of frailty measures was examined. Another type of validation is through the analysis of construct validity. Construct validity examines the degree to which a measure represents the studied concept, i.e. frailty [152, 153]. According to Cronbach and Meehl who established the concept of construct validity; the assessment of construct validity is essential in a measure that assesses a certain characteristic that is 'not operationally defined' or when there is no agreement on the factors that sufficiently define the measured characteristics [166]. Thus, when assessing the validity of frailty measures construct validity is an important tool, however, there does not appear to be a standard method for assessing construct validity.

There are variations in the literature in the methods used to examine construct validity. Two published reviews on the validity of frailty measures [60, 92] described the assessment of construct validity. One study used predictive validity to measure construct validity [60]. While the other study used several methods as the criteria of construct validity, including: correlation analysis, strength of association (cross-sectional and prospective), or AUC analysis between frailty measures and various frailty-related factors [92]. The authors reported it was difficult to categorise whether the assessment methods could be considered a true construct validity assessment [92]. The challenges were due to the variations in the use of the terms construct validity in the literature [151], as well as the unavailability of a gold standard or a reference standard for frailty.

In terms of correlation analysis, several studies have examined the correlation between frailty and other factors that are thought to be associated with frailty, including: age [76], comorbidity [52, 78], disability [56], physical function [48, 65, 78, 80, 93, 97], or quality of life [100]. The correlation of a frailty measure with another frailty measure had also been

evaluated as an assessment of construct validity [89, 94, 104, 105, 146]. The Frailty Index was assessed for its correlation with age. The correlation coefficient (r) was 0.91, which was considered a strong correlation [76]. The Edmonton Frail Scale was assessed for its correlation with a disability measure, which showed a moderate correlation (r= -0.58) and a cognitive impairment measure, which showed a weak correlation (r= -0.05) [78]. The correlation between Frailty Index and the Frailty Phenotype was assessed in one study [146] and the two scores were shown to have a moderate correlation (r= 0.65) [146]. A frailty measure was considered to have good construct validity when it showed a good correlation with other frailty-related factors or with other frailty measures. However, the majority of correlation analysis reported in the literature showed frailty measures had weak or moderate correlation with the majority of criteria. Another study used AUC analysis between different frailty measures. The study used two frailty measure, Frailty Phenotype and CSHA Clinical Frailty Scale, as the reference standard, which is a type of correlation analysis, in assessing the accuracy of five frailty measures in identifying frail older person [105]. While there was agreement across measures, no correlation with other outcomes was undertaken to confirm the results. There is no agreement on the use of correlation analysis for assessing the construct validity of frailty measures, however, correlation analysis is not a strong method for assessing validity as correlation can occur independent of the factor assessed.

The construct validity of frailty measures in the community-dwelling older Australian population is still not known. There was only one Australian study among hospitalised patients that has assessed the construct validity of the Reported Edmonton Frail Scale (REFS), which is an adaptation of Edmonton Frail Scale [167]. The REFS was found to have a moderate correlation, (r ranging between 0.49 and 0.61) with Geriatrician's Clinical Impression of Frailty, cognition measures, comorbidity, and daily activities.

1.4 Concluding summary of the literature concerning frailty measures

In conclusion, this review identified 52 frailty measures; however, very few had been assessed for predictive or construct validity. Only eleven frailty measures had been assessed for predictive validity and of these four were based on self-report (Groningen Frailty Indicator, Tilburg Frailty Indicator, and Sherbrook Postal Questionnaire) or clinician's judgment (CSHA Clinical Frailty Scale) (see table 1.3), and one of these also had an unacceptable AUC value for a prognostic measure. As discussed in section 1.2.4, self-report and clinician judgement may result in a biased and subjective assessment. This appears to have been verified by the poor assessment of predictive validity for at least one of these subjective measures. Of the seven measures remaining, two were uni-dimensional measures (Frailty Phenotype and Simplified Frailty Phenotype) and five were multidimensional measures (Frailty Index, FRAIL scale, Prognostic Frailty Score, FI-CGA, and Edmonton Frail Scale). Multidimensional measures are preferable as they are consistent with the definition of frailty being a multidimensional syndrome, however, the two uni-dimensional measures with good validity have been commonly used in frailty research. All seven measures were based on a combination of self-report and physical assessment, which is preferable when the tool is used for clinical assessment. In addition, the seven measures also had an acceptable predictive validity based on their AUC values. Based on this review of the literature, the following measures could be considered for exploring the association between frailty and medicine use in Australia: Frailty Index, FRAIL scale, Prognostic Frailty Score, FI-CGA, Edmonton Frail Scale, which are all multidimensional measures, and Frailty Phenotype and Simplified Frailty Phenotype, which while uni-dimensional measures have been used in a large body of prior research and have the advantage of not including as part of their criteria, medical conditions for which medicines may be used.

In the next chapter, the literature assessing association between frailty and medicine use will be reviewed.

Chapter 2:
The association between frailty and medicine use in older people: A literature review

In the previous chapter, the definition of frailty and its assessment was described. The literature showed that many frailty measures have been developed which all vary in terms of the variables used in their construction. Despite their differences, being identified as frail by the measures was significantly associated with an increased risk of adverse health outcomes [60, 92, 168]. Frailty and the use of medicine are common among the older population; however, there is still limited knowledge on the association between frailty and medicine use. Understanding frailty and its assessment may be an important step to better understanding the risks and benefits of medicine use in the older population [18, 169, 170]. This chapter presents a review of the literature on the association between frailty and medicine use among the community dwelling older population.

2.1 Introduction

The prevalence of frailty in community-dwelling older populations, as reported in a systematic review, varied greatly from 4% to 59% across different countries [171]. The variation in these estimates is likely to be due to the application of different frailty measures [171], or could be due to differences in the underlying prevalence of frailty in those populations. In Australia, the prevalence of frailty in the general older Australian population has not been reported. Australian studies have examined the prevalence of frailty among older men [102, 172] and among hospitalised patients [173-175]; finding that the prevalence of frailty among older men was between 9.4% and 15.2% [102, 172] and the prevalence

among older hospital patients ranged from 50.5% to 66% [173-175]. The frailty measures used in these studies were: FRAIL scale, Frailty Phenotype, Edmonton Frail Scale, or Frailty Index. These frailty measures were among those shown to have acceptable validity in Chapter one, section 1.3.3. Collectively, these studies suggest frailty is common in the elderly.

Similar to frailty, medicine use is common in the elderly, and just as frailty is associated with adverse outcomes [60, 92], medicine use has also been associated with an increased risk of adverse health outcomes [11, 14, 176]. Prescribing medicines in the older population provides challenges for doctors due to the limited availability of data from clinical trials on the safety and efficacy of medicine use in the elderly [18]. Doctors must prescribe medicines based on extrapolation of results from clinical trials conducted in younger populations; which may not be appropriate [16, 18, 177]. This can become more complex when the elderly are also frail. The older population is a heterogeneous population; with variable health and wellbeing [178], and within which some individuals will be considered frail. This heterogeneity means that the risks and benefits of treatment may vary between older individuals [44]. Age-related decline of multiple organ functions, as well as the presence of diseases, may affect the pharmacokinetics and pharmacodynamics of many medicines and can contribute to medication-related problems [6-8]. Pharmacokinetic changes can result in the accumulation of toxic concentration of medicines in the blood, whereas pharmacodynamic changes may result in increased sensitivity to the adverse effects of medicine. In the next section, the possible mechanisms underlying the association between frailty and medicine use are discussed.

2.1.1 Possible mechanisms underlying the association between frailty and medicine use

Many of the adverse effects of medicines can be aligned with the dimensions of frailty that were outlined in Chapter one. For example, medicine adverse effects that could affect the

physical dimension of frailty include sedation, confusion or dizziness, all of which have the potential to affect physical assessments such as gait speed. Adverse effects such as neuropathy or muscle weakness would have the potential to affect grip strength. Nausea, vomiting, and diarrhoea are all common adverse effects of medicines, which also have the potential to affect the nutrition element of the physical dimension. Similarly, the psychological dimension could be affected by medicines where medicines cause adverse effects such as depression or anxiety. Where an individual is on medicines and suffering adverse effects that have the potential to affect dimensions assessed within the frailty measure, the medicines may be contributing to the assessment of being frail, and in this instance a discontinuation or a dose reduction of the concerned medicine may be warranted in order to improve health.

Alternatively, the effects of medicine use could improve characteristics assessed in the frailty measures, which then may decrease the likelihood of being frail. For example, the use of paracetamol for pain management in osteoarthritis could help older individuals in maintaining their mobility as well as their independence in undertaking activities of daily living (ADL). Mobility and ADL are important characteristics often measured within the physical dimension of frailty (Chapter 1, section 1.2.3.1). Similarly, the use of antiemetics for nausea or antacids for indigestion could assist in preventing weight loss, which is another characteristic often measured within the physical dimension of frailty assessment (Chapter 1, section 1.2.3.1).

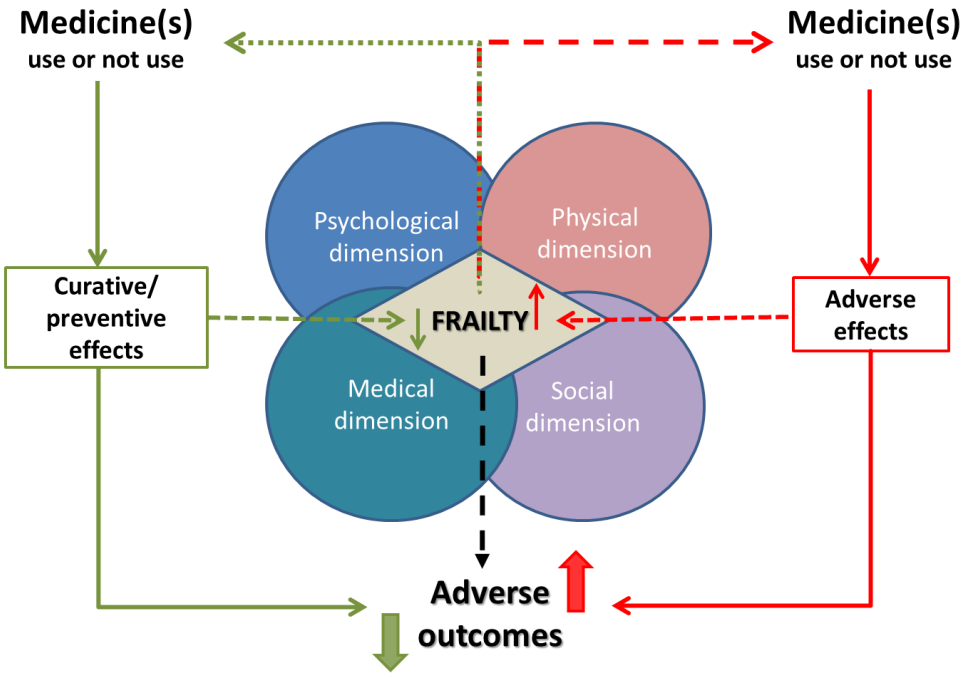
A contrasting situation could arise where an individual is frail, independent of any medicine use, and it is frailty that places the individual at greater risk of adverse events from medicine, because frailty itself is a marker of increased sensitivity to medicines. One of the reasons that

it is important to identify individuals as frail, is that it has been shown that frail individuals take longer to recover from the same medical event (e.g., illness or adverse event) than non-frail persons [19]. The implication of this is that a frail older person may take a longer time to recover from medicine adverse effects than a non-frail older person. Additionally, the impact of the adverse effects may be greater in the frail person compared to the non-frail person. In this scenario, *a-priori* knowledge of an individual's frailty status could assist doctors to prescribe lower dosages or alternative therapies. Particularly where there were documented adverse effects of the medicines that could potentially intensify the characteristics of frailty.

Another potential problem is medicine use in the frail population. Being identified as frail may discriminate against an older person, as medicines that may be beneficial may not be prescribed due to concern about the risk of adverse effects being greater in the frail person. For example, warfarin is an effective and recommended medicine in reducing the risk of ischemic stroke among older patients with atrial fibrillation (AF) [179], but has a high risk of bleed. Studies have shown that there is underuse of warfarin among older patients with AF with no documented contraindications [173, 180-183]. The underuse of warfarin has been associated with an increased risk of poorer health outcomes [183]. In this case, knowledge that the medicine benefit/risk was acceptable, even in the presence of frailty assessment may potentially assist doctors to safely prescribe warfarin, which could then contribute to the rational use of medicines among older population

The examples above are illustrated in the framework provided in Figure 2.1. It shows that the there is potential for a complex interplay between frailty and medicine use in relation to their contribution to adverse outcomes.

Figure 2. 1 The association between frailty and medicine use: a framework



Therefore, understanding the association between frailty and medicine use in older population is likely to provide important knowledge on the risks and benefits of medicine use. The first step would be to determine whether there is an association between frailty and medicine use. In this chapter, a review of the literature of the association between frailty and medicine use in the older population is presented. The aim of this review is to determine the association between assessment of frailty and medicine use in a community dwelling, older population. Gaps in the literature will be discussed.

2.2 Methods

2.2.1 Scope of review and definitions

The inclusion criteria for this review were: studies that included community-dwelling older people aged 65 years or over, assessed frailty using a validated frailty measure, and aimed to examine the association between frailty and medicine use. The term frailty, in this review, refers to frail older people that were identified as frail using a validated frailty measure that had been shown to be able to identify older people with an increased risk of adverse health

outcomes, as evidenced by predictive validity assessment [60, 92]. The list of validated frailty measures that were considered based on the literature review in chapter one is presented in Table 2.1.

Table 2. 1 The list of validated frailty measures considered in the review of frailty and medicine use

Validated frailty measures
Frailty Index (Mitnitski et al., 2001) [66]
Frailty Phenotype (Fried et al., 2001) [21]
Frailty Index from Comprehensive Geriatric Assessment (FI-CGA) (Jones et al., 2004)[50]
The Edmonton Frail Scale (Rolfson et al., 2006) [78]
Prognostic Frailty Score (Ravaglia et al., 2008) [73]
Simplified Frailty Phenotype (Kiely et al., 2009) [74]
FRAIL scale (Hyde et al., 2010) [102]

2.2.2 Data source and study selection

A literature search was conducted using the electronic databases: MEDLINE, Embase, CINAHL, Scopus, and International Pharmaceutical Abstracts (IPA) from the beginning date of the databases until 14 December 2014. The Medical Subject Heading (MeSH) terms and keywords used were: 'frail', 'frailty', 'older', 'aged', 'ageing', 'elder', 'geriatric', 'prescribing', 'pharmacotherapy', 'pharmacology', 'medication', 'medicine', 'drug therapy', 'drug use', 'population-based' and 'community dwelling'.

The title and the abstract of studies identified in the search were reviewed by one reviewer to determine if the study met the inclusion criteria. The reference lists of identified studies were also screened for potential inclusion.

Data extraction included information on the study population and study design, types of frailty measure, types of medicine examined, and the measure of association between frailty and medicine use.

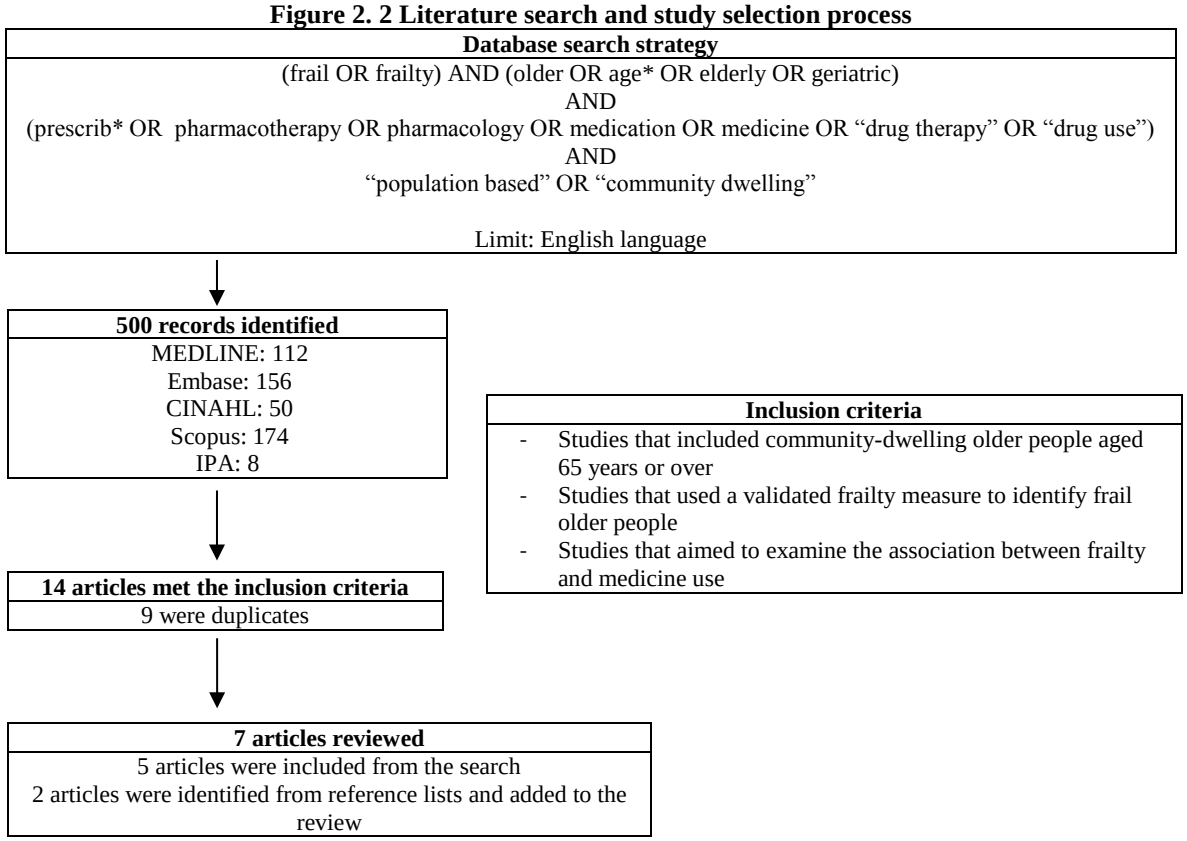
The quality of the reviewed articles was assessed by one reviewer using criteria shown in Table 2.2, which was sourced from the United States (US) National Institutes of Health

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [184]. The detailed guidance on the assessment of the quality assessment criteria is presented in Appendix C.

2.3 Results

Seven articles met the inclusion criteria (Figure 2.1). Four of the seven articles were based on two studies, which make a total of five studies were identified. The studies were from the US [185, 186], Australia [187, 188], Brazil [189], Ireland [190], and Finland [191]. Three articles reported the results of cross-sectional studies [189-191] and four articles reported the results of two longitudinal studies: the Women's Health Initiative Observational Study (WHI-OS) [185, 186] and the Concord Health and Ageing in Men Project (CHAMP) [187, 188].

Figure 2. 2 Literature search and study selection process



2.3.1 Quality of the identified articles

Four articles from the two large observational studies, WHI-OS and CHAMP, were deemed to be of good quality (Table 2.2). In four articles, sample sizes were not justified but variance estimates were provided. In general, the three cross-sectional studies by Miguel et al., Frewen et al., and Koponen et al. [189-191] were of poorer quality than the cohort studies, primarily due to the use of a cross-sectional study design. The study published by Miguel et al. [189] did not report the measurement method of the exposure variable, which is the number of medicines used; limiting its quality.

Table 2. 2 Quality assessment of the included articles

Criteria*	LaCroix et al., 2008[185]	Gray et al., 2009[186]	Gnjidic et al., 2012[187]	Gnjidic et al., 2013[188]	Miguel et al., 2012[189]	Frewen et al., 2013[190]	Koponen et al., 2013[191]
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was a sample size justification, power description, or variance and effect estimates provided?	Yes	Yes	Yes	No	Yes	Yes	No
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	No	No	No
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	No	No	No
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	No	No	Yes
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Not reported	Yes	Yes
Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	No	No	Yes
Overall quality	Good	Good	Good	Good	Poor	Fair	Fair

*Sourced from US National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [184]

2.3.2 The assessment of frailty

In all seven articles, frailty was assessed using the same frailty measure, the Frailty Phenotype [21]. This measure assesses five characteristics: shrinking (weight loss or loss of muscle mass), weakness, exhaustion, slow walking speed, and low physical activity [21]. Each of the studies varied in the assessment criterion used for weight loss and there was some variation for muscle weakness and walking speed of the Frailty Phenotype score as shown in Table 2.3. Additionally, the classification of frailty differed across the seven studies: four studies classified frailty into: frail, pre-frail, and non-frail, while one study had only two categories: frail and non-frail. Four of the five studies reported the prevalence of frailty, which ranged from 9% to 22%.

Table 2. 3 Frailty assessment

	LaCroix et al., 2008[185] and Gray et al., 2009[186]	Gnjidic et al., 2012[187] and Gnjidic et al., 2013[188]	Miguel et al., 2012[189]	Frewen et al., 2013[190]	Koponen et al 2013[191]
Frailty measure	Unintentional weight loss >5% of body weight	Lower current weight by ≥15% than highest lifetime self-reported weight	Unintentional weight loss (≥4.5kg)	Unintended weight loss (≥10 pounds)	Weight loss of ≥5% of body weight
	Self-reported indicator of muscle weakness	Weak grip strength	Weak grip strength	Weak grip strength	Weak grip strength
	Self-reported exhaustion	Self-reported exhaustion	Self-reported exhaustion	Self-reported exhaustion	Self-reported exhaustion
	Self-reported indicator of slow walking speed	Slow walking speed	Slow walking speed	Gait and balance test: timed-up-and-go	Slow walking speed
	Low physical activity	Low physical activity	Low physical activity	Low physical activity	Low physical activity
Frailty classification	Non-frail: 0 criteria Pre-frail: 1/2 criteria Frail: ≥3 criteria	Non-frail: 0 criteria Pre-frail: 1/2 criteria Frail: ≥3 criteria	Non-frail: 0 criteria Pre-frail: 1/2 criteria Frail: ≥3 criteria	Non-frail: 0 criteria Frail: ≥1 criteria	Non-frail: 0 criteria Pre-frail: 1/2 criteria Frail: ≥3 criteria
Frailty prevalence	Frail: 14%	Frail: 9%	Frail: 22%	Frail: not reported	Frail: 11%

2.3.2 The association between frailty and medicine use: cross-sectional analyses

Only two cross-sectional studies examined the association between frailty and the number of medicines used (Table 2.4). One study involving 1662 older Australian men found that participants who were classified as frail were more likely to have polypharmacy, defined by concurrent use of five or more medicines, than those who were classified as non-frail (unadjusted odds ratio (OR)=4.91, 95% confidence interval (CI): 3.42-7.05, adjusted OR=2.5, 95% CI: 1.69-3.84). The adjustment for comorbidity may contribute to the difference in unadjusted and adjusted estimates. The mean number of medicines used was higher among frail participants than in those who were classified as non-frail or pre-frail (Table 2.3) [187]. In a smaller study (N=58) among an older Brazilian population with osteoarthritis, there was a statistically significant difference with regard to the number of medicines used by frail, pre-frail and non-frail participants, with the mean number of medicines being seven, five, and four respectively [189].

In terms of the association between frailty and types of medicines used, there were three studies that examined this association. One study that was conducted among older Australian men found that frail participants were more likely to be taking more medicines, with the mean number of 6.1 and standard deviation (SD)= 3.4 than the non-frail participants (mean= 3.3, SD 2.5). The frail participants also used more medicines with anticholinergic or sedating effects (mean= 0.4, SD 0.5), as identified by the drug burden index (DBI), than non-frail participants (mean= 0.1, SD 0.3) [187]. Another study in an older Finnish population [191] found that frail participants were more likely to use any type of analgesic compared to those who were non-frail (adjusted OR= 2.96; 95% CI 1.38-6.36). Additionally, this study found that the prevalence of paracetamol as well as opioid use in frail participants was significantly higher than in non-frail or pre-frail participants; there was no significant difference in the

prevalence of non-steroidal anti-inflammatory drug (NSAID) use between different frailty categories [191]. A study of an older Irish population found that frail older people with atrial fibrillation (AF) were less likely to be without an oral anticoagulant than non-frail persons [190]. The study among older Australia men, also published results on the use of statins [188]. The study examined the difference in the prevalence of frailty between statin users and non-users [188]; there was no statistically significant difference found in the proportion of frail participants among statin users and non-users, 7.6% and 10.4% respectively (Table 2.4).

Table 2. 4 A cross-sectional analysis of the association between frailty and medicine use

References	Study population	Assessment of medicine use	Non-frail	Pre-frail	Frail	p-value
		Frailty and number of medicines used				
Gnjidic et al., 2012[187]	N= 1662 Men only Mean age (SD): 76.9 (5.4)	**Polypharmacy** OR (95%CI) - unadjusted OR (95%CI) - adjusted[a]	**N= 830** Reference	**N= 676** 2.13 (1.72-2.65) 1.53 (1.2-1.95)	**N= 156** 4.91 (3.42-7.05) 2.55 (1.69-3.84)	
		Hyperpolypharmacy OR (95%CI) - unadjusted OR (95%CI) - adjusted[a]	Reference	2.86 (1.57-5.2) 1.94 (1.04-3.59)	10.65 (5.58-20.31) 5.8 (2.9-11.61)	
		Number of medicine use mean (SD)	3.3 (2.5)	4.5 (2.9)	6.1 (3.4)	<0.0001
Miguel et al., 2012[189]	N= 58 Osteoarthritis group Mean age (SD): 74 (5.5)	**Number of medicine use** mean (SD)	**N= 17** 4 (2)	**N= 28** 5 (2)	**N= 13** 7 (2)	0.001
		Frailty and types of medicines used				
Gnjidic et al., 2012[187]	N= 1662 Men only Mean age (SD): 76.9 (5.4)	**Anticholinergic and sedative burden (DBI)** mean (SD)	0.1 (0.3)	0.2 (0.4)	0.4 (0.5)	<0.0001
Gnjidic et al., 2013[188]	N= 1665 Men only Mean age (SD): 76.9 (5.5)	**Prevalence of statin use** N (%)	n/a	n/a	**N= 147** users: 53 (7.6) non-users: 94 (10.4)	0.08
Koponen et al., 2013[191]	N= 605 Mean age (SD): 81.9 (4.5)	**The use of analgesics** OR (95%CI) - unadjusted OR (95%CI) – adjusted[b]	**N= 237** Reference	**N= 299** 1.76 (1.25-2.49) 1.4 (0.9-2.17)	**N= 69** 3.14 (1.78-5.54) 2.96 (1.38-6.36)	
		Prevalence of any analgesic use# - N (%)	96 (40.5)	163 (54.5)	47 (68.1)	<0.001
		Prevalence of paracetamol use - N (%)	45 (19)	103 (34.4)	37 (53.6)	<0.001
		Prevalence of NSAIDs use - N (%)	58 (24.5)	72 (24.1)	15 (21.7)	0.894
		Prevalence of opioids use - N (%)	9 (3.8)	31 (10.4)	12 (17.4)	0.001
Frewen et al., 2013[190]	N= 147* Atrial fibrillation (AF) group Age: ≥50	**The absence of oral anticoagulant use** OR (95%CI) – adjusted[c]	Reference	0.43 (0.19 – 0.96)		0.004

Polypharmacy: ≥5 medicines, hyperpolypharmacy: ≥10 medicines, OR: odds ratio, CI: confidence interval SD: standard deviation, DBI: drug burden index, [a]adjusted for: age, education, marital status, and comorbidity MMSE: mini-mental state examination, FCI: functional comorbidity index, #prescription and non-prescription, [b]adjusted for: age, sex, mini-mental state examination (MMSE) score, functional comorbidity index (FCI) score, self-rated health, and musculoskeletal pain, [c]adjusted for: age, sex, and education, *Sample size was calculated from the reported prevalence of AF – 3%, total study population: 4890

The Australian study also examined whether the doses of medicines that were used varied by frailty status. The mean daily dose of 16 commonly used medicines was examined across different frailty categories. Out of the 16 medicines examined, a significant difference was found for three medicines: allopurinol, frusemide, and ramipril [187]. Allopurinol and ramipril users who were frail had a lower mean daily dose compared to the non-frail or pre-frail users (Table 2.5), whereas frusemide users who were frail had a higher mean daily dose than each of the non-frail or pre-frail users. The mean daily doses of the three medicines among the study participants were all within the recommended dose range (Table 2.4).

Table 2. 5 The differences in mean daily dose of medicines across frailty categories

Medicines	Recommended dose[192]	Mean daily dose (mg) – standard deviation (SD)			
		Non-frail	Pre-frail	Frail	p-value
Allopurinol (N= 176)	Maintenance dose: 100-300mg daily or 100mg alternate days in severe renal impairment	234 (91.6)	249.3 (230.5)	170.8 (95.5)	0.01
Frusemide (N= 115)	Maintenance dose: 20-400mg daily	37.3 (14.2)	43.9 (30.7)	54.5 (29.7)	0.02
Ramipril (N= 132)	Initially 1.25mg daily (maximum 10mg daily)	7.3 (2.8)	7.1 (5.4)	4.6 (3.3)	0.01

2.3.3 The association between medicine use and frailty: longitudinal analyses

Two large longitudinal studies from the US [185, 186] and Australia [187] examined the risk of developing frailty among medicine users over follow-up periods of three years and two years, respectively (Table 2.6). Both studies excluded individuals who were classified as frail at baseline, but included those who were pre-frail. The research question in the US study was whether the use of specific medicines at baseline was associated with lower risk of developing frailty within the next three years compared to participants who were non-users of the medicine examined [185, 186]. It examined the baseline use of statin [185] and angiotensin-converting enzyme inhibitor (ACEI) [186]. The findings were that the risk of developing frailty was similar between the baseline users and non-users of statin or ACEI after adjustment for a number of variables (Table 2.6). The duration of use prior to study entry which ranged from less than one year to more than five years, and different dosages,

classified as low, medium, and high, was not associated with risk of frailty (Table 2.6). The unadjusted results were not reported in the articles.

The Australian study also examined the risk of developing frailty over two years, among non-frail and pre-frail participants who had polypharmacy, hyperpolypharmacy (defined as ten or more medicines), or any anticholinergic and sedative burden (DBI) exposure at baseline [187]. The results from the adjusted analyses showed that there was a significant association between baseline polypharmacy, hyperpolypharmacy, or DBI exposure and the risk of being classified as frail at two-year follow up (Table 2.6). A breakdown of the results of frailty status at two-year by the baseline pre-frail and non-frail status was not reported.

Table 2. 6 Medicine use and the risk of frailty

Reference	Study population	Statin use[a]	Pre-frail OR (95% CI)	Frail OR (95% CI)
LaCroix et al., 2008 [185]	N= 25378 Women only Non-frail Age: 65-79 years	**Baseline users (N=2122)** **<1 year use (N=612)** **1-3 years use (N= 710)** **>3 years use (N= 800)** **Low dose (N= 404)** **Medium dose (N=1088)** **High dose (N= 620)**	0.99 (0.88-1.11) 0.98 (0.8-1.21) 0.90 (0.75-1.22) 1.07 (0.89-1.28) 0.71 (0.54-0.92) 1.11 (0.95-1.30) 0.99 (0.80-1.21)	1.00 (0.85-1.16) 1.19 (0.92-1.54) 0.94 (0.73-1.22) 0.88 (0.68-1.14) 0.81(0.58-1.14) 1.03 (0.83-1.27) 1.07 (0.83-1.39)
Reference	**Study population**	**ACEI use[b]**	**Pre-frail OR (95% CI)**	**Frail OR (95% CI)**
Gray et al., 2009 [186]	N= 27378 Women only Non-frail Age: 65-79 years	**Baseline users (N= 2192)** **<2 years use (N= 725)** **2-5 years use (N= 698)** **>5 years use (N= 769)** **Low dose (N= 633)** **Medium dose (N= 903)** **High dose (N= 637)**	1.00 (0.88-1.14) 1.16 (0.95-1.42) 0.91 (0.74-1.12) 0.95 (0.78-1.16) 1.09 (0.88-1.35) 0.95 (0.78-1.14) 1.00 (0.80-1.25)	0.96 (0.82-1.13) 0.96 (0.75-1.24) 0.96 (0.74-1.24) 0.97 (0.76-1.24) 0.88 (0.67-1.16) 0.95 (0.75-1.19) 1.08 (0.83-1.41)
Reference	**Study population**	**Medicine use[c]**	**Pre-frail OR (95% CI)**	**Frail OR (95% CI)**
Gnjidic et al., 2012[187]	N= 1242 Men only Non-frail and pre-frail Mean age (SD): 76.9 (5.4)	**Polypharmacy (N= n/a)** Unadjusted Adjusted **Hyperpolypharmacy (N= n/a)** Unadjusted Adjusted **Anticholinergic and sedative burden (DBI) (N= n/a)** Unadjusted Adjusted	 2.08 (1.62-2.68) 1.59 (1.20-2.10) 3.69 (1.64-8.28) 2.51 (1.10-5.76) 1.87 (1.42-2.46) 1.62 (2.12-2.15)	 4.97 (3.04-8.14) 2.45 (1.42-4.23) 5.4 (1.72-16.95) 2.50 (0.76-8.26) 3.19 (1.94-5.23) 2.14 (1.25-3.64)

OR: odds ratio, CI: confidence interval, SD: standard deviation, ACEI: angiotensin-converting enzyme inhibitor, DBI: drug burden index
[a]compared to statin non-users (N= 23256), OR adjusted for age, income, education, ethnicity, body mass index (BMI), smoking, alcohol use, physical activity, hormone replacement therapy (HRT) use, live alone, self-reported health, diabetes, hypertension, depression, arthritis, and history of cancer
[b]compared to ACEI non-users (N= 25186), OR adjusted for age, income, education, ethnicity, BMI, smoking, alcohol, physical activity, HRT use, live alone, self-reported health, diabetes, depression, arthritis, history of cancer, history of coronary heart disease, systolic and diastolic blood pressure, number of antihypertensives, and statin use
[c]OR adjusted for age, education, marital status, and comorbidity
Polypharmacy: ≥5 medicines, hyperpolypharmacy: ≥10 medicines, drug burden index exposure (>0)

2.4 Discussion

This review identified only seven articles that examined the association between frailty and medicine use in a community-dwelling older population. All of the studies identified in this review assessed frailty using the Frailty Phenotype, which is a uni-dimensional measure that only focuses on the physical characteristics of frailty [23]. The current consensus is that frailty assessment should be a multidimensional measure, which means that the frailty measure should also include measures of psychological and social characteristics in addition to assessment of physical characteristics [23]. However, there is an advantage of using this frailty measure when determining the association between frailty and medicine use because this frailty measure does not include comorbidities, the latter which are often treated with medicines.

Studies that used multidimensional frailty measures to examine the association between frailty and medicine use have been conducted among hospitalised older people [173, 175, 194, 195]. However, the multidimensional frailty measures used in the hospital studies included comorbidities [195] that required the use of medicines as treatment, number of medicines used [173, 175], or both [194], as criteria to assess frailty. The inclusion of variables that related to medicine use to determine frailty status introduces bias when assessing the association between medicine use and frailty, due to the lack of independence between the frailty measure and the outcome.

In terms of determining the association between frailty and medicine use, the results from the cross-sectional analyses found that there were more frail older people than those who were non-frail that used multiple medicines (polypharmacy or hyperpolypharmacy) and medicines with anticholinergics or sedating effects as assessed using DBI [187, 189]. Depending on

individual's conditions, the use of multiple medicines can either be considered appropriate or inappropriate [196, 197]. In the study, no assessment was made on whether the presence of multiple chronic conditions among the frail older people was the indication for the use of multiple medicines. The presence of multiple chronic conditions is sometime used as a criterion within the medical dimension of frailty assessment (Chapter 1, section 1.2.3.3). No information was provided on whether the use of multiple medicines is appropriate in this population in view of their frailty status. The high use of DBI medicines is likely to be inappropriate for use in older population, due to the sedative and anticholinergic actions of the medicines included in the DBI [198-200]. The use of anticholinergic medicines has been associated with an increased risk of hospitalisation related to confusion or dementia [201] and a number of their side effects including dry mouth, blurred vision, nausea, vomiting, constipation, urinary retention have potential to contribute to frail status, as the side effects can influence some of the factors commonly assessed in the physical dimension of frailty assessment. Cognitive function is one of the characteristics often measured within the psychological dimension of frailty assessment (Chapter 1, section 1.2.3.2). However, one of the limitations of cross-sectional analysis is that it is not possible to determine whether the DBI medicines or DBI medicines use contributed to frailty development.

Contrary to the other studies on the use of anticoagulants among older people with atrial fibrillation, one of the cross-sectional studies showed that frail participants with atrial fibrillation were more likely to be treated with anticoagulants [190]. The study, however, used a classification of frailty that combined pre-frail and frail participants into the frail group. Therefore, the inclusion of pre-frail participants may have confounded the relationship between frailty and the use of anticoagulants. At the population level, there is evidence that shows the benefit of these medicines outweighs the risk in the older population. However, it

is not possible to determine whether the use of anticoagulants is appropriate in the study population, because the presence of cognitive impairment associated with frailty is not known. A person who was considered frail and where cognitive impairment was a major contributor to his or her frail status may not have the skills to manage the dietary and monitoring requirements of the anticoagulant, and so at the individual level a different risk profile exists.

The longitudinal studies attempted to address the question of whether medicines contribute to the development of frailty. These studies assessed medicine use at baseline in non-frail or pre-frail participants and then determined whether medicine use was associated with developing frailty. One longitudinal study in non-frail and pre-frail, older Australian men found that the use of potentially inappropriate medicines (polypharmacy and DBI medicines) was associated with an increased risk of being classified as frail at follow-up [187]. While this could suggest that the use of potentially inappropriate medicines lead to the development of frailty, the results were not stratified by non-frail and pre-frail status at baseline. The majority of those who became frail in this study were pre-frail at baseline (67 of 77 people). Further, at baseline, the pre-frail group were more likely to be taking the potentially inappropriate medicines. This confounds the relationship as to whether it was the pre-frail status or the medicine use at baseline that made the major contribution to the development of frailty.

Another longitudinal study found that among a non-frail cohort, the use of medicines that were considered preventive medicines, statin or ACEI [202, 203], did not lead to differences in the risk of being classified as frail at follow-up among the users and non-users of statin or ACEI [185, 186]. Preventive medicines may potentially lead to a decrease in the likelihood of

frailty, when their use results in improvement of characteristics related to frailty assessment. However, these studies only assessed the use of medicines at baseline; the use of medicines during follow-up was not assessed. Neither of the studies were time to event analyses, nor did they censor participants when exposure to the medicines under study ceased. It is not known whether the preventive medicines were stopped due to adverse events, stopped prior to or after the development of frailty, or if issues such as end-of-life care influenced use. Further research is needed to investigate whether changes in the use of medicines, such as discontinuation, can influence the risk of frailty.

Another limitation of the published studies on the association between frailty and medicine use was the selection of confounding factors. The United States study included physical activity as a confounding factor however it was also used as a criterion to assess frailty [185, 186]. The Australian study [187] included number of comorbidities as a confounder where the causal relationship between the comorbidity and frailty is unclear [23]. Since comorbidity may be on the causal pathway (intermediate variable) between medicine use and frailty; which means that the effect of medicines use may influence comorbidity which then may impact the risk of frailty, therefore the inclusion of comorbidity as a confounder may be inappropriate [204, 205].

2.4.1 Research gaps

Overall, the studies suggest that there is an association between frailty status and the use of certain medicines. However, the studies did not enable a determination of the direction of the association between frailty and medicine use. Since the majority of studies were cross-sectional, it is unclear whether frailty causes the use of certain medicines or the use of medicines causes frailty. There were only two longitudinal that focused on the effect of

medicine use on developing frailty, however, one, which assessed the contribution of potentially inappropriate medicine use to frailty development included both non-frail and pre-frail participants at baseline, potentially confounding the association as pre-frail participants had higher use of potentially inappropriate medicines at baseline. Another study which assessed whether preventive medicines might lessen the risk of frailty, found that there was no difference in the frailty status at the end of follow-up. This may be due to the fact that the study did not censor participants upon cessation of medicines; which may underestimate the effect of preventive medicines on frailty. No studies in the community dwelling population were located that examined whether frailty status at baseline influenced the use of medicines over time.

Only five studies were identified in this review that examined the association between frailty and medicine use in the community-dwelling older population. Only one study was conducted in Australia and that study was undertaken only among older men population, which limits the generalisability of the study.

All of the available studies used a uni-dimensional frailty measure, whereas the current standard definition of frailty now includes a multidimensional assessment of frailty characteristics. The association between frailty as assessed using the multidimensional measure and medicine use is still not known.

One study showed that the use of potentially inappropriate medicines was associated with an increased risk of frailty, and another study showed that the use of preventive medicines was not associated with risk of frailty. However, it is not known whether stopping potentially inappropriate medicines or continuing preventive medicines influences the risk of frailty; understanding these associations may provide evidence to support the safe and effective use

of medicines that can include reducing the use of potentially inappropriate medicines use or increasing the use of preventive medicines in the older population.

The list of medicines examined in the available studies was not comprehensive. Only the Australian study examined 16 commonly used medicines in an older population in terms of the association between mean daily dose and frailty. The association between frailty and other commonly used medicines in an older population is still unknown.

2.5 Conclusion

In this chapter, a review of the literature on the association between frailty and medicines use in community-dwelling older population was presented. The findings suggest that there is an association between frailty and medicines use. However, due to the complex interplay between frailty and medicine use as well as the limitations of the available studies, there remains uncertainty as to the direction of association between frailty and medicine use. No studies examined how frailty status influenced medicine use. There were several gaps identified including the lack of research in the Australian setting, with only one Australian study located. Further, frailty was only assessed using a uni-dimensional measure, and the list of medicines examined was not comprehensive. In the next chapter the aim of this thesis is described and an overview of the studies undertaken to address these aims is presented.

Chapter 3:
Research aims and overview of studies

3.1 Introduction

As was shown in the review of the literature presented in Chapter 1, frailty is a multidimensional syndrome that may be used to classify older people for their risk of adverse health outcomes [23, 92]. There are, however, several challenges in the assessment of frailty. In the absence of a gold standard, as well as the lack of consensus on the variables needed to assess frailty, there been 52 frailty measures developed, often using different criteria as the basis of the assessment, which results in potential for different measures to estimate frailty differently. However, when limited to measures that have acceptable predictive performance, only seven measures have been found to have acceptable accuracy (AUC: 0.6-0.85) for a prognostic measure. These were the Frailty Phenotype [21], the Simplified Frailty Phenotype [74], the Frailty Index [66], the FRAIL scale [102], the Prognostic Frailty Score [73], the Frailty Index from Comprehensive Geriatric Assessment (FI-CGA) [50], and the Edmonton Frailty Scale [78].

In terms of frailty prevalence, the prevalence of frailty among the community-dwelling older population varied from 4% up to 59%, across studies [171]. The studies often used different frailty measures and no studies were located that have examined the extent to which different frailty measures identify the same people as frail (i.e. the overlap in the assessment of frailty in the same person across measures). In Australia, the prevalence of frailty in a general older population has also not been reported. The two Australian studies that have been undertaken, used two different frailty measures to identify frailty in two different populations of older

men. The studies reported prevalence estimates of frailty of 9.4% using the Fried Frailty Phenotype in one population [172] and 15.2% using the FRAIL scale in a different population [102]. It is not known if the different estimates are due to a difference in actual prevalence in the different populations or whether it is a feature of the different frailty measures used.

There has not been an Australian study that has examined the validity of frailty measures in a community-dwelling older Australian population. The benefit of identifying a valid frailty measure for the Australian community dwelling population is that it will assist with the development and application of frailty measures in wider Australian health care databases. Australia has a number of population wide data sets that are applicable to the community dwelling population, including federally: the Australian Government Department of Veterans' Affairs (DVA) data, the Pharmaceutical Benefits Schedule (PBS), Medicare, and the National Aged Care Data Clearinghouse (NACDC). At the state and territory levels, Australia is investing in data linkage units to enable linked health and social services data to be established [206]. Before progressing to see the applicability of frailty measures and their potential for adaptability in national data sets, the initial step would be to validate the measures in a high quality Australian data set.

Frailty has been associated with adverse health outcomes [60, 75, 92]. Similarly, medicine use and medicine-related problems among the older population has also been associated with adverse health outcomes [176]. In Chapter 2, the review of the literature found there had only been five published studies assessing the association between frailty and medicine use and, only one of these studies was conducted in Australia, and that was undertaken in a sample of older Australian men. The studies found an association between frailty and medicines use.

However, limitations of study design, including the cross sectional design of three studies and the inclusion of the pre-frail participants at baseline in the cohort studies have limited any conclusions that can be made about whether certain medicines were used because people were frail or the medicines themselves contributed to worsening frailty.

The studies in this thesis address the gaps in the literature. Firstly, by assessing the extent of frailty among older Australians. Secondly, by identifying a valid frailty measure to use in the Australian setting, and finally by examining the association between frailty and medicine use over time in an Australian population.

3.2 Research aims

Specific aims of the research are:

1. To determine the prevalence of frailty among the Australian older population.
2. To determine the validity of existing internationally validated frailty measures in an Australian older population.
3. To examine the association between frailty and medicine use changes over time.

3.3 Data source

This research used data from the Australian Longitudinal Study of Ageing (ALSA) which is a population based cohort study with a representative sample of 2087 older people aged 65 years and over [207]. The study participants were selected randomly from the South Australian electoral roll. The ALSA data set contains data from 1992 to 2014. There were 13 waves of data collection; waves 1, 3, 6, 7, 9, 11, and 13 involved interviews in the participants' home and clinical examinations. The other waves involved phone interviews. The ALSA data set was chosen for this research because it includes information on all frailty

dimensions: physical, psychological, medical, social, and environmental, as well as data on adverse health outcomes. In addition, the data collection methods that were used were similar to the methods used in the existing internationally validated frailty measure studies; data were collected by interviews and clinical examinations.

3.4 The frailty measures

Four frailty measures were selected for analysis using the following criteria: the measure had been validated for its predictive ability for mortality, the validity study was undertaken in a community-based population of older people, and used assessment criteria that did not involve clinical judgment, and the variables of the measure were available in the ALSA dataset. Additionally, all four measures had to have had published validity studies with acceptable accuracy scores for a prognostic measure, AUC values between 0.6 and 0.85.

Of the four frailty measures selected, two were multidimensional measures: the Frailty Index, developed by Mitnitski et al., [66], and the Prognostic Frailty Score, developed by Ravaglia et al., [73]. Two uni-dimensional measures were also selected: the Frailty Phenotype, developed by Fried et al., [21]; the Simplified Frailty Phenotype, developed by Kiely et al., [74]. The two uni-dimensional measure were chosen because Frailty Phenotype had been used in prior studies of frailty and medicine use [185-187], while the Simplified Frailty Phenotype is a related measure.

3.5 Overview of studies

3.5.1 Study 1: How common is frailty in older Australians?

In Chapter 4, a study that addressed the first aim of this thesis, which was to determine the prevalence of frailty in an older Australian population, is presented. Four internationally

validated measures: Frailty Phenotype, Simplified Frailty Phenotype, Frailty Index, and Prognostic Frailty Score, were selected to measure the prevalence of frailty in the ALSA population. Since limited information exists on the extent of overlap between frailty measures, an analysis was also undertaken to compare the extent to which the frailty measures identified the same person as frail. It was hypothesised that the different frailty measures would identify the same individuals as frail.

3.5.2 Study 2: Predictive performance of four frailty measures in an older Australian population

The study presented in Chapter 5 examined the predictive validity of the four frailty measures, therefore this study was not hypothesis-driven. The study aimed to examine the accuracy of four internationally validated frailty measures in predicting adverse outcomes for the purpose of identifying the frailty measure with the best predictive validity. The measure with the best predictive validity was then selected for use in subsequent studies of the association between medicine use and changes in frailty over time.

3.5.3 Study 3: Construct validity of four frailty measures in an older Australian population: A Rasch analysis

In study 2, the predictive validity of the frailty measures examined were similar. Therefore, the construct validity of the frailty measures was assessed and presented in Chapter 6. The availability of a gold standard is important in determining the accuracy of a measure. Because there is no gold standard of frailty, relying on the accuracy assessment alone to compare the validity of frailty measures may not be suitable. Therefore, the study presented in Chapter 6 aimed to compare the construct validity of the four frailty measures using an approach called Rasch analysis, again with the aim of identifying the frailty measure with the best construct validity, which would then enable selection of the frailty measure to be used in subsequent studies of the association between medicine use and changes in frailty over time. This study was not hypothesis-driven as it was aimed to assess the validity of the four measures.

3.5.4 Study 4: Selection and validation of frailty measure for a medicine use study

In the assessment of the predictive and construct validity of the four frailty measures, the frailty measure with the best predictive and construct validity was one that included morbidities, the Frailty Index. The morbidities in the Frailty Index included many that are commonly treated with medicines. For the purposes of research to understand the association between medicine use and changes in frailty over time, a measure is required that does not include morbidities treated by medicines. The inclusion of morbidities that are treated by medicines as criteria by which frailty is determined would bias the research as the frailty criteria and medicine use would not be independent. For this reason, a further study was conducted with the aim of determining the predictive validity and construct validity of a modified version of the measure when morbidities were excluded. Similar to Study 2 and Study 3, there was no hypothesis postulated in this study. This is the fourth study of thesis and is also presented in Chapter 6.

3.5.5 Study 5: Understanding the association between medicine use and frailty changes over time

The last study in this thesis is presented in Chapter 7. This study was conducted to address the last aim of this thesis; to examine the association between frailty and medicine use over time. In undertaking this research, both a cross sectional and cohort study was employed.

The cross sectional study tested the *a-priori* hypothesis that the distribution of frailty scores is independent of the number of medicines used.

The cohort study examined the effect of ceasing medicines on frailty score changes. Cohorts of older people using the same medicines at baseline were established. Subsequently, the

change in frailty scores was compared between those who ceased using medicines and those who continued using medicines. Three *a-priori* hypotheses were tested:

1. Older people who discontinued the use of potentially inappropriate medicines would have no difference in changes to their frailty scores compared to those who continued.
2. Older people who discontinued the use of symptom relieving medicines would have no difference in changes to their frailty score compared to those who continued.
3. Older people who discontinued the use of preventive medicines would have no difference in changes to their frailty score compared to those who continued.

Chapter 4:
How common is frailty in older Australians?

This chapter examined the first aim of the thesis, which was to determine the prevalence of frailty in general older Australian population. Four internationally validated frailty measures were used to identify frailty. The agreement between the four measures in assessing frailty was also examined. The null hypothesis underpinning the comparison between the four measures was that the different frailty measures would identify the same individuals as frail. This chapter presents the manuscript as published in the Australasian Journal on Ageing. Since this study was conducted, six systematic reviews of frailty measures as well as individual studies on frailty measures have been published. This is why there are more frailty measures reviewed in Chapter 1 (52 frailty measures), than referred to in the published paper (21 frailty measures).

4.1 Abstract

Aim: To determine the prevalence of frailty in a cohort of older Australians

Methods: Frailty status of the 2087 participants of the Australian Longitudinal Study of Ageing (ALSA) was assessed based on the questionnaire responses at the baseline interview. Frailty status and prevalence were assessed using four measures: two uni-dimensional measures (Frailty Phenotype, and Simplified Frailty Phenotype) and two multidimensional measures (Frailty index, and Prognostic Frailty Score). The agreement in frailty assignment between the four measures was determined.

Results: The multidimensional measures identified more people as frail (17.5% and 49.4%) than the uni-dimensional (2% and 8.8%). There was little agreement between the measures, only 0.5% of the participants were identified as frail by all four measures

Conclusions: The apparent prevalence of frailty varied when different measures were used. It is important for clinicians and researchers to be aware that different frailty measure may identify different groups of older people as frail.

Keywords: Australia, frailty, frailty measure, older people, prevalence

4.2 Introduction

Frailty has been defined as "*a multidimensional syndrome characterised by decreased reserve and diminished resistance to stressors"* [23]. Being frail has been associated with an increased risk of adverse health outcomes, including mortality, hospitalisation, nursing home admission, falling, and medicine-related problems [10, 21, 73, 159, 162, 173, 183, 187]. Identifying frail individuals is increasingly recognised as an important issue to mitigate adverse outcomes [83, 208].

At least 21 measures to identify frailty have been developed; however, there is no consensus on the elements that contribute to frailty status [23, 60, 83, 209]. The available frailty measures can be categorised into two broad types: uni-dimensional and multidimensional. Uni-dimensional measures assess a range of physical characteristics to determine frailty such as: physical activity, muscle weakness or nutritional status. There is an overlap between the assessment of the physical characteristics of frailty and sarcopenia, which included assessment of muscle mass, strength, and function [210]. Accordingly the uni-dimensional measures can be referred to as the sarcopenic frailty measure. Multidimensional measures assess a combination of physical characteristics and psychological factors, social factors,

environmental factors, or medical factors. The multidimensional measures were in line with the expert consensus that *"frailty is multidimensional and may involve psychological, social, emotional and spiritual aspects in addition to physical components"* [23]. Frailty measures also vary in how they classify frailty. Some measures classify frailty status dichotomously: non-frail and frail, whereas other measures classify frailty into three categories: non-frail, pre-frail, and frail.

Estimates of the prevalence of frailty vary. A systematic review found that the prevalence ranged from 4% up to 59% depending on the frailty measure used [171]. Studies that compared different frailty measures in the same population also found that the prevalence of frailty varied according to the measure used [159, 162, 211].

In Australia, there have been few studies on the prevalence of frailty. Studies have been conducted in specific patient populations such as hospitalised patients [174, 212] or males [102]. Australian studies that used a uni-dimensional frailty measure estimated that 66% of the hospitalised older patients were frail [174] and 9% of the older men were frail [212]. Another study using a multidimensional measure, estimated that the prevalence of frailty among older men was 15% [102]. The prevalence of frailty among the wider population of older Australians has not been reported. This study aimed to determine the prevalence of frailty among the older Australians.

4.3 Methods

4.3.1 Study population

This study used the baseline data of a longitudinal survey; the Australian Longitudinal Study of Ageing (ALSA) [207]. The study population included 2087 older persons who were resident in Adelaide, South Australia aged 70 years or over and their spouses aged 65 years

and over; who were recruited by random sampling from the South Australian electoral roll [207]. Baseline data were collected in 1992 by interview and clinical examination. In the interview, participants were asked a range of questions to obtain information about their health-related problems, physical activity level, self-rated health and difficulty in daily activities. Clinical examination included measurement of weight, height, vision, and hearing, grip strength, as well as psychological testing. Full details of the data collected can be found at the ALSA's website, http://www.flinders.edu.au/sabs/fcas/alsa/.

4.3.2 Frailty measures

We reviewed 21 different frailty measures [60] and selected four for analysis using the following criteria: the measure had been validated for its predictive ability for mortality, the validity study was undertaken in a community-based population of older people, that used the assessment criteria that did not involve clinical judgment, and the variables of the measure were available in the ALSA dataset. Of the four frailty measures selected, two were uni-dimensional measures: frailty phenotype – developed by Fried et al [21]; simplified frailty phenotype – developed by Kiely et al [74]; and two were multidimensional measures: frailty index – developed by Mitnitski et al [66], and the prognostic frailty score – developed by Ravaglia et al [73]. The ALSA variables included in the analysis were a combination of self-report and direct physical examination in all of the frailty measures except in the frailty index, where only self-reported variables were used.

4.3.2.1 Frailty phenotype

The frailty phenotype is a uni-dimensional measure which assesses physical characteristics of frailty; it included five variables (Table4.1). Frailty status was categorised into three levels:

frail, pre-frail, and non-frail. Subjects with missing data on two or more of the five variables assessed were excluded from the analysis, thus the residual sample for analysis was 1566 subjects.

4.3.2.2 Simplified frailty phenotype

The simplified frailty phenotype is a short version of the frailty phenotype which; it included only three variables of physical characteristics (Table 4.1). This measure categorised frailty status into three levels: frail, pre-frail, and non-frail. Of the 2087 ALSA participants, 1173 subjects with complete data in all of the three variables were included in this analysis.

4.3.2.3 Frailty Index

The frailty index includes a multidimensional assessment of frailty: physical, medical, psychological, and social factors [66]. It included 39 variables (Table 4.1), which were based on those used previously in the ALSA dataset [213]. The frailty index variables were coded as binary (0= absence, 1= presence of frailty variables) or ordinal (0, 0.25, 0.5, 0.75 or 1) to allow grading of frailty variables [214]. Only two frailty variables were coded ordinally in this study (Table 4.1). Frailty was determined by dividing the total scores by total number of available variables assessed in one subject. The frailty index is scored from 0 to 1; a score of 0.25 or greater is the criteria for frailty [146]. All of the ALSA participants were included in the analysis, as most participants had complete data on all 39 variables, only 0.6% (13/2087) of the participants had two or more missing data. No participants had 10 or more missing data.

Table 4. 1 Application of four internationally validated frailty measures in the ALSA dataset

Frailty phenotype

Frailty phenotype	ALSA application
Unintentional weight loss: ≥4.5kg or ≥ 5% within one year (self-report)	BMI < 20
Low grip strength: - In the lowest 20% at baseline *(adj. for sex and BMI)*	Low grip strength: - In the lowest 20% at baseline *(adj. for sex and BMI)*
Self-rated exhaustion (CES-D scale) - Feel that everything was an effort or could not get going for 3/> days in the last week	Self-rated exhaustion (CES-D scale) - Feel that everything was an effort or could not get going for 3/> days in the last week
Walking time/15 feet(4.5m): - Slowest 20% at baseline *(adj. for sex and height)*	Walking time/8 feet(2.4m): - Slowest 20% at baseline *(adj. for sex and height)*
Low physical activity: - Low energy expenditure (M <383 , F <270 Kcals/week)	Low physical activity: - Walking for exercise/recreation in the past 2 weeks
Frail = presence of 3/> variables Pre-frail = presence of 1-2 variables Non-frail = absence of variables	

Simplified frailty phenotype

Simplified frailty phenotype	ALSA application
Unintentional weight loss > 4.5kg in last year (self-report)	BMI < 20
Unable to rise from chair 5times without use of arms	Unable to rise from chair 5times without use of arms
Low energy level (CES-D scale) - Could not get going for 3/> days in the last week	Low energy level (CES-D scale) - Could not get going for 3/> days in the last week
Frail = presence of 2/> variables Pre-frail = presence of 1 variables Non-frail = absence of variables	

Frailty index

Frailty index	ALSA application
Live alone	Live alone
Self-rated health *(coding details not available)*	Self-rated health - Poor = 1 - Fair = 0.75 - Good = 0.5 - Very good = 0.25 - Excellent = 0 *(coding criteria based on Searle et al [214])*
Arthritis	Arthritis
Asthma	Asthma
History of heart attack	History of heart attack
Hypertension	Hypertension
Migraine	Migraine
Parkinson's disease	Parkinson's disease
History of stroke	History of stroke
Thyroid disease	Thyroid disease

Ear, nose, throat problem	Ear, nose, throat problem
Mental disorder	Mental disorder
Genito-urinary problem	Genito-urinary problem
Diabetes	Diabetes
Cancer	Cancer
Chest pain	Chest pain
Constipation	Constipation
Dental problem	Dental problem
Sleep problem *(coding details not available)*	Sleep problem - Rarely/never = 0 - Sometimes = 0.5 - Often/almost always = 1
Spinal problem	Spinal problem
Hearing difficulty	Hearing difficulty
Eye trouble	Eye trouble
Skin problem	Skin problem
Hands shaking problem *(coding details not available)*	Hands shaking problem - No difficulty at all or a little difficulty = 0 - Some/ a lot of difficulty or just unable to do = 1 *(coding criteria based on Beckett et al [215] and Bannerman et al [216])*
Stooping/crouching/kneeling problem *(coding details not available)*	Stooping/crouching/kneeling problem - No difficulty at all or a little difficulty = 0 - Some/ a lot of difficulty or just unable to do = 1 *(coding criteria based on Beckett et al [215] and Bannerman et al [216])*
Difficulty with bathing	Difficulty with bathing
Difficulty with personal grooming	Difficulty with personal grooming
Difficulty with dressing	Difficulty with dressing
Difficulty with eating	Difficulty with eating
Difficulty with toileting	Difficulty with toileting
Difficulty with going out	Difficulty with going out
Difficulty with moving around	Difficulty with moving around
Difficulty with laundry/linen	Difficulty with laundry/linen
Difficulty with housework	Difficulty with housework
Difficulty with preparing meal	Difficulty with preparing meal
Difficulty with using telephone	Difficulty with using telephone
Difficulty with managing money	Difficulty with managing money
Difficulty with using public transport	Difficulty with using public transport
Difficulty with shopping	Difficulty with shopping
Frailty index score: (total variables score) / (39 – missing variables) Frail : ≥ 0.25	

Prognostic frailty score	
Prognostic frailty score	**ALSA application**
Age ≥80 year	Age ≥80 year
Male gender	Male gender
Low physical activity : - < 4h/week of moderate intensity activity	Low physical activity : - Walking for exercise/recreation in the past 2wks
Comorbidity: - Daily use of 3/> drugs and 2/> chronic diseases	Comorbidity: - Daily use of 3/> drugs and 2/> chronic diseases.
Sensory deficits - blind/deaf	Sensory deficits - blind/deaf
Calf circumference <31cm	Calf circumference <31cm
IADL dependency - any dependency on: - Using telephone - Travelling - Managing money - Taking medicines	IADL dependency - any dependency on: - Using telephone - Travelling - Managing money - (taking medicines n/a in ALSA)
Gait and performance score ≤24 (tinetti gait and balance test)	Presence of gait abnormalities
Pessimism about self-health (health worse than others)	Pessimism about self-health (health worse than others)
Frail = presence of 3/> variables Non-frail = absence of variables	

4.3.2.4 Prognostic frailty score

The prognostic frailty score is also multidimensional; it contained nine variables (Table 4.1) and assessed four different characteristics of frailty: age, physical, medical, and psychological [73]. It uses two categories of frailty status: frail and non-frail. The analysis for this measure included 1485 subjects with complete or only one missing item of the nine variables were included in the analysis.

4.3.3 Statistical analysis

The data analysis was performed using SAS software (Version 9.3 of the SAS system for Windows. Copyright 2011 SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to show the baseline characteristics of the study population, as well as the prevalence of frailty and proportion identified as frail by all measures. Only participants with complete data on all four frailty measures variables were included in the comparison analysis to examine the similarities between the frailty groups.

4.4 Results

Table 4.2 shows the baseline characteristics of the ALSA population. The frailty index classified 17.5% of participants as frail and 49.4% of participants were frail according to the prognostic frailty score; both of which are multidimensional. The uni-dimensional measures identified only 2% and 8.8% of participants as frail according to the simplified frailty phenotype and the frailty phenotype respectively. Of the uni-dimensional measures, frailty phenotype classified 57.7% of the population as pre-frail whereas the simplified frailty phenotype identified 14.8% as pre-frail. The characteristics of the frail participants as identified by the four measures are shown in table 4.2.

Table 4. 2 Prevalence of frailty among the selected ALSA population characteristics

Baseline characteristics	All participants (N= 2087)	Frailty phenotype (N= 1566)	Simplified frailty phenotype (N= 1173)	Frailty index (N= 2087)	Prognostic frailty score (N=1485)
Frailty prevalence – N (%)	**N/A**	**137 (8.8%)**	**24 (2%)**	**366 (17.5%)**	**733 (49.4%)**
Age – mean (SD)	78.2 (6.7)	81.6 (6.42)	81.3 (5.2)	82 (6.7)	80.3 (6.1)
Gender – N (%)					
Male	1056 (50.6%)	67 (48.9%)	11 (45.8%)	145 (39.6%)	492 (67.1%)
Female	1031 (49.4%)	70 (51.1%)	13 (54.2%)	221 (60.4%)	241 (32.9%)
Living arrangement – N (%)					
Community living	1961 (93.9%)	120 (87.6%)	22 (91.7%)	315 (86.1%)	690 (94.1%)
Institution	126 (6.1%)	17 (12.4%)	2 (8.3%)	51 (13.9%)	43 (5.9%)
≥1 IADL difficulty – N (%)	716 (34.3%)	94 (68.6%)	17 (70.8%)	291 (79.5)	335 (45.7%)
≥1 ADL difficulty – N (%)	359 (17.2%)	58 (42.3%)	3 (12.5%)	227 (62.0%)	175 (23.9%)
Number of comorbidities – median (IQR)	5 (3 – 7)	6 (4 – 9)	7 (5 – 11)	8 (6 – 10)	6 (4– 8)
Number of medicines – median (IQR)	3 (1 – 5)	4 (3 – 7)	4.5 (3 – 7)	5 (3 – 7)	4 (2 – 5)

SD: standard deviation; IQR: interquartile range; ADL: activity of daily living; IADL: instrumental activity of daily living

Frailty scores were available for all four measures for 1113 people. Table 4.3 shows that there was only minimal agreement between the four different frailty measures; with 35.2% (392/1113) of participants identified as frail by only one measure, 9.3% (103/1113) by two measures, 3.1% (34/1113) by three measures, and only 0.5% (6/1113) by all four measures (Table 4.3).

Table 4. 3 Proportion of overlap between frail participants identified by four measures

Frailty measure	Frail participants – N (%)
No overlap (one measure only)	
SFP	1 (0.1%)
FP	14 (1.3%)
FI	25 (2.2%)
PFS	352 (31.6%)
Total	392 (35.2%)
Two measures overlap	
SFP – FP	1 (0.1%)
FP – FI	3 (0.3%)
FI – PFS	75 (6.7%)
PFS – SFP	5 (0.4%)
SFP – FI	0 (0)
FP – PFS	19 (1.7%)
Total	103 (9.3%)
Three measures overlap	
SFP – FP – FI	0 (0)
FI – PFS – SFP	6 (0.5%)
FI – PFS – FP	24 (2.2%)
SFP – PFS – FP	4 (0.4%)
Total	34 (3.1%)
Four measures overlap	
SFP – FP – FI – PFS	6 (0.5%)
Total	6 (0.5%)

SFP: Simplified frailty phenotype; FP: Frailty phenotype; FI: Frailty index; PFS: Prognostic frailty score

4.5 Discussion

We found that the apparent prevalence of frailty varied widely when different frailty measures were used. The uni-dimensional measures, which focus only on physical characteristics, classified fewer participants as frail (2% and 8.8%) compared to the multidimensional measures, which in addition to physical characteristics also take psychological and medical characteristics into account (17.5% and 49.4%). A measure that identifies half of older people as frail is unlikely to be suitable to identify frail older people in practice as it would identify too many people for intervention. Similarly the measure that only identifies 2% of frailty is a constrictive measure. In addition, feasibility is an important issue in the application of available frailty measures; of the four measures used in this study only frailty index was able to be implemented to all 2087 ALSA participants, whereas the other three measures had excluded a number of participants due to missing data.

There was little overlap between the four frailty measures, with only 0.5% of participants identified as frail by all four measures. The fact that all measures have been shown to be predictive of adverse outcomes [21, 73, 74, 213], the minimal overlap means that there are many factors that contributes to frailty and no available measure incorporates all of these factors.

Our results suggest that older people would only be identified as frail when a particular frailty measure was used, in other words frailty status changes depending on the measure used. This creates a significant challenge in identifying the frail older people. Therefore a standardised frailty measure is required to identify such people and to determine their needs as well as their risk of adverse health outcomes.

This was the first Australian study to examine the prevalence of frailty in a cohort of community-dwelling older participants. A study by Mitnitski et al had assessed the correlation of frailty and mortality in the ALSA dataset, but did not report the prevalence of frailty [213]. Previous Australian studies examined the prevalence of frailty among the older Australian men and among hospital patients [102, 174, 212].

In applying the frailty measure we needed to make modifications to some of the variables to construct each frailty measure in the ALSA dataset. For example, the variable – unintentional weight loss of 5 kg was not available in the baseline ALSA dataset. We used a low BMI of <20 as the indication for underweight to replace unintentional weight loss [216]. As a result participants with a BMI $\geq$ 20 who underwent unintentional weight loss may have been overlooked, on the other hand this modification may have caused incorrect assessment of participants who had a BMI <20 but whose weight was stable. This could contribute to the

variations between the prevalence of frailty found in this study with the prevalence found in the other studies using the same frailty measure.

Using the simplified frailty phenotype, our study found only 2% of participants was frail whereas another study that used the weight loss variable found 4% were frail [74]. In addition, our data were collected in 1992 and were limited to the residents of South Australia; therefore our results might not be representative of the current situation of older Australians.

4.6 Conclusions

The apparent prevalence of frailty varied widely when different frailty measures were used. Each frailty measure identified a different group of older people as frail, with only limited agreement between the measures. Therefore, it is important for clinicians to be aware that frailty status can change depending on the measures used. Further research is needed to strengthen the definition of frailty so as to contribute to a better understanding of what variables are necessary to construct a standardised frailty measure.

4.7 Summary

The research in this chapter found that the prevalence of frailty varied from 2% to 49% depending on the frailty measure used. The null hypothesis that different frailty measures would identify the same person as frail, was not supported. In fact, there was very little overlap between all four measures, with only six people (0.5% of the total population) identified as frail by all four measures. For the 392 frail participants (35% of total sample), there was no overlap between frailty measures, meaning that the different measures identified different people as frail. This raises questions as to which frailty measure is identifying the true frail population. In order to understand this, the next chapters of this thesis presents a study examining the validity of the four measures to determine which measure has the best validity in the Australian setting.

Chapter 5:
Predictive performance of four frailty measures in an older Australian population

In the previous chapter, the prevalence estimates of frailty were found to vary depending on the frailty measure used. In addition, there was found to be minimal overlap of frail groups between the four measures. This means that an older person may be identified as frail by one measure but may not be identified as frail by the other measure. This raises the question as to which frailty measure is most valid. This chapter presents a study that aimed to examine the predictive validity and accuracy of the four frailty measures. This chapter contains a manuscript that has been published in the Journal of Age and Ageing.

5.1 Abstract

Background: there are several different frailty measures available for identifying the frail elderly. However, their predictive performance in an Australian population has not been examined.

Objective: to examine the predictive performance of four internationally validated frailty measures in an older Australian population.

Methods: a retrospective study in the Australian Longitudinal Study of Ageing (ALSA) with 2087 participants. Frailty was measured at baseline using: frailty phenotype (FP), simplified frailty phenotype (SFP), frailty index (FI), and prognostic frailty score (PFS). Odds ratios (OR) were calculated to measure the association between frailty and outcomes at wave 3 including: mortality, hospitalisation, nursing home admission, fall, and a combination of all outcomes. Predictive performance was measured by assessing sensitivity, specificity, positive and negative predictive values (PPV and NPV), and likelihood ratio (LR). Area under the

curve (AUC) of dichotomised and the multi-level or continuous model of the measures was examined.

Results: Prevalence of frailty varied from 2% up to 49% between the measures. Frailty was significantly associated with an increased risk of any outcome, OR (95% confidence interval) for FP: 1.9 (1.4-2.8), SFP: 3.6 (1.5-8.8), FI: 3.4 (2.7-4.3), and PFS: 2.3 (1.8-2.8). PFS had high sensitivity across all outcomes (sensitivity: 55.2% - 77.1%). The PPV for any outcome was highest for SFP and FI (70.8% and 69.7% respectively). Only FI had acceptable accuracy in predicting outcomes, AUC: 0.59 – 0.70.

Conclusions: Being identified as frail by any of the four measures was associated with an increased risk of outcomes; however their predictive accuracy varied.

Keywords: frail elderly, sensitivity, specificity, Australia

5.2 Introduction

Ageing is associated with declining health; therefore the increase in the ageing population is likely to have significant impact on health care services [22]. Not all older people have the same rate of declining health, some are at higher risk of adverse health outcomes than the others, and this is often recognized as frailty [21, 22, 156, 217].

Identifying frailty is becoming increasingly important in clinical decision making, particularly when considering the risks and benefits of treatment in an older population [19, 75, 83, 218]. Many frailty measures have been developed to help identify frail older people and the measures have shown that frailty is associated with an increased risk of adverse outcomes, including falls, nursing home admission, hospitalization, and death [79, 159, 162]. Several population-based studies have examined the predictive performance of frailty measures in predicting adverse outcomes [154, 159, 161, 162]. However, no study has assessed the predictive performance of frailty measures in the Australian setting.

Our study aimed to compare the accuracy of four internationally validated frailty measures for predicting mortality, hospitalisation, nursing home admission, fall, and these outcomes combined in an older Australian population.

5.3 Methods

5.3.1 Study population

This study used data from the Australian Longitudinal Study of Ageing (ALSA) which is a population-based cohort study of 2087 older people aged 70 years and over, or their spouses aged 65 years and over [207]. The ALSA dataset contains 11 waves of data, collected between 1992 and 2010. Baseline data (wave 1) were used to measure frailty status. Outcome variables were obtained from wave 3 follow up data. The follow up time from wave 1 to wave 3 was up to 3 years. Further details of the ALSA study can be found at: http://www.flinders.edu.au/sabs/fcas/alsa/.

5.3.2 Frailty measures

The four frailty measures selected in this study were: frailty phenotype (FP) – developed by Fried et al [21], simplified frailty phenotype (SFP) – developed by Kiely et al [74], frailty index (FI) – developed by Mitnitski et al [213], and the prognostic frailty score (PFS) – developed by Ravaglia et al [73].

5.3.2.1 Frailty phenotype

The FP is a uni-dimensional measure which only assesses the physical characteristic of frailty. In the original study it included five variables: unintentional weight loss, low grip strength, self-rated exhaustion - assessed using two questions from the Center of Epidemiologic Studies Depression (CES-D) Scale, low physical activity – assessed by calculating energy expenditure (Kcals/week), and slow walking time [21]. In our study, the FP was compiled as: body mass index (BMI) <20, low grip strength, self-rated exhaustion -

assessed using two questions from the Center of Epidemiologic Studies Depression (CES-D) Scale, physical activity – assessed using a question on walking for exercise or recreation in the past 2 weeks, and slow walking time. Frailty status was categorised into three levels: frail, pre-frail, and non-frail. The presence of 3 or more variables was defined as frail, and pre-frail was defined by the presence of up to 2 variables. Non-frail was the absence of any variables. Participants with two or more missing variables were excluded from the analysis.

5.3.2.2 Simplified frailty phenotype

The SFP is a short version of FP; it included only three variables of physical characteristics: unintentional weight loss, inability to rise from a chair 5 times without use of arms and low energy level (assessed using one question from the CED-S scale) [74]. In our study, only the unintentional weight loss variable was modified to BMI <20. This measure also categorised frailty status into three levels: participants with two or more variables present were classified as frail and the presence of one variable was categorised as pre-frail. Only participants with complete data in all of the three variables were included in the analysis.

5.3.2.3 Frailty Index

The FI is a multidimensional measure; it assesses four different characteristics of frailty: physical, medical, psychological, and social contributors [66, 213]. In this study we used Frailty Index with 39 variables (Appendix D) that was previously used by Mitnitski et al [213] in assessing frailty among ALSA population. Frailty was calculated by dividing the number of deficits present with the total number of deficits assessed for each subject. The frailty score is a continuous score which ranges from 0 to 1, a greater score indicates increased frailty. The score was dichotomised to allow comparison with other frailty measures [133, 146]. Consistent with previous research that has dichotomised the Frailty Index, a frailty score of 0.25 or greater was the criteria for frailty; a score of less than 0.25

was classified as non-frail [133, 146]. Participants with 10 or more missing variables were excluded in the analysis.

5.3.2.4 Prognostic frailty score

The PFS is also a multidimensional measure; it assesses four different characteristics of frailty: age, physical, medical, and psychological contributions [73]. The score consists of 9 variables: age ≥80 years, male gender, low physical activity defined as less than 4 hours per week of moderate intensity activity, co-morbidity, sensory deficit, calf circumference <31 cm, instrumental activity of daily living (IADL) dependence, gait problem, or health pessimism [73]. In this study the 9 variables were: age ≥80 year old, male gender, low physical activity – assessed by a question on walking for exercise/ recreation in the past 2 weeks, co-morbidity, sensory deficit, calf circumference <31 cm, IADL dependence, gait problem, health pessimism. Frailty was classified as the presence of 3 or more variables, and the presence of 2 or less variables was classified as non-frail [73]. Participants with complete data or those with only one missing variable of the nine variables were included in the analysis.

5.3.3 Reference standard

In assessing the accuracy of a measure, a reference standard is needed to differentiate between persons with a target condition and those without [157]. There is no available consensus on the clinical or laboratory markers of frailty [217], which can be used as a reference standard. In this situation, the prognostic value of a measure can be used as a reference standard [157, 158]. Experts have agreed that a frailty measure '*can help in identifying and stratifying older persons at high risk of disability and/or other adverse outcomes'* [217], therefore the presence of adverse outcomes has been commonly used as a reference standard in assessing the performance of a frailty measure [154]. There is no

agreement yet of which adverse outcomes are important to assess and whether to assess them individually or as a combined variable [156].

Studies validating frailty measures have used a number of outcomes including, mortality and adverse health outcomes such as hospitalisation, fall, or nursing home admissions [21, 73, 74, 162, 213]. In this study, the adverse outcomes chosen as the reference standard were death, nursing home admission in the last 12 months, hospitalisation in the past year, fall – at least one fall in the past year, and a combination of these outcomes. Death data was obtained from the Registry of Births, Deaths and Marriages [207], while other outcomes were obtained from self-reports at wave 3. As interviews occurred at the subjects' place of residence, nursing home admission is likely to be verified by the interviewer. Outcome variables were coded as binary variables: presence or absence of outcomes. Disability was not chosen as the reference standard in this study, because difficulties in daily activities which are used to define disability were also used in FI and PFS. Of the 1679 participants at wave 3, adverse outcomes data were missing in 81, 8, and 7 participants, for data on nursing home admission, hospitalisation, and fall respectively.

5.3.4 Statistical analysis

The proportion of participants with each adverse outcome was examined for each frailty status and compared with those with no frailty status because of missing data. A logistic regression analysis was used to examine the association between frailty as identified by each of the measures and adverse outcomes. This analysis used a dichotomised frailty status (frail and non-frail), for those measures that had a pre-frail group, this was combined into non-frail. For each measure the sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) were calculated. The area under the curve (AUC) values were used to examine the ability of each measure to differentiate between the frail and non-frail participants. In this study AUC values between 0.6 – 0.85 were considered

as acceptable accuracy for a prognostic measure [160, 219]. The AUC values for the full model (i.e. multi-level or continuous scale) of the frailty measures were also assessed.

Because the Frailty Index is a continuous measure, not a dichotomous measure, the predictive performance of the Frailty Index was also assessed using different cut-off points to determine if the predictive performance differed where different cut-off points were employed (Appendix D). To determine if the predictive validity of the frailty measures using full population data were comparable; we also undertook a secondary analysis where the predictive performance of the four measures was compared on the sub-sample of the population which had complete data for all four measures (Appendix D). No adjustment was made for age or gender because, the prognostic frailty score includes age and sex in the assessment of frailty. All analyses were undertaken using the SAS software (Version 9.3 of the SAS system for Windows. Copyright 2011 SAS Institute Inc., Cary, NC, USA).

5.4 Results

Baseline characteristics of the ALSA participants are presented in table 5.1. Participants with missing data were older and more likely to be living in an institution compared to those in the analysis group. The majority of participants were living in the community. The prevalence of frailty varied between the measures; the SFP identified the lowest number of frail participants - 2%, whereas the PFS identified the highest number of frail participants - 49%.

Figure 5.1 shows the distribution of adverse outcomes by frailty status for all participants. The proportion of adverse outcomes across frailty status was different for all four measures; except for nursing home admission across frailty status identified by FP. Participants with missing data had a greater proportion of any adverse outcomes than their non-frail and pre-frail counterpart, but were often had less proportion of any adverse outcomes than those who were identified as frail.

In all four measures those identified as frail were more likely to have adverse outcomes than the pre-frail or non-frail (Table 5.2). The odds of death within three years was highest among the frail group identified by FP - odds ratio (OR): 3.6, 95% confidence interval (CI): 2.4 – 5.3. The SFP identified frail participants with the highest odds of hospitalisation and new nursing home admission. The odds of a fall were highest among the frail group identified by FI.

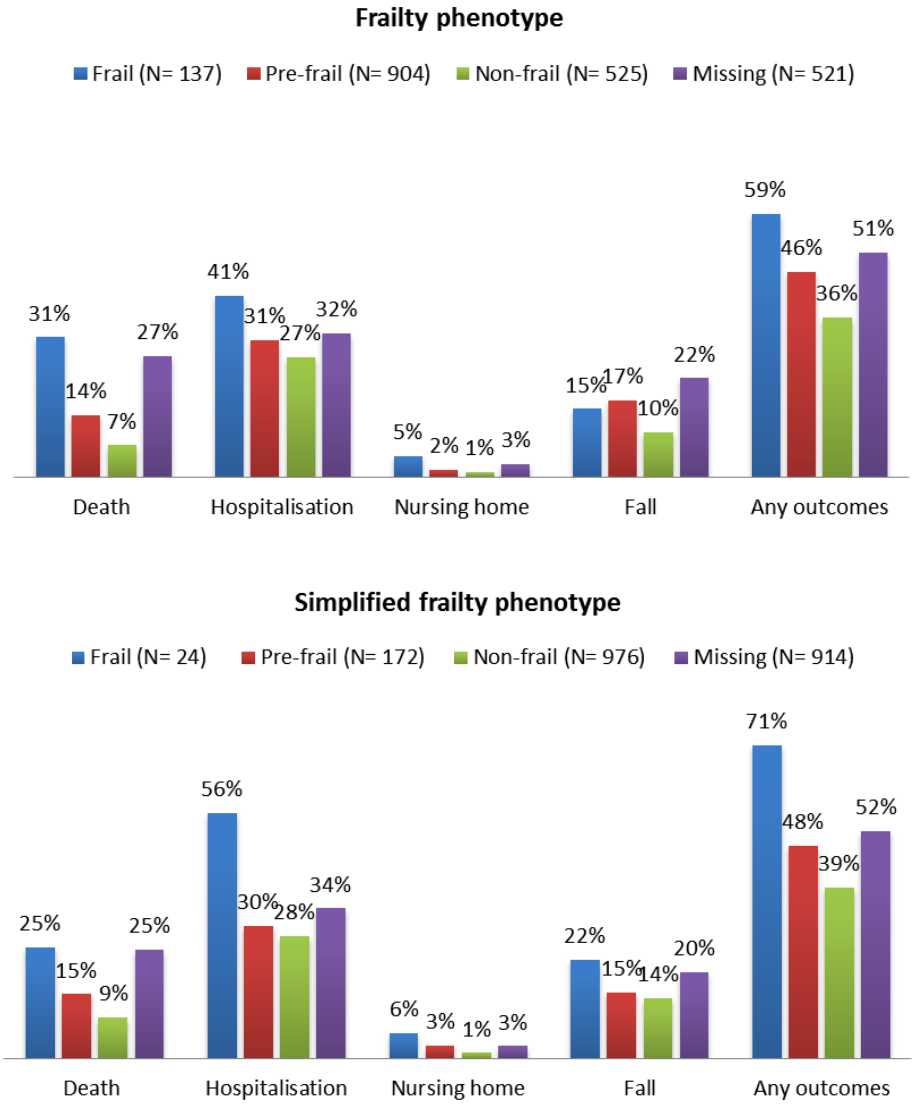
The PFS had the highest sensitivity values (58.6% – 77.1%); however, its specificity values were the lowest (54.7% - 59.5%) across all outcomes. The other three measures had <50% sensitivity but had high specificity (>80%). In all four measures, the PPV was highest when assessed for a combined outcome (59.1% - 70.8%) than for any individual outcome. The NPV was higher in all four measures for individual outcomes than for combined outcomes. PFS had low LR values (1.22 – 1.70) in all of the adverse outcomes assessed, compared to a range of 1.99 – 2.76 from another multidimensional measure - FI.

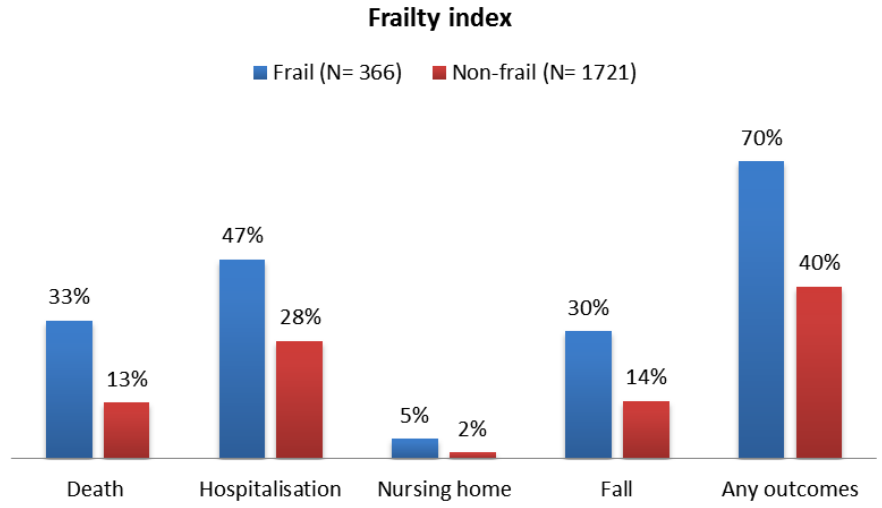
The AUC values of the dichotomised model of frailty measures were comparable to those of the multi-level or continuous model (Table 5.2). Of the 2087 participants, only, 1113 had complete data on the variables of all four measures; the predictive performance of all four measures was reduced when applied in this group (Appendix D).

Table 5. 1 Baseline characteristics and prevalence of frailty across four measures

Characteristic	Frailty phenotype			Simplified frailty phenotype			Frailty index	Prognostic frailty score		
	Analysis (N=1566)	Missing (N=521)	p-value	Analysis (N=1173)	Missing (N=914)	p-value	Analysis (N=2087)	Analysis (N=1485)	Missing (N=602)	p-value
Age – mean (SD)	77.4 (6.4)	80.5 (7.01)	<0.0001	76.7 (6.0)	80.1 (6.99)	<0.0001	78.2 (6.7)	77.3 (6.3)	80.4 (7.03)	< 0.0001
Gender – N (%)										
Male	816 (52.1%)	240 (46.1%)	0.0169	606 (51.7%)	450 (49.2%)	0.2710	1056 (50.6%)	766 (51.6%)	290 (48.2%)	0.1581
Female	750 (47.9%)	281 (53.9%)		567 (48.3%)	464 (50.8%)		1031 (49.4%)	719 (48.4%)	312 (51.8%)	
Living arrangement – N (%)										
Community living	1505 (96.1%)	456 (87.5%)	<0.0001	1148 (97.9%)	813 (88.9%)	<0.0001	1961 (94%)	1428 (96.2%)	533 (88.5%)	< 0.0001
Institution	61 (3.9%)	65 (12.5%)		25 (2.1%)	101 (11.1%)		126 (6%)	57 (3.8%)	69 (11.5%)	
Frailty prevalence – N (%)										
Frail	137 (8.8%)	n/a	n/a	24 (2%)	n/a	n/a	366 (17.5%)	733 (49.4%)	n/a	n/a
Pre-frail	904 (57.7%)			172 (14.8%)			-	-		
Non-frail	525 (33.5%)			976 (83.2%)			1721 (82.5%)	752 (50.6%)		

Figure 5. 1 Adverse outcomes by frailty status




Frailty index
Frail (N= 366)
Non-frail (N= 1721)
33%
13%
47%
28%
5%
2%
30%
14%
70%
40%
Death
Hospitalisation
Nursing home
Fall
Any outcomes

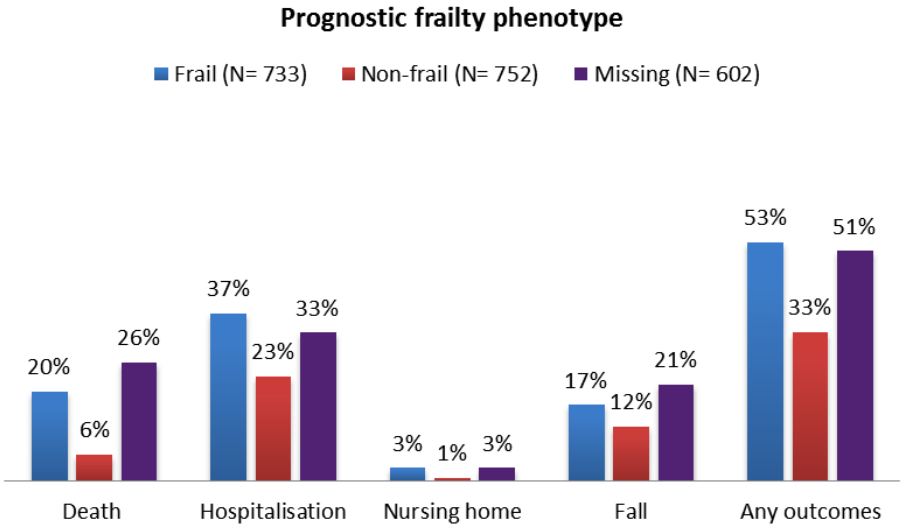

Prognostic frailty phenotype
Frail (N= 733)
Non-frail (N= 752)
Missing (N= 602)
20%
6%
26%
37%
23%
33%
3%
1%
3%
17%
12%
21%
53%
33%
51%
Death
Hospitalisation
Nursing home
Fall
Any outcomes

Table 5. 2 Predictive performance of four frailty measures in predicting adverse outcomes.

Frailty measure	Prevalence of outcome	% outcome (frail/non-frail*)	Odds ratio – OR (95% CI)	Sensitivity	Specificity	PPV	NPV	LR	AUC (dichotomised model)	AUC (full model)†
Death at wave 3										
Frailty phenotype	205 (13.1%)	31.4 / 11.3	3.6 (2.4 – 5.3)	20.9	93.1	31.4	88.7	3.03	0.57	0.63
Simplified frailty phenotype	122 (10.4%)	25.0 / 10.1	2.9 (1.2 – 7.6)	4.9	98.3	25.0	89.9	2.88	0.52	0.55
Frailty index	346 (16.6%)	32.5 /13.2	3.2 (2.4 – 4.1)	34.4	85.8	32.5	86.8	2.42	0.60	0.66
Prognostic frailty score	188 (12.7%)	19.8 / 5.7	4.1 (2.8 – 5.8)	77.1	54.7	19.8	94.3	1.70	0.66	0.66
Hospitalisation										
Frailty phenotype	404 (30.1%)	40.8 / 29.3	1.7 (1.1 – 2.5)	9.9	93.8	40.8	70.7	1.59	0.52	0.54
Simplified frailty phenotype	292 (28.4%)	55.6 / 27.9	3.2 (1.3 – 8.3)	3.4	98.9	55.6	72.1	3.09	0.51	0.52
Frailty index	513 (30.6%)	46.7 / 27.6	2.3 (1.7 – 3.0)	23.8	88.1	46.7	72.4	1.99	0.56	0.59
Prognostic frailty score	379 (29.8%)	37.3 / 23.2	1.9 (1.6-2.5)	58.6	58.3	37.3	76.8	1.40	0.58	0.58
Nursing home admission										
Frailty phenotype	22 (1.7%)	4.6 / 1.5	3.2 (1.0 – 9.5)	18.2	93.4	4.6	98.5	2.76	0.56	0.59
Simplified frailty phenotype	15 (1.5%)	5.6 / 1.4	4.1 (0.5 – 33.1)	6.7	98.3	5.6	98.6	3.94	0.53	0.59
Frailty index	31 (1.9%)	4.7 / 1.5	3.3 (1.6 – 7.0)	35.5	85.8	4.7	98.5	2.5	0.61	0.7
Prognostic frailty score	21 (1.7%)	2.8 / 0.8	3.9 (1.4 – 10.6)	76.2	54.8	2.8	99.3	1.69	0.66	0.66
Fall										
Frailty phenotype	195 (14.5%)	15.3 / 14.5	1.1 (0.6 – 1.9)	7.7	92.8	15.3	85.5	1.07	0.50	0.57
Simplified frailty phenotype	143 (13.9%)	22.2 / 13.8	1.8 (0.6 – 5.5)	2.8	98.4	22.2	86.2	1.75	0.50	0.51
Frailty index	270 (16.1%)	29.9 / 13.5	2.7 (2.0 – 3.7)	28.9	87.0	29.9	86.5	2.22	0.58	0.61
Prognostic frailty score	183 (14.4%)	16.9 / 12.1	1.5 (1.1 – 2.0)	55.2	54.7	16.9	87.9	1.22	0.55	0.55
Any outcomes										
Frailty phenotype	686 (43.8%)	59.1 / 42.3	1.9 (1.4 – 2.8)	11.8	93.6	59.1	57.7	1.84	0.53	0.57
Simplified frailty phenotype	478 (40.8%)	70.8 / 40.1	3.6 (1.5 – 8.8)	3.6	98.9	70.8	59.9	3.27	0.51	0.54
Frailty index	949 (45.5%)	69.7 / 40.3	3.4 (2.7 – 4.3)	26.8	90.3	69.7	59.7	2.76	0.59	0.64
Prognostic frailty score	640 (43.1%)	53.3 / 33.1	2.3 (1.8 – 2.8)	61.1	59.5	53.3	66.9	1.51	0.60	0.60

* non-frail group from frailty phenotype and simplified frailty phenotype analysis were combined with pre-frail group; † full model includes: multi-level or continuous version of the frailty measure; %outcome: proportion of outcome among frail and non-frail group; CI: confidence interval; sensitivity: probability of persons with outcome who are classified as frail; specificity: probability of persons without outcome who are classified as non-frail; PPV: probability that a person has the outcome if he/she was identified as frail; NPV:probability that a person has no outcome if he/she was identified as non-frail; Likelihood Ratio (LR): [sensitivity/100-specificity] – how much more likely is a person with the outcome to be classified as frail than those without the outcome; AUC: area under the curve

5.5 Discussion

This is the first study in an older Australian population that examined four internationally validated frailty measures for their accuracy in predicting adverse outcomes. Our findings showed that being identified as frail by each of the four measures was associated with a range of adverse health outcomes. The PFS was found to be the most sensitive measure in our population; this means that the PFS correctly identified people who were at higher risk of adverse outcomes as frail more often than the other three measures. However, the low PPV values indicate that only a small number of those who were identified as frail had the adverse outcomes. The probability of having any of the adverse outcomes was highest among the frail older people identified by the SFP and the FI (PPV = 70%). Therefore, SFP and FI may be more useful in clinical practice, as recognising the high probability of adverse outcomes can provide better information for clinicians when considering the risks and benefits of a treatment for their frail older patients.

FI was the only measure that was able to be used to assess frailty in all participants without any loss of participants due to missing data. Between 25% up and 44% of participants were unable to be assessed by the other three measures due to missing data. Participants who were excluded because of missing data had a higher proportion of adverse outcomes than the pre-frail or the non-frail group. Given the purpose of frailty measure is to identify individuals with higher risk of adverse outcomes [23], the large proportion of adverse outcomes among the missing group may have influenced the measure's performance. This may have contributed to the lower accuracy for the FP, SFP, and PFS.

Several modifications to the variables used in the assessment of frailty were needed in this study; due to lack of data availability. These modifications may have some effects on the

predictive performance of the four measures. A similar population-based study of the Italian older population examined the predictive accuracy of PFS (without modifications) and SFP (with a different modification from our study) [73]. The Italian study used adverse outcomes including death, hospitalisation, nursing home admission, and fall, with a 4-year follow up. It reported comparable sensitivity values for the PFS 48% - 78%, however, the AUC values were slightly better: 0.65 – 0.83 [162]. For SFP, the Italian study reported higher sensitivity values 11% - 36% compared to 2.8% - 6.7% in our study [162].

A limitation of our study was the reliance on self-report data for some of the reference standards including hospitalisation and fall. We cannot rule out recall bias; further, the frail elderly may have been more likely to have had cognitive impairment that led to poorer recall. Nursing home admission was less likely to suffer from self-report bias as it could have been validated by the interviewer at the time of the interview at the subjects' residence. While these limitations exist, the results of the self-reported outcomes were concordant with the outcome for death.

Overall, our analysis showed that all four frailty measures had low discriminating ability with LR values that were <5 [166, 220]. However, based on the AUC values, the FI had acceptable accuracy for a prognostic measure with AUC between 0.59 – 0.7 [160, 219].

To improve the validity of frailty measures, future research could focus on assessing other aspects of validity such as construct validity.

5.6 Conclusions

Our study showed that being identified as frail by any of the four measures was significantly associated with an increased risk of adverse outcomes. However, only the FI had acceptable predictive accuracy.

5.7 Summary

The study in this chapter found that the four frailty measures had similar predictive validity but variable accuracy. Thus, the assessment of predictive validity and accuracy alone was insufficient to determine which measure is best. For this reason, in the next chapter, the construct validity of the four measures will be examined to determine which measure has the best validity to use in a study on medicine use.

Chapter 6:
Construct validity of four frailty measures in an older Australian population

In the previous chapter, the predictive performance of four internationally validated frailty measures in an older Australian population was examined. The findings showed that all of the four measures had similar predictive validity in predicting adverse health outcomes, however, only the Frailty Index had acceptable accuracy. This chapter presents further evaluation of the validity of the four frailty measures to determine which of the four measures is best to use for studying the association between frailty and medicine use in this thesis. The first section of this chapter presents a manuscript examining the construct validity of the four measures. This manuscript has been accepted for publication in the Journal of Frailty and Aging. The frailty measure with the best construct validity included morbidities as part of the assessment criteria for identifying frailty. As medicines are commonly used to treat morbidity, the second section of the chapter includes a study that examined a modified frailty measure, where morbidities were excluded, to determine if the modified measure would be suitable to employ in a medicine use study.

6.1 Construct validity of four frailty measures in an older Australian population: A Rasch analysis

6.1.1 Abstract:

Individuals identified as frail have been shown to be at an increased risk of adverse health outcomes. However, there is no gold standard frailty measure and frailty status can vary depending on the measure used, suggesting the measures perform differently. Construct

validity can be used to assess a measure's performance. This study aimed to examine the construct validity of four frailty measures in an Australian older population using Rasch analysis. Frailty status among the 2087 participants aged 65 years and above from the Australian Longitudinal Study of Ageing (ALSA) was assessed using: frailty phenotype - FP, simplified frailty phenotype - SFP, frailty index - FI, and prognostic frailty score – PFS. Rasch analysis was used to assess the uni-dimensionality of the measures, which is the extent to which the underlying characteristic of frailty is assessed. The criteria for uni-dimensionality from principal component analysis of the residuals was when 50% or more of the raw variance was explained by the measures, and less than 5% was unexplained variance. Only FI meet the uni-dimensionality criteria with 74% of explained variance and 2.1% of unexplained variance. SFP did not show a uni-dimensional construct with 13.3% of explained variance and 47.1% of unexplained variance. FP and PFS had 39.6%, 18.1% and 46.5%, 8.7% of explained and unexplained variance, respectively. Our findings showed that FI has better construct validity than the other three measures in assessing frailty among the Australian older population.

Key words: frailty, older population, construct validity, Rasch analysis

6.1.2 Introduction

There are a number of different frailty measures that have been developed to assess frailty [92]. The measures have been shown to have good predictive validity for assessing adverse outcomes, with participants identified as having a significantly increased risk of a range of adverse outcome [92]. However, research has shown that there is little overlap in frailty status as measured by different methods. An Australian study found only 0.6% of the study population were identified as frail by all four frailty measures, despite the measures individually providing frailty estimates ranging from 2% to 49% of the population[221]. This

suggests that each frailty measure identified a different type or aspect of frailty. To date, there is limited study on the construct validity of the available frailty measures [92]. Construct validity is the degree to which a measure represents the studied concept [152].

Rasch analysis, which examines the performance of a measure for assessing the degree of a single underlying characteristic [222], can be used to assess construct validity [222, 223]. The analysis was developed by a Danish mathematician, Georg Rasch [224]; it uses a statistical model, the Rasch model, which is based on the expected probability of relationships between individuals who have the assessed characteristic and the variables used to measure the characteristic [222]. The Rasch model represents the expected performance of an ideal measure that identifies an underlying characteristic on an ordinal scale [222].

The purpose of a frailty measure is to identify an underlying characteristic in older persons that differentiates those at higher and lower risk of experiencing adverse health outcomes [23]; which is consistent with the concept of the Rasch model. However, Rasch analysis has not been used to investigate the construct validity of available frailty measures. Therefore, this study aimed to assess the construct validity of frailty measures using a Rasch analysis.

6.1.3 Methods

6.1.3.1 Study population and frailty measures

The study population was from the Australian Longitudinal Study of Ageing (ALSA) which is a population based cohort study with a representative sample of 2087 older people aged 70 years or over and their spouses aged 65 years or over [207]. The study was approved by the Clinical Investigation Committee of Flinders Medical Centre [207]. Written informed consent was obtained from each participant in the study [207]. In this study baseline data collected in 1992 was used. The data collection involved interviews and clinical examinations.

This study examined four frailty measures that had all been shown to have predictive validity, including: Frailty Phenotype [21], the Simplified Frailty Phenotype [74], both of which were developed as screening tools and so have a limited range of criteria for assessment, and the Frailty Index [213], and the Prognostic Frailty Score [73], both of which were developed as diagnostic tools and include a larger number of variables. The Frailty Phenotype has five variables. Individuals with missing data on two or more of the five variables were excluded from the analysis, leaving 1566 participants for analysis. For the Simplified Frailty Phenotype includes three variables, 1173 participants with complete data in all of the three variables were included in the analysis. All 2087 participants were included in the Frailty Index assessment as most participants had complete data on all 39 variables. In the analysis using the Prognostic Frailty Score, which has nine variables, there were 1485 participants with complete or only one missing item included in the analysis. In this study, some of the variables from the four frailty measures were modified due to the availability of data in the ALSA dataset. The details of the modification have been described elsewhere [221]. Table 1 showed the application of the four frailty measures in the ALSA data and their scoring criteria.

Table 6. 1 Frailty measures application

Frailty measures	Scoring
Frailty phenotype	
BMI < 20	Yes = 1; No = 0
Low grip strength:	Yes = 1; No = 0
- In the lowest 20% at baseline (adj. for sex and BMI)	
Self-rated exhaustion (CES-D scale)	Yes = 1; No = 0
- Feel that everything was an effort or could not get going for 3/> days in the last week	
Walking time/8 feet(2.4m):	Yes = 1; No = 0
- Slowest 20% at baseline (adj. for sex and height)	
Low physical activity:	Yes = 1; No = 0
- Walking for exercise/recreation in the past 2wks	
Frail = presence of 3/> variables	
Pre-frail = presence of 1-2 variables	
Non-frail = absence of variables	
Simplified frailty phenotype	
BMI < 20	Yes = 1; No = 0
Unable to rise from chair 5times without use of arms	Yes = 1; No = 0
Low energy level (CES-D scale)	Yes = 1; No = 0
- Could not get going for 3/> days in the last week	
Frail = presence of 2/> variables	
Pre-frail = presence of 1 variables	
Non-frail = absence of variables	
Frailty index	
Live alone	Yes = 1; No = 0
Self-rated health	Poor = 5; Fair = 4; Good = 3; Very good = 2; Excellent = 1
Arthritis	Yes = 1; No = 0
Asthma	Yes = 1; No = 0
History of heart attack	Yes = 1; No = 0
Hypertension	Yes = 1; No = 0
Migraine	Yes = 1; No = 0
Parkinson's disease	Yes = 1; No = 0
History of stroke	Yes = 1; No = 0
Thyroid disease	Yes = 1; No = 0
Ear, nose, throat problem	Yes = 1; No = 0
Mental disorder	Yes = 1; No = 0
Genito-urinary problem	Yes = 1; No = 0
Diabetes	Yes = 1; No = 0
Cancer	Yes = 1; No = 0
Chest pain	Yes = 1; No = 0
Constipation	Yes = 1; No = 0
Dental problem	Yes = 1; No = 0
Sleep problem	Often/almost always = 3; Sometimes = 2; Rarely/never =1;
Spinal problem	Yes = 1; No = 0
Hearing difficulty	Yes = 1; No = 0
Eye trouble	Yes = 1; No = 0
Skin problem	Yes = 1; No = 0
Hands shaking problem	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Stooping/crouching/kneeling problem	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Difficulty with bathing	Yes = 1; No = 0
Difficulty with personal grooming	Yes = 1; No = 0
Difficulty with dressing	Yes = 1; No = 0
Difficulty with eating	Yes = 1; No = 0
Difficulty with toileting	Yes = 1; No = 0
Difficulty with going out	Yes = 1; No = 0
Difficulty with moving around	Yes = 1; No = 0
Difficulty with laundry/linen	Yes = 1; No = 0
Difficulty with housework	Yes = 1; No = 0

Difficulty with preparing meal	Yes = 1; No = 0
Difficulty with using telephone	Yes = 1; No = 0
Difficulty with managing money	Yes = 1; No = 0
Difficulty with using public transport	Yes = 1; No = 0
Difficulty with shopping	Yes = 1; No = 0
Frailty index score: (total variables score) / (39 – missing variables)	
Frail : ≥ 0.25	
Frailty prognostic score	
Age ≥80 year	Yes = 1; No = 0
Male gender	Yes = 1; No = 0
Low physical activity :	Yes = 1; No = 0
- Walking for exercise/recreation in the past 2wks	
Comorbidity:	Yes = 1; No = 0
- Daily use of 3/> drugs and 2/> chronic diseases	
Sensory deficits - blind/deaf	Yes = 1; No = 0
Calf circumference <31cm	Yes = 1; No = 0
IADL dependency - any dependency on:	Yes = 1; No = 0
- Using telephone	
- Travelling	
- Managing money	
Presence of gait abnormalities	Yes = 1; No = 0
Pessimism about self-health (health worse than others)	Yes = 1; No = 0
Frail = presence of 3/> variables	
Non-frail = absence of variables	

6.1.3.2 Rasch analysis

This study used WINSTEPS Rasch measurement software version 3.81.0 to conduct Rasch analysis. The partial credit model was applied in the analysis of the Frailty Index, because it can accommodate a combination of dichotomous and categorical variables [225]. The other frailty measures consist of dichotomous variables only; therefore the partial credit model was not required.

Construct validity was assessed by examining the following criteria, uni-dimensionality, reliability and separation index. Uni-dimensionality in Rasch analysis is the extent to which a single characteristic is assessed by a measure [222]. The principal component analysis of the residuals (PCAR) was used to assess uni-dimensionality [226]. PCAR was used to examine the variance of the measure [158, 227]. Uni-dimensionality was considered present when 50% or more of the raw variance was explained by the measures [157, 158]. An additional criteria for uni-dimensionality is that the value of unexplained variance in the 1st contrast should be less than 5% [157, 158].

Item fit analysis, which was based on a chi-square analysis, was also used to examine uni-dimensionality [226]. It is used to examine how well each of the individual variables that make up a measure fit the Rasch model requirements [226]. In this study the criteria for a good fit was based on the recommended criteria of a clinical observation test, which is when the mean square (MnSq) ranges from 0.5-1.7 [226]. Infit MnSq was chosen instead of outfit MnSq because infit is not influenced by outliers and any misfit based on the infit value would pose a greater threat to the measurement than with the outfit value [228]

Person reliability and the separation index was also assessed to determine the consistency of the measure and the ability of a measure to distinguish different levels of frailty [225]. Person reliability of ≥0.8 and person separation of ≥2 was used as the criteria for a measure with a good discriminating ability – able to separate individuals into three or more groups [157, 229]. A high person reliability and separation value means that the measure has good consistency and discriminating ability in separating between persons with lower and higher score [222]. The reliability showed in the Rasch analysis is similar to that of the Cronbach's Alpha reliability, which shows the repeatability of the measure [225].

In terms of missing values, the Rasch analysis incorporates missing values in the assessment. The Rasch model aims to estimate the expected probability of relationships between individuals and the variables used to assess an underlying characteristic; therefore missing values are important information of the measure's construct validity.

6.1.4 Results

The prevalence of frailty and the results from the Rasch analysis are presented in table 2. The Simplified Frailty Phenotype identified only 2% of the population as frail, whereas the Prognostic Frailty Score identified 49% as frail. In the assessment of uni-dimensionality, only

Frailty Index met the criteria for uni-dimensionality: 74% of raw variance was explained by the measure and there was only 2.1% of unexplained variance in the 1st contrast. Item fit analysis showed that each variable in the four frailty measures had acceptable fit with MnSq values within the range of 0.5 – 1.7. None of the measures met the criteria for person reliability or person separation.

Table 6. 2 Rasch analysis results

	Frailty phenotype (N= 1566)	Simplified frailty phenotype (N= 1173)	Frailty index (N= 2087)	Prognostic frailty score (N=1485)
Uni-dimensionality				
PCAR				
Raw variance explained by measure	39.6%	13.3%	74.0%	46.5%
Raw unexplained variance in 1st contrast	18.1%	47.1%	2.1%	8.7%
Item infit MnSq (min-max)	0.85 – 1.20	0.95 – 1.06	0.84 – 1.13	0.87 – 1.13
Person reliability and separation index				
Person-reliability index	0	0	0.70	0.45
Person-separation index	0	0	1.55	0.91

PCAR: principal component analysis of the residuals, MnSq: mean square

6.1.5 Discusssion

This study is the first to utilise Rasch analysis to assess the construct validity of frailty measures in an older Australian population. The Frailty Index had the best construct validity, while the other three measures did not meet the criteria for uni-dimensionality. None of the measures met the criteria for person reliability and separation index, suggesting there is still a need to develop and improve frailty measurement. All of the measures had good infit MnSq values which indicate that all four measures did not contain any variables that were not relevant to frailty assessment. Given, the measures contain different variables; this may be suggestive that a measure combining the elements of each of the indices would be advantageous. This hypothesis is consistent with the findings that none of the measures had good person-separation which indicates that there are insufficient variables in the measures to assess frailty [229].

The poor person-separation index of the Frailty Phenotype and the Simplified Frailty Phenotype, both of which had the lowest scores, is likely to be due to the small number of variables these measures use to assess frailty, with only five and three variables respectively. The Frailty Phenotype and the Simplified Frailty Phenotype were developed to assist geriatricians in their daily practice, therefore, contain a smaller number of variables to be suitable for a busy clinical practice setting. Further study may consider whether rescaling the binary responses into categorical will improve the person-separation index of the Frailty Phenotype and the Simplified Frailty Phenotype.

According to the guideline for developing Frailty Index, the higher number of variables included in the Frailty Index the better the predictive performance [214]. A total number of variables between 30 and 40 has been shown to have good predictive accuracy [213]. Our study used a Frailty Index with 39 items; therefore, it is likely that adding more variables to the Frailty Index will improve the person-separation index.

Our findings showed that the Frailty Index had a better construct validity than the other three measures. However, the analysis also found that none of the measures included sufficient variables to provide good person separation, suggesting further optimisation of the frailty measures is required. Future research could consider if an index combining the characteristics measured in all the indices improved the construct validity further.

6.1.6 Implication of findings

The Frailty Index developed by Mitnitski et al., [66] was found to have better construct validity than the other three measures in an older Australian population. Taking into consideration that the Frailty Index also had better predictive performance than the other three measures (Chapter 5), the Frailty Index was selected to assess frailty in the study of

medicine use in this thesis. However, the Frailty Index contains comorbidity variables, including arthritis, asthma, diabetes, and hypertension. Since these conditions are treated with medicines, their inclusion in the measure may confound a study assessing the relationship between frailty and medicines use. In the following section, the validity of a modified Frailty Index that excluded comorbidity variables will be examined.

6.2 The validity of a modified Frailty Index

6.2.1 Validity assessment

In this study, the validity of the modified Frailty Index with regard to construct validity and predictive validity was assessed. The construct validity of the modified Frailty Index (Table 6.3) was examined using Rasch analysis. For the Rasch analysis, the assessment criteria for construct validity included uni-dimensionality and the person reliability and separation index. Correlation analysis was conducted to determine whether the modified Frailty Index correlated with the original Frailty Index. The original Frailty Index was considered as a gold standard in the correlation analysis.

The performance of the modified Frailty Index in predicting a range of adverse outcomes at wave 3 including death, hospitalisation, nursing home admission, falls, and a combined outcome was examined. The predictive validity was assessed by measuring the odds ratio (OR) of the association between frailty and outcomes, as well as the analysis of sensitivity, specificity, and positive and negative predictive values (PPV and NPV). The dichotomised version of the Frailty Index with the cut-off score of ≥0.25 was used to classify frailty [133, 146]. The area under the curve (AUC) values of both dichotomous and continuous version of the modified Frailty Index was calculated, with AUC values between 0.6 and 0.85 considered acceptable [160, 219]. The Rasch analysis was conducted using WINSTEPS Rasch

measurement software version 3.81.0. All other analyses were conducted using the SAS statistical software (Version 9.4 of the SAS system for Windows. Copyright 2011 SAS Institute Inc., Cary, NC, USA).

Table 6. 3 The modified frailty index

The modified frailty index	
Variables	**Scoring**
Live alone	Yes = 1; No = 0
Self-rated health	Poor = 1; Fair = 0.75; Good = 0.5; Very good = 0.25; Excellent = 0
Dental problem	Yes = 1; No = 0
Hearing difficulty	Yes = 1; No = 0
Stooping/crouching/kneeling problem	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Difficulty with small objects	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Difficulty with bathing	Yes = 1; No = 0
Difficulty with personal grooming	Yes = 1; No = 0
Difficulty with dressing	Yes = 1; No = 0
Difficulty with eating	Yes = 1; No = 0
Difficulty with toileting	Yes = 1; No = 0
Difficulty with going out	Yes = 1; No = 0
Difficulty with moving around	Yes = 1; No = 0
Difficulty with laundry/linen	Yes = 1; No = 0
Difficulty with housework	Yes = 1; No = 0
Difficulty with preparing meal	Yes = 1; No = 0
Difficulty with using telephone	Yes = 1; No = 0
Difficulty with managing money	Yes = 1; No = 0
Difficulty with using public transport	Yes = 1; No = 0
Difficulty with shopping	Yes = 1; No = 0
Frailty index score: (total variables score) / (20 – missing variables) Frailty: ≥0.25	

6.2.2 Construct validity

6.2.2.1 Rasch analysis

The modified Frailty Index had good uni-dimensionality, with the PCAR results showing 76.7% of variance was explained by the measure and there was only 1.8% of unexplained variance (Table 6.4). There was no misfit items, as measured by MnSq values ranging from 0.79 – 1.37. The results for person reliability and separation index were slightly lower than the original Frailty Index.

Table 6. 4 Rasch analysis of the modified Frailty Index

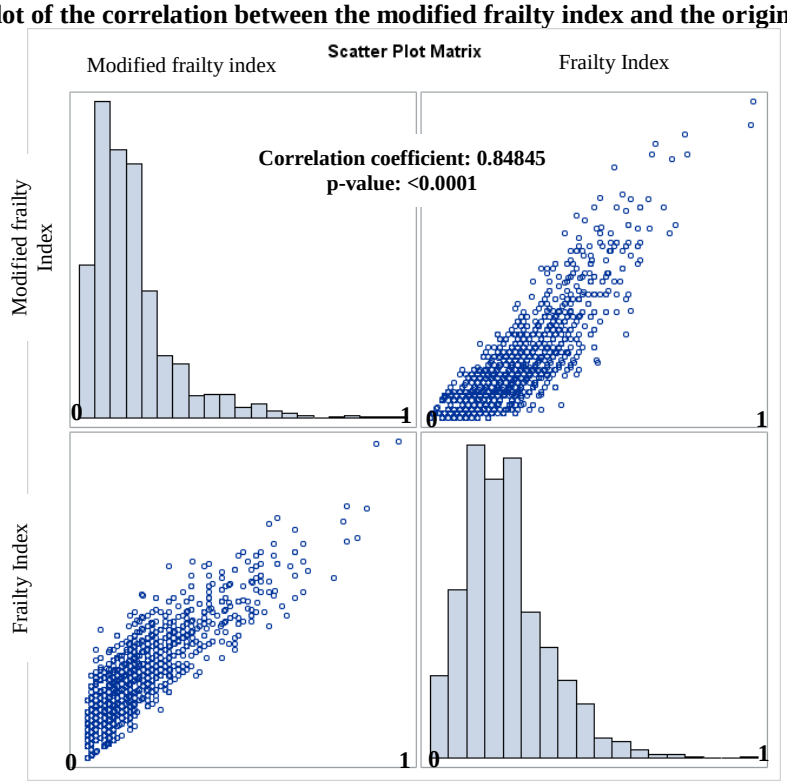
	Modified Frailty Index	Original Frailty Index
Uni-dimensionality		
PCAR		
Raw variance explained by measure	76.7%	74.0%
Raw unexplained variance in 1st contrast	1.8%	2.1%
Item infit MnSq (min-max)	0.79 – 1.37	0.84 – 1.13
Person reliability and separation index		
Person-reliability index	0.58	0.70
Person-separation index	1.19	1.55

PCAR: principal component analysis of the residuals, MnSq: mean square

6.2.2.2 Correlation analysis

The modified Frailty Index had a high correlation with the original Frailty Index, with a correlation coefficient of 0.848 and a p-value of <0.0001 (Figure 6.1).

Figure 6. 1 Plot of the correlation between the modified frailty index and the original frailty index



6.2.3 Predictive validity

Being identified as frail by the modified Frailty Index was associated with an increased risk of a range of adverse outcomes, OR (95% confidence interval): 3.3 (2.6 – 4.2) for mortality, 1.7 (1.3 – 2.1) for hospitalisation, 2.3 (1.8 – 3.0) for falls, 5.2 (2.5 – 10.9) for nursing home admission, and 2.6 (2.1 – 3.1) for the combined outcomes. The modified Frailty Index was

most sensitive in predicting nursing home admission (sensitivity: 64.5%), the PPV was highest for predicting all outcomes (61.5%). The AUC values of the continuous model of the modified Frailty Index met the criteria for acceptable accuracy (Table 6.4). The predictive performance results were comparable to that of the original Frailty Index (Chapter 5).

Table 6. 5 Predictive performance of the modified Frailty Index

	OR (95% CI)	Sensitivity	Specificity	PPV	NPV	AUC dichotomous	AUC continuous
Modified Frailty Index							
Mortality	3.3 (2.6 – 4.2)	54.4	73.4	28.8	89.0	0.64	0.67
Hospitalisation	1.7 (1.3 – 2.1)	35.7	74.9	38.5	72.6	0.55	0.59
Nursing home	5.2 (2.5 – 10.9)	64.5	74.1	4.7	99.1	0.69	0.72
Falls	2.3 (1.8 – 3.0)	43.9	74.6	24.8	87.4	0.59	0.62
Any outcomes	2.6 (2.1 – 3.1)	42.2	77.9	61.5	61.8	0.60	0.64
Original Frailty Index							
Mortality	3.2 (2.4 – 4.1)	34.4	85.8	32.5	86.8	0.60	0.66
Hospitalisation	2.3 (1.7 – 3.0)	23.8	88.1	46.7	72.4	0.56	0.59
Nursing home	3.3 (1.6 – 7.0)	35.5	85.8	4.7	98.5	0.61	0.7
Falls	2.7 (2.0 – 3.7)	28.9	87.0	29.9	86.5	0.58	0.61
Any outcomes	3.4 (2.7 – 4.3)	26.8	90.3	69.7	59.7	0.59	0.64

OR: odds ratio, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

6.3 Conclusion

The findings in this study suggest that the Frailty Index is a robust measure, in terms of construct validity. The construct validity of the Frailty Index after modification was also found to be satisfactory, with good uni-dimensionality and a high correlation with the original Frailty Index, but slightly poorer person reliability and separation. The predictive validity of the modified Frailty Index was comparable to the original Frailty Index.

In this chapter, the studies have demonstrated the use of Rasch analysis to examine the construct validity of frailty measures. The results showed that the Frailty Index had the best construct validity and that a modification of the Frailty Index, where morbidities were excluded also had satisfactory construct validity. In the next chapter, the modified Frailty Index that has been validated in this chapter will be employed to assess frailty and examine its association with medicine use among an older Australian population.

Chapter 7:
Understanding the association between frailty and medicine use

In this chapter, a study using the modified Frailty Index that examines the association between medicine use and frailty changes over time is presented. A cross sectional study is presented that describes the distribution of frailty scores among medicine users and a subsequent cohort study examines compares changes in frailty score among people who stop using medicine to those who continue using the medicines.

7.1 Introduction

Medicine-related problems are common in the older population and can lead to adverse health outcomes such as: hospitalisation and mortality [9-12, 77]. In terms of hospitalisation, it is estimated that 30% of hospital admissions among Australians aged 65 years and over are due to medicine-related problems [77]. In terms of mortality, an Italian survey of 81 hospitals involving 28411 patients examined the risk factors for hospital admission related to adverse drug reactions and found that the risk of serious adverse drug reactions that can result in death was 50% higher in adults aged 65 years and over compared to those under 65 years of age [10].

In 2011, the European Medicines Agency (EMA) identified the need to assess frailty as part of the efforts to improve the safe use of medicines in older people [18]. Just as medicines have been associated with increased risk of adverse health outcomes [9-12, 77], frailty has also been associated with an increased risk of adverse health outcomes, including mortality,

disability, nursing home admission, hospitalisations, and falls [60, 75, 92]. However, whether frailty adds to the burden of adverse outcomes in medicines users is not yet known.

Research concerning the association between frailty and medicine use is limited. The literature review presented in Chapter 2, identified only seven published papers that examined the association between medicine use and frailty in community-dwelling, older populations. The cross-sectional studies included in the review showed that older people who were identified as frail were more likely to use analgesics [191] or to take inappropriate medicines as measured by the drug burden index, which includes sedative and anticholinergic medicines [187, 230]. Another study showed higher use of anticoagulant medicines in the frail compared to non-frail participants. The limitations of these cross-sectional studies was that the appropriateness of therapy at the level of the individual was not assessed, nor was the design able to assess the temporal association between medicine use and frailty changes. A further limitation of prior research is that the association with frailty has only been assessed for a limited range of specific medicines: analgesics, sedatives, anticholinergics, statins, anticoagulants, and angiotensin-converting enzyme inhibitors (ACEIs).

The effect of medicines use on the development of frailty over time has been examined in two longitudinal studies that were published in three papers [185-187]. The studies used longitudinal analyses to examine incidence of frailty with the use of statins [185] and ACEIs [186], both medicines for disease prevention, or high-risk prescribing as defined by use of multiple medicines (polypharmacy), and use of sedative or anticholinergic medicine [187]. For the studies assessing the effect of statins and ACEIs on frailty, there was a similar incidence of frailty at the three-year follow up among users and non-users of statins (16% and 13% respectively) [185], and among users and non-users of ACEIs (20% and 14% respectively) [186]. The study which examined incidence of frailty in older man with high-

risk prescribing, defined as multiple medicine use, and sedative or anticholinergic medicine use, found that those with high-risk prescribing were more likely to develop frailty at the two-year follow-up time [187]. However, these studies were limited by the inclusion of the pre-frail as well as non-frail in the initial cohorts, with the resultant issue being the inability to distinguish whether pre-frailty status or medicine use affected the outcome, as there were more pre-frail participants using the medicines at baseline.

Published frailty studies have only assessed medicine use at baseline when assessing the association between frailty and medicine use. Frailty development has subsequently been assessed at a single fixed time point two or three years later. The studies did not consider changes in medicine use during the follow-up period nor did they identify frailty at the time of changes in medicine use. Whether the study participants who developed frailty at the follow-up time were still taking the medicines was not assessed. No study has yet examined the differences in frailty when medicines are stopped

In the practice of geriatric medicine, the medicines examined in the published frailty studies [185-187] can be categorised into two broad categories: 1) potentially inappropriate medicines, such as polypharmacy, sedatives, and anticholinergics [43, 200, 231], and 2) preventive medicines, such as statins and ACEIs [98]. Potentially inappropriate medicines, including sedative and anticholinergic medicines have been associated with poorer physical function [232] and increased mortality risk in the older population [233]. Statins and ACEIs has been shown in large randomised trials to improve cardiovascular outcomes among the older population [202, 203] and so may have the potential to reduce the risk of developing frailty over time as good cardiovascular health supports good physical function. Ceasing preventive medicines may have the potential to contribute to worsening frailty.

The aim of this study was twofold: first, to determine the distribution of frailty among older people who use medicines, second, to examine whether there was a difference in frailty scores over time with continuation or discontinuation of specific medicines. The study was conducted with the *a-priori* hypotheses that the distribution of frailty score will be the same, regardless of the number of medicines used, and that older people who discontinued or continued the use of potentially inappropriate medicines, symptom-relief medicines, or preventive medicines, would have no difference in frailty score changes over time.

7.2 Methods

7.2.1 Study population

The study used data from the Australian Longitudinal Study of Ageing (ALSA) which is a population based cohort of 2087 participants aged 65 years and over [207]. Participants were recruited by random sampling from the South Australian electoral roll. The ALSA dataset contains information on the health and wellbeing of its participants, data collection was undertaken by interviews and clinical examinations. There were 13 waves of data collected. Medicine use data were collected in wave 1, 3, 6, 7, 9, and 11. Due to loss to follow up, some of the reasons of which were unknown and the diminishing sample sizes in the later waves, this study used data from baseline (wave 1) which was collected in 1992 and also data from the first follow-up period (wave 3) which was conducted between 1994-1995. Additional information on the ALSA study can be found at http://www.flinders.edu.au/sabs/fcas/alsa/.

7.2.2 Frailty assessment

Frailty assessment was conducted using a modified version of Frailty Index (FI) by Mitnitski et al [213]. In this study, the chronic disease variables were excluded from the Frailty Index; the modified measure in this study population has comparable validity (Chapter 6). The modified Frailty Index included 20 variables (Table 1.1). Frailty scores for each person were

calculated by dividing the number of deficit variables present with the total number of deficits assessed for each person. The frailty score is a continuous score which ranges from 0 to 1, a greater score indicates increased frailty. Participants with more than 20% missing variables were excluded in the analysis [234]. A frailty score was calculated for each person at baseline and at wave 3.

Table 7. 1 The modified frailty index

The modified frailty index	
Variables	**Scoring**
Live alone	Yes = 1; No = 0
Self-rated health	Poor = 1; Fair = 0.75; Good = 0.5; Very good = 0.25; Excellent = 0
Dental problem	Yes = 1; No = 0
Hearing difficulty	Yes = 1; No = 0
Stooping/crouching/kneeling problem	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Difficulty with small objects	Some/ a lot of difficulty or just unable to do = 1; No difficulty at all or a little difficulty = 0
Difficulty with bathing	Yes = 1; No = 0
Difficulty with personal grooming	Yes = 1; No = 0
Difficulty with dressing	Yes = 1; No = 0
Difficulty with eating	Yes = 1; No = 0
Difficulty with toileting	Yes = 1; No = 0
Difficulty with going out	Yes = 1; No = 0
Difficulty with moving around	Yes = 1; No = 0
Difficulty with laundry/linen	Yes = 1; No = 0
Difficulty with housework	Yes = 1; No = 0
Difficulty with preparing meal	Yes = 1; No = 0
Difficulty with using telephone	Yes = 1; No = 0
Difficulty with managing money	Yes = 1; No = 0
Difficulty with using public transport	Yes = 1; No = 0
Difficulty with shopping	Yes = 1; No = 0
Frailty Index score: (total variables score) / (20 – missing variables)	

7.2.3 Medicine use assessment

Medicine use was collected at home interview where participants were asked to show the medicines containers, including non-prescription medicines, and interviewers were instructed to write down information from the container labels where possible [207]. The use of medicines was examined using cross-sectional and longitudinal analyses. Results by specific medicines are only reported for the top 25 most commonly used medicines at baseline. In the longitudinal analysis, the 25 medicines were categorised into: potentially inappropriate, symptom-relief, and preventive medicines (Table 7.2). Six of the 25 medicines analysed have been considered as potentially inappropriate medicines in older populations due to the risk of adverse outcomes associated with their use, including: non-steroidal anti-inflammatory drugs

(NSAIDs), which are associated with risk of gastrointestinal bleeding [43, 200, 231, 235], benzodiazepines, which are associated with risk of falls and cognitive impairment [43, 200, 231, 235], digoxin, which is associated with risk of toxicity [43, 200, 231], allopurinol, which is associated with risk of toxicity [236-238], aspirin for pain relief, which is associated with risk of gastrointestinal bleeding [43, 235], and opioids, which are associated with risk of constipation, falls, and cognitive impairment [231, 239-241]. The Australian Medicines Handbook (AMH) was used to classify symptom-relief medicines [241]. Five medicines were considered as symptom-relief, including: antacids, paracetamol, H2-antagonist, short-acting beta agonists (SABA), and stimulant laxatives. The other 14 medicines were considered as preventive medicines based on their rationale for use, which is to prevent disease complications. Medicine use was then categorised as continued or stopped, based on wave 3 data.

Table 7. 2 The 25 most common medicines in ALSA

Medicines use analysis list
Potentially inappropriate medicines - Non-steroidal anti-inflammatory drugs (NSAIDs) - Benzodiazepines - Digoxin - Allopurinol - Aspirin (high-dose) - Opioids
Symptom-relief medicines - Antacids - Paracetamol - Histamine2(H2)–antagonist - Short-acting beta agonists (SABA) - Stimulant laxatives
Preventive medicines - Aspirin (low-dose) - Beta blockers - Calcium channel blockers (CCBs) - Frusemide - Angiotensin-converting enzyme inhibitor (ACEIs) - Nitrates - Potassium(K)-sparing diuretics - Thiazides and related diuretics - Thyroxine - Sulfonylureas - Inhaled corticosteroids (ICS) - Statins - Calcium supplement - Potassium supplement

7.2.4 Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study population. Median Frailty Index scores for each group of medicine users at baseline and follow-up were examined. In the cross-sectional analysis, the non-parametric test (Wilcoxon Rank Sums test/ Kruskal-Wallis test) was used to examine if there was a difference in the distribution of frailty scores in relation to the number of medicines used.

In the longitudinal analysis, chi-square tests and t-tests were used to compare the baseline characteristics: gender, age, number of conditions and number of medicines between those who continued and those who stopped using medicine. The non-parametric test was used to compare the baseline median frailty score between those who continued and those who stopped using medicine. The mean changes in frailty scores were compared between the two groups using a t-test, with a p-value of <0.05 considered to be significant. For each individual, frailty score changes were calculated by subtracting baseline frailty score from frailty score at wave 3.

Adjustments for age, number of medicines, and comorbidities were not considered in this study. Frailty is a condition that changes over time in a non-linear trend, with no consensus on the age at onset of frailty [23], therefore controlling for age may not be appropriate when assessing frailty changes. The number of medicines and comorbidities are interdependent, and comorbidities have been shown to be overlap with frailty status; but there is limited understanding of the causal relationship between comorbidity and frailty [23]. This results in lack of clarity as to whether the overall number of medicines taken and the overall number of comorbidities a person has are true confounders or whether they are in the causal pathway [204, 205]. For this reason, subgroup analysis was conducted when there was a significant difference in the baseline characteristics between those who continued and those who stopped

using medicine. The analyses were undertaken using SAS version 9.4 for Windows (copyright 2011, SAS Institute Inc., Cary, NC, USA).

7.3 Results

7.3.1 Baseline analysis

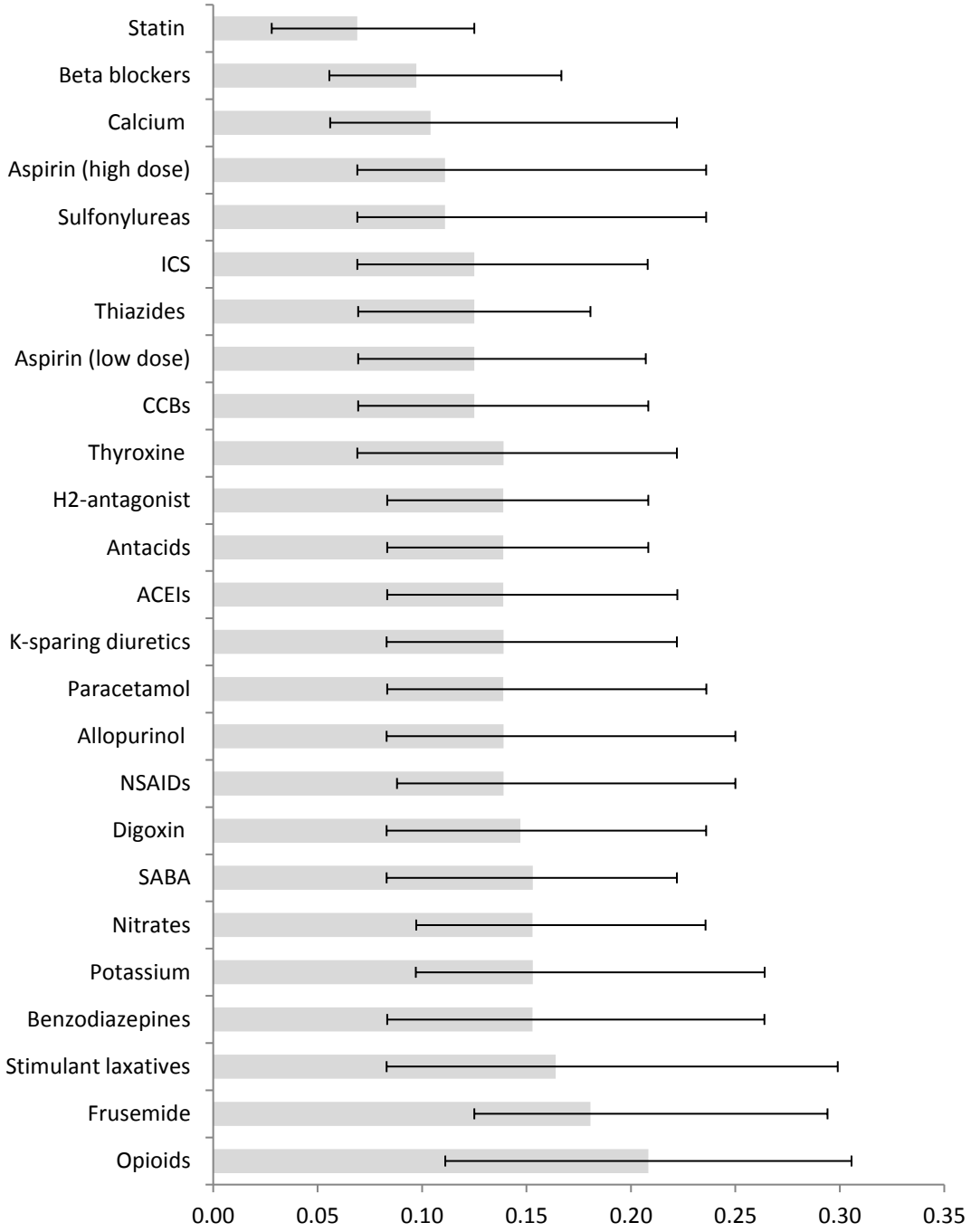
A total of 2086 participants were included in the analysis. Table 7.3 shows the baseline characteristics of the ALSA population. Low-dose aspirin was the most common medicine used in the ALSA population with prevalence of 20.3%.

Table 7. 3 Baseline characteristics of the ALSA population

Baseline characteristics (N= 2086)	
Age – mean (SD)	78.2 (6.7)
Gender – N (%)	
Female	1030 (49.4%)
Male	1056 (50.6%)
Living arrangement – N (%)	
Community living	1961 (94%)
Institution	125 (6%)
Medicine use – N (%)	
Aspirin (low-dose)	424 (20.3%)
Non-steroidal anti-inflammatory drugs (NSAIDs)	367 (17.6%)
Beta-blockers	343 (16.4%)
Calcium-channel blockers (CCBs)	313 (15%)
Antacids	312 (14.9%)
Paracetamol	306 (14.7%)
Benzodiazepines	292 (13.9%)
Frusemide	285 (13.7%)
Angiotensin-converting enzymes inhibitors (ACEIs)	214 (10.3%)
Histamine(H2)-antagonist	212 (10.2%)
Nitrates	196 (9.4%)
Potassium(K)-sparing diuretics	187 (8.9%)
Digoxin	179 (8.6%)
Thiazides and related diuretics	133 (6.4%)
Short acting beta agonist (SABA)	117 (5.6%)
Stimulant laxatives	108 (5.2%)
Thyroxine	90 (4.3%)
Sulfonylureas	86 (4.1%)
Inhaled corticosteroid (ICS)	83 (3.9%)
Allopurinol	83 (3.9%)
Potassium	73 (3.5%)
Aspirin (high dose)	67 (3.2%)
Opioids	65 (3.1%)
Statin	61 (2.9%)
Calcium	60 (2.9%)
Number of medicines – median (IQR)	3 (1 – 5)
Number of conditions – median (IQR)	5 (3 – 7)

The median baseline frailty score of participants by medicine used is shown in Figure 7.1. Participants who reported use of statins had the lowest median frailty score, whereas those who reported use of opioids had the highest median frailty score.

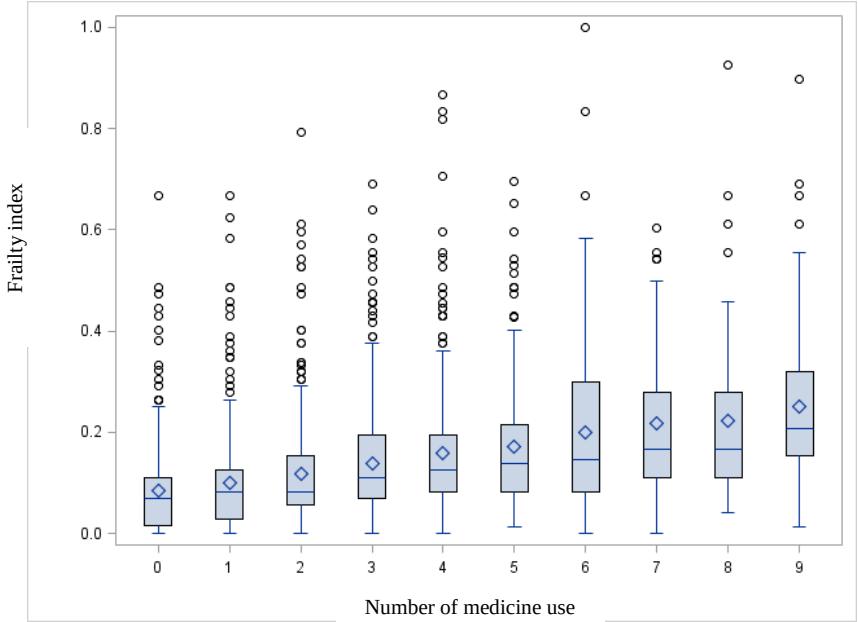
Figure 7. 1 Median and interquartile range (IQR) of frailty scores at baseline by medicine use



ICS: inhaled corticosteroid, H2: histamine2, CCBs: calcium-channel blockers, ACEIs: angiotensin-converting enzyme inhibitors, K: potassium, NSAIDs: non-steroidal anti-inflammatory drugs, SABA: short-acting beta agonist

There was a significant association between frailty and the number of medicine used (p-value <0.0001) (Figure 7.1). The frailty score increased with increasing numbers of medicines used.

Figure 7. 2 Distribution of frailty at baseline by the number of medicines used



7.3.2 Longitudinal analysis

Baseline characteristics of those who continued and those who stopped using medicine were largely similar (Table 7.4), with the exception of the number of medicines used. The groups who stopped using antacids and nitrates had a lower baseline number of medicines compared to those who continued. While in SABA and thiazides users those who stopped using the medicines had a statistically significant higher number of medicines at baseline than those who continued. The baseline frailty score in participants who stopped using statins was significantly higher than those who continued, with median score of 0.138 and 0.063 respectively.

Table 7. 4 Baseline characteristics of medicine use groups

Medicines	N	Male N (%)	Age mean (SD)	Number of conditions mean (SD)	Number of medicines mean (SD)	Frailty Index median (IQR)
Potentially inappropriate medicines						
Non-steroidal anti-inflammatory drugs (NSAIDs)						
Continued	164	71 (43.3%)	76.4 (6)	5.9 (2.8)	4.1 (2.1)	0.122 (0.063 – 0.175)
Stopped	96	51 (53.1%)	76.3 (6)	6.6 (3.1)	4.2 (2.3)	0.113 (0.069 – 0.188)
Benzodiazepines						
Continued	151	55 (36.4%)	78.2 (6.2)	6.5 (2.9)	4.8 (2.3)	0.125 (0.063 – 0.238)
Stopped	29	16 (55.2%)	79.1 (5.5)	5.7 (3.1)	5.2 (2.4)	0.125 (0.063 – 0.188)
Digoxin						
Continued	103	65 (63.1%)	80.5 (5.6)	6.8 (3.1)	4.8 (2.2)	0.113 (0.075 – 0.188)
Stopped	12	6 (50%)	77.6 (7.2)	7.1 (4.2)	5.4 (2)	0.131 (0.081 – 0.179)
Allopurinol						
Continued	43	34 (79.1%)	77.3 (5.5)	6.5 (2.9)	4.8 (2.2)	0.1 (0.075 – 0.225)
Stopped	10	7 (70%)	79.7 (5.3)	5.5 (2.3)	4.5 (2.6)	0.106 (0.013 – 0.138)
Aspirin (high-dose)						
Continued	28	12(42.9%)	77.8 (5.6)	5 (3.2)	3.1 (1.7)	0.075 (0.063 – 0.131)
Stopped	20	11 (55%)	79.9 (5.8)	5.9 (2.9)	4.4 (2.5)	0.106 (0.075 – 0.269)
Opioids						
Continued	25	5 (20%)	76.1 (5.5)	7.3 (3.3)	5.4 (2.4)	0.175 (0.088 – 0.25)
Stopped	18	6 (33.3%)	77.6 (7.9)	7.1 (3.2)	4.9 (1.9)	0.194 (0.063 – 0.275)
Any potentially inappropriate						
Continued	390	187 (47.9%)	77.8 (6.1)	6.1 (2.9)	4.2 (2.1)	0.113 (0.063 – 0.175)
Stopped (≥1)	169	88 (52.1%)	77.4 (6.3)	6.4 (3.1)	4.5 (2.4)	0.113 (0.063 – 0.188)
Symptom-relief medicines						
Antacids						
Continued	181	104 (57.5%)	77.7 (6)	6.8 (3.1)	4.6 (2.3)*	0.125 (0.075 – 0.188)
Stopped	34	18 (52.9%)	77.4 (7)	5.7 (2.4)	3.5 (2.2)	0.1 (0.075 – 0.175)
Paracetamol						
Continued	176	70 (39.8%)	77.5 (6.3)	6.2 (3)	4.4 (2.2)	0.125 (0.075 – 0.213)
Stopped	33	19 (57.6%)	77.8 (6.2)	6.7 (2.9)	3.6 (2.2)	0.125 (0.063 – 0.175)
H2-antagonist						
Continued	113	66 (58.4%)	77.3 (5.5)	6.9 (3.2)	4.6 (2.3)	0.125 (0.075 – 0.188)
Stopped	29	17 (58.6%)	76.9 (6.8)	6.6 (2.6)	3.9 (2.2)	0.1 (0.075 – 0.188)
Short-acting beta agonist (SABA)						
Continued	66	35 (53%)	76.1 (6.2)	6.3 (2.9)	4.8 (2.3)*	0.125 (0.075 – 0.188)
Stopped	12	3 (25%)	73.3 (5.7)	7 (3.1)	6.6 (2.8)	0.188 (0.081 – 0.356)
Stimulant laxatives						
Continued	46	14 (30.4%)	77.9 (6.6)	6.2 (2.9)	4.4 (2.2)	0.125 (0.075 – 0.225)
Stopped	18	6 (33.3%)	78.5 (5.8)	6.4 (3.2)	3.8 (2.2)	0.109 (0.05 – 0.225)
Any symptom-relief						
Continued	356	170 (47.8%)	77.3 (6.2)	6.2 (2.9)	4.2 (2.2)	0.125 (0.063 – 0.188)
Stopped (≥1)	101	49 (48.5%)	77.3 (6.4)	6.5 (2.9)	3.9 (2.4)	0.113 (0.063 – 0.188)
Preventive medicines						
Aspirin (low-dose)						
Continued	249	141 (56.6%)	77.3 (5.5)	5.9 (2.8)	4.2 (2.1)	0.088 (0.063 – 0.163)
Stopped	34	21 (61.8%)	78.6 (5.7)	6.1 (3.5)	4.3 (2.8)	0.131 (0.063 – 0.238)
Beta blockers						
Continued	212	105 (49.5%)	75.5 (4.9)	5.8 (2.7)	4 (2)	0.088 (0.038 – 0.138)
Stopped	49	26 (53.1%)	75.9 (5.4)	6 (2.9)	4.2 (2)	0.1 (0.075 – 0.163)
Calcium-channel blockers (CCBs)						
Continued	182	91 (50%)	76.9 (5.5)	6.2 (2.8)	4.7 (2.3)	0.113 (0.063 – 0.188)
Stopped	29	15 (51.7%)	77.4 (6.4)	6.2 (3.1)	3.9 (1.9)	0.088 (0.05 – 0.2)
Frusemide						
Continued	143	71 (49.7%)	79.8 (6.1)	5.2 (3)	3.4 (2.5)	0.15 (0.113 – 0.263)
Stopped	23	12 (52.2%)	80.5 (7.9)	4.2 (2.2)	2.4 (1.8)	0.163 (0.088 – 0.225)

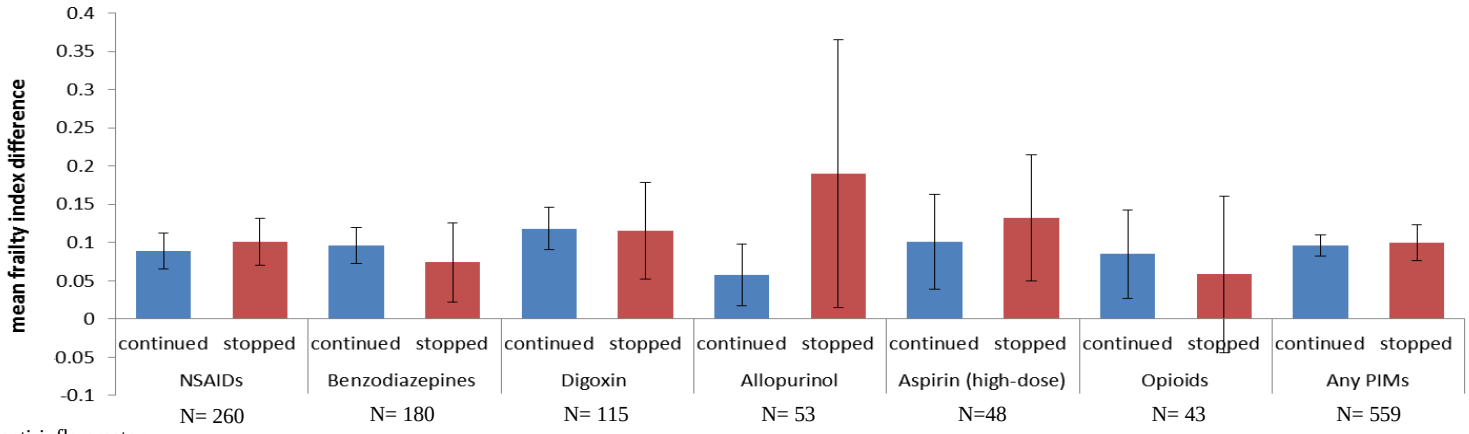
Table 7.4 Baseline characteristics of medicine use groups (cont.)

Preventive medicines						
Angiotensin-converting enzyme inhibitors (ACEIs)						
Continued	113	49 (43.4%)	77.7 (5.6)	6.1 (2.7)	4.6 (2.2)	0.125 (0.063 – 0.188)
Stopped	20	8 (40%)	77.2 (6.1)	5.5 (2.9)	4.7 (2.7)	0.069 (0.025 – 0.213)
Nitrates						
Continued	109	53 (48.6%)	79.3 (5.7)	6.6 (2.8)	5.6 (2.1)*	0.138 (0.075 – 0.25)
Stopped	22	14 (63.6%)	79.6 (6.9)	5.7 (2.8)	4.1 (1.7)	0.125 (0.075 – 0.163)
Potassium sparing diuretics						
Continued	88	36 (40.9%)	78.2 (6)	6.3 (2.8)	4.5 (1.9)	0.113 (0.075 – 0.175)
Stopped	41	19 (46.3%)	78 (6.3)	6.5 (3.3)	4.5 (2)	0.125 (0.075 – 0.197)
Thiazides						
Continued	73	17 (23.3%)	76.2 (6.4)	5.7 (2.2)	4.3 (1.9)*	0.088 (0.063 – 0.138)
Stopped	31	13 (41.9%)	76.9 (6.5)	6.5 (3)	5.2 (2)	0.113 (0.053 – 0.175)
Thyroxine						
Continued	65	4 (6.2%)	75.8 (5.4)	6.5 (3.3)	4.2 (2.4)*	0.113 (0.063 – 0.15)
Stopped	2	0	79.5 (9.2)	8.5 (2.1)	8 (1.4)	0.306 (0.113 – 0.5)
Sulfonylureas						
Continued	48	25 (52.1%)	76.9 (6.5)	6.2 (2.9)	4.9 (2.2)*	0.096 (0.056 – 0.163)
Stopped	2	1 (50%)	78 (2.8)	7.5 (3.5)	6 (0)	0.125 (0.025 – 0.225)
Inhaled corticosteroids (ICS)						
Continued	46	25 (54.4%)	76.3 (6.2)	6.1 (2.3)	5.2 (2.2)	0.113 (0.063 – 0.188)
Stopped	11	5 (45.5%)	75.5 (6.7)	7 (3.8)	4.8 (2.8)	0.1 (0.025 – 0.325)
Statin						
Continued	44	11 (25%)	72.4 (4.5)	5.2 (2.6)	4.1 (2)	0.063 (0.025 – 0.088)*
Stopped	7	1 (14.3%)	74.9 (4.9)	4 (2.2)	4.3 (2.9)	0.138 (0.063 – 0.163)
Calcium						
Continued	36	2 (5.6%)	76.6 (6.5)*	6.3 (3.2)*	4.6 (1.9)	0.088 (0.05 – 0.156)
Stopped	6	1 (16.7%)	73.7 (1.9)	4.2 (0.8)	4.2 (1.7)	0.094 (0 – 0.125)
Potassium						
Continued	29	11 (37.9%)	80.6 (8.5)	5.9 (3.2)	5.4 (2.2)	0.138 (0.088 – 0.2)
Stopped	16	6 (37.5%)	78.3 (9.2)	6.6 (3.2)	5.1 (1.7)	0.119 (0.081 – 0.206)
Any preventive						
Continued	667	310 (46.5%)	77.2 (5.9)	5.8 (2.8)	3.8 (2.1)	0.1 (0.063 – 0.163)
Stopped (≥1)	251	121 (48.2%)	77.5 (6.5)	6.1 (2.9)	4.4 (2.2)	0.113 (0.063 – 0.2)

*p-value <0.05

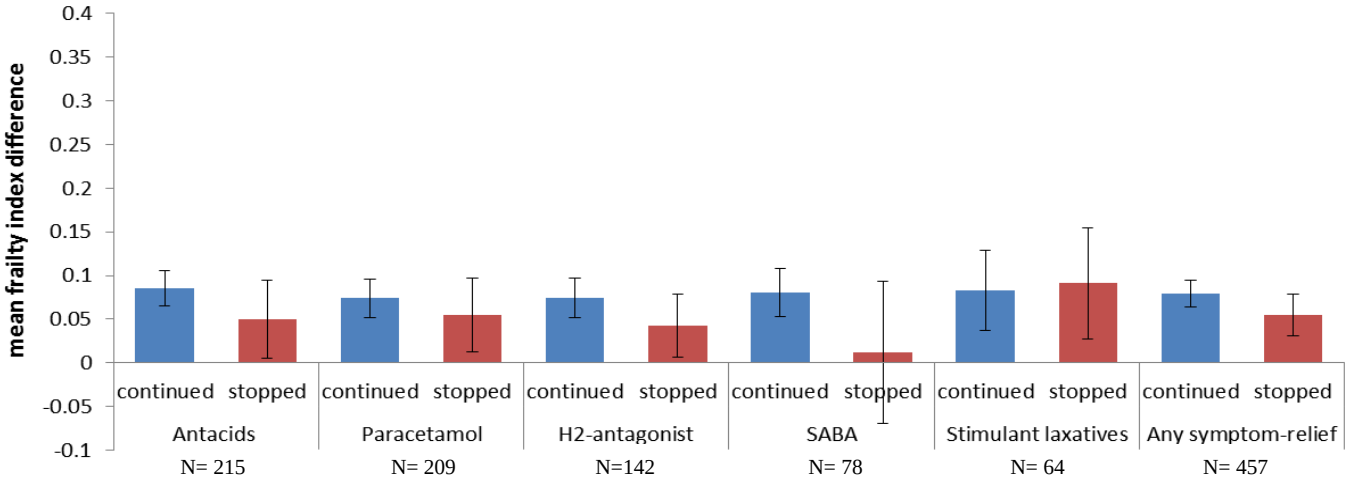
There were no statistically significant differences in the mean frailty score changes among participants who continued or stopped using potentially inappropriate medicines (PIMs) (Figure 7.3) or symptom-relief medicines (Figure 7.4). Participants who stopped at least one of the preventive medicines at wave 3 were found to have a higher increase in mean frailty score changes than those who continued using them (p=0.01). For the individual preventive medicines, stopping beta blockers or potassium-sparing diuretics was associated with a greater increase in frailty score compared to continuing these medicines (Figure 7.5).

Figure 7. 3 Mean frailty index differences – potentially inappropriate medicines (PIMs)



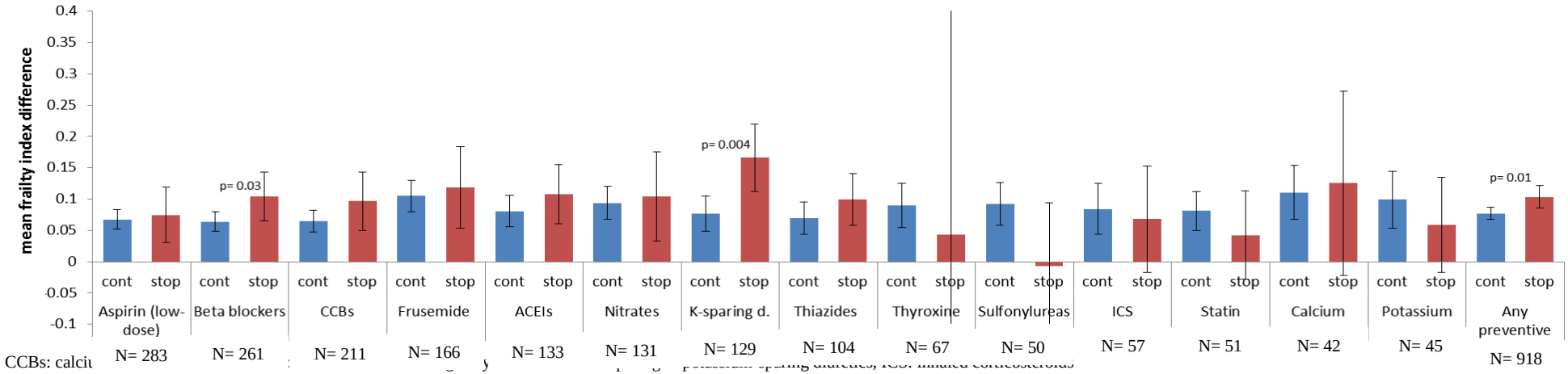
NSAIDs: non-steroidal anti-inflammatory drugs

Figure 7. 4 Mean frailty index differences – symptom-relief medicines



SABA: short-acting beta agonists

Figure 7. 5 Mean frailty index differences – preventive medicines



CCBs: calciu

7.4 Discussion

7.4.1 Cross-sectional analysis

This study was the first to examine the distribution of frailty scores across the total number of medicines used and by different types of medicines among a community-dwelling older population in Australia. The study showed that using greater numbers of medicines was associated with higher frailty scores; therefore the first hypothesis, that the distribution of frailty scores is independent of the number of medicines used, was not supported. This result is consistent with a previous Australian study undertaken among older men that also showed that the greater the number of medicines used the higher the frailty score [187].

This study also showed that among participants who did not use medicines, their frailty score varied (Figure 7.2); which suggests that frailty is not limited solely to the medical dimension, as some people on no medicines were judged to be frail. This is in accord with the multidimensional definition of frailty which in addition to the medical dimension may also include physical, psychological, social and environmental dimensions.

The highest baseline median frailty score was found among opioid users, 0.2, while the lowest median frailty score was among statins users, 0.07. Half of the opioid users had a frailty score between 0.1 and 0.3, compared to 0.03 and 0.13 in statin users. The modified Frailty Index included daily activities functioning to assess frailty. Opioids are used for pain management and pain has been associated with reduced physical function and performance [242, 243], which could affect the daily activities functioning and may be a reason for the higher frailty score observed among opioid users. In terms of statin users, the findings may not reflect the current situation, as at the time of data collection in 1992, statins had been

recently marketed, and therefore their use was limited. By comparison, in 2014, statins were among the top most commonly dispensed medicines in Australia [244].

When considering medicines as preventive, symptom-relief and potentially inappropriate, the cross-sectional analysis shows that in general people on preventive medicines, such as antihypertensives had lower frailty scores at baseline than people on symptom-relief medicines, and potentially inappropriate medicines. In general, people on potentially inappropriate medicines had higher frailty scores at baseline.

7.4.2 Longitudinal analysis

This study was the first to examine the differences in frailty changes between those who continued using medicines and those who stopped using medicines. The baseline characteristics between the two groups were largely similar, with the exception of the baseline number of medicines used. Despite the similarity in the number of conditions and frailty scores, there was a significant difference in the baseline number of medicines used among people using antacids, nitrates, SABA, and thiazides use (Table 7.4). The baseline number of medicines used was higher in participants who continued using antacids or nitrates than in those who stopped; while participants who continued using SABA or thiazides had a lower number of medicines use. This may suggest that baseline number of medicines is a potential confounder in the association between medicine use and frailty change However due to limited sample size, a post-hoc subgroup analysis of baseline number of medicines used was not possible. Further research is needed to examine whether number of medicines influences the continuation or discontinuation of certain medicines.

In terms of potentially inappropriate medicine use, the *a-priori* hypotheses was supported, with the results showing that there was no difference in the changes in frailty scores between

those who stopped using potentially inappropriate medicines and those who continued using them. The finding showed that there was a non-statistically significant lower increase in the mean frailty score among those who stopped benzodiazepines and opioids, than those who continued. The small numbers of participants who stopped using benzodiazepines and opioids may have limited the power in this study. Benzodiazepine use in older populations is not usually recommended due to their adverse effects [199]. A large prospective cohort study among 9360 community-dwelling older people who did not report impairment in mobility and activity of daily living (ADL), found that the risk of developing mobility or ADL impairment among benzodiazepines users was higher than among non-users: hazard ratio (HR): 1.23, 95% confidence interval (CI): 1.09-1.39 for mobility impairment, and HR (95%CI): 1.28 (1.09-1.52) for ADL impairment [245]. Mobility and ADL impairment contribute to frailty development, therefore further research to better understand the effect of benzodiazepines on frailty development is required, as without this knowledge, physicians may not link changes in frailty status or activities of daily living with medicine use and thus, preventive actions, such as ceasing the medicine, are unlikely to be implemented. This is particularly important considering that benzodiazepine use is common in Australia, with an Australian study using a General Practitioner (GP) database finding that the 16% (95%CI 11-21%) of patients aged 65 years or older used benzodiazepines [246].

The results for the use of symptom-relief medicines showed agreement with the *a-priori* hypothesis. There was no statistically significant difference in the change of frailty scores between those who stopped using symptom-relief medicines and those who continued using them. Symptom-relief medicines are often used intermittently and the extent of intermittent use at baseline compared to follow up could not be assessed in this study. Large differences in the extent of intermittent use across groups may have the potential to confound the result.

In terms of preventive medicines, the *a-priori* hypothesis was not supported. The results showed that those who continued using any preventive medicines had a lower increase in frailty scores than those who stopped using them. This was also found at the class level for beta-blockers and potassium-sparing diuretics. Moreover, there was a consistent pattern of non-statistically significant higher increases in frailty scores among participants who stopped taking preventive therapies including: low-dose aspirin, CCBs, frusemide, ACEIs, nitrates, thiazides, and calcium supplements compared to those who continued. While this could be suggestive that the medicines lessen the risk of developing frailty, it was not possible to determine the reason for cessation of preventive therapies. It is possible that worsening frailty led to discontinuation of preventive medicines rather than use of preventive medicines stopped the development of frailty. The higher increase in frailty scores among participants who discontinued using preventive medicines may be due to several reasons including the development of side effects which may lead to the need to discontinue the medicine and limit the participant benefiting from the medicine. Another reason is the worsening of health conditions, or the development of new conditions all of which may in turn contribute to increasing frailty and may require discontinuation of certain medicines; particularly where there may be contraindications to their use. Additionally, among people who were approaching the end-of-life, preventive medicine may be proactively ceased as the person has insufficient life-expectancy to benefit from preventive therapies.

A larger study with sufficient power may confirm whether the use of preventive medicines may be beneficial in reducing frailty development in the older population. Additionally, the study would need to include assessment of the doctors' reason for cessation and frailty assessment at the time of cessation, to provide further insight as to whether ceasing

preventive therapy increases the risk of frailty or whether worsening frailty was a factor contributing to the doctor's decision to cease the medicine.

7.4.3 Strengths and limitations of the study

This study was the first study that examined the association between medicine use and frailty over time in a community-dwelling older population using a multidimensional frailty measure. Previous studies have used uni-dimensional measures [185-187] or have been limited to populations of older men [187] or older women [185, 186]. To the best of our knowledge this study was also the first study to consider how cessation of medicine use may affect changes in frailty scores over time.

One of the limitations of this study was that the data were collected between 1992 and 1995; this limitation is particularly evident when considering the utilisation of statins. Statins were introduced in the early 1990s [247], and the low prevalence of use of statins in our study population, 2.9%, is markedly different from the current prevalence of use among older Australian aged 64-74 years, which is estimated to be over 40% [230]. However, the majority of medicines examined in this study, including low-dose aspirin, thiazides, beta blockers, paracetamol, and NSAIDs are still the most common medicines used among older Australians currently [230].

Another limitation of this study is that information on the time of medicine discontinuation was not available, nor was information to ascertain the duration of medicine discontinuation prior to the frailty assessment at follow-up available. Additionally, there was no information on the reasons for either continuation or discontinuation of medicines. Therefore, it was not possible to assess whether frailty changes were due to medicines cessation or whether

medicine use changes were due to frailty progression. Further study which utilises data that offer the ability to measure frailty at the time of medicine discontinuation, as well as the availability of comprehensive information on the reason of discontinuation, is necessary to understand the association between frailty and medicine use.

7.5 Conclusion

This study found that there was a significant positive association between frailty score and the number of medicines used at baseline. Of the 25 medicines examined, opioid users at baseline had the highest median frailty score, 0.2, while statins users had the lowest median frailty score, 0.07.

During the three-year follow up period, there was an increase in the mean frailty scores in all medicines user groups examined. This study found no difference in frailty scores among participants who continued and discontinued the use of potentially inappropriate medicines. In terms of preventive medicines, participants who stopped using any preventive medicines had a greater increase in mean frailty score than those who continued using the medicine. However, further study that includes assessment of frailty at the time of discontinuation as well as examination on the reasons for either continuation or discontinuation of medicines is warranted to determine if frailty changes were due to medicine use changes or vice versa.

This chapter showed that there was an association between frailty and the numbers of medicines used. Across different types of medicine users frailty scores varied. Among all participants there was an increase in the mean frailty score over time. In the following chapter, a summary of the findings from studies conducted in this thesis and a discussion on the future directions in the research on frailty assessment and the use of medicines is presented.

Chapter 8: Conclusion

8.1 Discussion of findings

This thesis has examined the validity of four frailty measures in an older Australian population and assessed the association between frailty and medicine use. Four internationally validated frailty measures: Frailty Phenotype, Simplified Frailty Phenotype, Frailty Index and Prognostic Frailty Score were used to assess frailty. The findings showed that the prevalence of frailty varied depending on the measure used and each frailty measure identified a unique type of frail older person; less than 1% of the study population were identified as frail by all four measures (Chapter 4). The Frailty Index was found to have the best validity to assess frailty in the Australian study population (Chapter 5 and Chapter 6). Based on the Frailty Index, the prevalence of frailty in older Australians is estimated to be 17.5%. Prior to this thesis, there had been no studies identifying the prevalence of frailty in a community-dwelling, older, Australian population. Previous studies had focused on hospitalised older patients [167, 173-175, 195] or older men [187]. This thesis was also the first to examine both the predictive and construct validity of four internationally validated frailty measures in an older Australian population, finding that all four measures had similar predictive validity; however, the Frailty Index had the best construct validity.

The studies in this thesis provide useful additional knowledge on the validity of frailty measures, particularly in the Australian population. The findings from this thesis were in accord with the findings from several international studies, which found that there is moderate predictive performance of the existing frailty measures [159, 161-165]. This thesis, however, was the first to use Rasch analysis in assessing the construct validity of frailty

measures, finding Rasch analysis was able to provide further discrimination between the measures and enabling the Frailty Index to be selected as the measure with the best construct validity. Future frailty studies can explore the use of Rasch analysis in developing frailty measures with better construct validity.

A limitation of the research was that it only examined the internationally validated frailty measures using data that were available from the Australian Longitudinal Study of Ageing (ALSA) dataset, thus the validity of the results may not be generalizable to clinical data sets. However, a strength of the research is that it does provide evidence of the comparative performance of the four measures, the purpose of which was to identify the best measure to use for further research in other data sets, including, potentially, clinical data sets and administrative data sets.

Prior to assessing the association between frailty and medicine use, a modified Frailty Index was developed. This modification was necessary as the Frailty Index included assessment of chronic conditions which are often treated with medicines. The omission of chronic conditions was to avoid the bias that would result because of the interdependency between chronic conditions and medicines use (Chapter 6). The modified Frailty Index was found to have acceptable predictive and construct validity.

This research was the first to utilise a multidimensional frailty measure in a study of the association between frailty and medicine use in an older community-dwelling population. Previous studies using the multidimensional frailty measures that examined frailty and medicine use have been limited to hospitalised patients [173, 175, 195].

When analysing the association between frailty scores and medicine use, the cross-sectional analysis found that the users of different types of medicine had variable baseline median frailty scores; ranging from 0.07 among older persons using statins to 0.2 among older persons using opioids (Chapter 7). Although this research was based on data collected in 1992, the medicines examined are still commonly used among older people at the present time, examples of these commonly used medicines are opioids, beta blockers, antacids, and aspirin. A limitation of the analysis was that the frailty score could not be determined at time of initiation of the medicines. Future studies could investigate how frailty scores vary among medicine users at the time of prescribing. Additionally, future studies could also examine whether assessment of frailty at the time of prescribing can assist doctors' choice of medicines or doses, and whether the assessment of frailty can assist in the reduction of adverse drug events among older frail patients.

Prior to this research there had been only a small number of studies that examined the association between frailty and medicine use. In Australia, the studies were conducted among specific patient populations; older men [187, 188] and hospitalised patients [173, 175, 195]. No studies had examined the impact of stopping medicines on frailty scores. The longitudinal analysis undertaken as part of this research found that there was no change in frailty scores associated with the discontinuation of potentially inappropriate medicines. This finding met the *a-priori* hypothesis, which was that among participants who continue and those who discontinue the use of potentially inappropriate medicine there would be no difference in the change in frailty score over time. In terms of preventive medicine use, the *a-priori* hypothesis was not supported as there was a statistically significant, lower increase in frailty score changes between participants who continued the use of any preventive medicines and those who discontinued use. However, these findings were limited by the lack of information

on the time and reason for the discontinuation of the medicines. It was not possible to ascertain if the preventive medicines were discontinued because patients became frailer or if the continued use of preventive medicines reduced the risk of frailty. A further limitation was the small sample size. Therefore, further research using a larger sample and that includes a documented reason for discontinuation and an assessment of frailty at the time of discontinuation is needed to understand whether frailty changes influence discontinuation of medicines or the discontinuation of medicine is influenced by frailty development. A large study with sufficient numbers of older people in a range of different age categories will also be beneficial to understand whether age is also influencing the decision to stop the use medicines.

This thesis provides insight into the assessment of frailty and the association between frailty and medicine use among the community-dwelling older Australians. This thesis as well as the other Australian studies [175, 187, 195] found that older people with polypharmacy had a higher frailty score than those without. Further investigation is warranted to understand whether the use of polypharmacy is the consequence of the progression of frailty or the use of polypharmacy contributes to frailty progression. Considering the limitations of this thesis and the limited number of existing studies, there is a need for future studies to further describe the association between frailty and changes in the use of medicines over time, which would contribute to the effort to improve evidence on the risks and benefits of medicines use in older population.

8.2 Future directions

8.2.1 Development and validation of a standardised frailty measure

The work in this thesis demonstrated the significance of frailty assessment in an older population. However, the differences in the validity of the four measures in our study population highlight the need for further research to develop and validate a standardised frailty measure that is applicable across different settings.

The accuracy of the four frailty measures examined in this thesis was only assessed based on their discriminant ability; their calibration ability was not examined. A well calibrated measure is when the predicted risk corresponds to the observed risk. The limited numbers of outcome events that were available in this research restricted the application of calibration analysis [248] in our study population. However, calibration analysis is of greater importance when a frailty measure is used in clinical practice, where the estimate of a patient's risk of outcome is essential, as it influences clinical decision making and this could be the focus of future work.

Additionally, further research could examine the feasibility of applying frailty measures in administrative healthcare databases. Administrative databases have become an important tool in public health practice for monitoring, planning, and surveillance purposes, because of their large population coverage and the readily availability of data [249]. The large population coverage and the range of information collected in an administrative database may provide useful information to identify the characteristics of the frail elderly as well as the ability to ascertain the temporal association between frailty development and medicines use. Therefore, having determined the predictive and construct validity of the Frailty Index and the modified

Frailty Index in the ALSA database, a next step would be to determine the suitability of using the measures in an administrative database.

Comparison of the validity of information from an administrative database and survey data has been examined in several studies undertaken in other countries [250-252]. The studies identified variables from an administrative claims database that corresponded to the variables obtained from a survey, then compared the predictive validity of the variables on several adverse health outcomes. The finding was that variables obtained from the administrative database provide similar predictive validity when compared to the survey-based variables [250-252]. Similar research would be possible to undertake in Australia. As an example, the Australian Government Department of Veterans' Affairs (DVA) database contains a number of variables that are consistent with the variables that were used from the ALSA database which may enable a valid Frailty Index to be used. Potential variables to construct the Frailty Index that are available from the DVA database for a selected population include information on living arrangements, mobility issues, ability to transfer, bathe and toilet, activities of daily living scores, the supply of incontinence products, walking aids, mobility aids, vision and hearing aid, as well as dental services, and mental health services. In addition, data are available for all claims for hospital admissions, which include information on diagnoses and procedures, as well as claims for medical and allied health provider visits, all medicines that are subsidised, aged-care services as well as rehabilitation and appliance aids. Future research that aims to develop a standardised and validated frailty measure using administrative database is necessary, particularly with the increasing use of electronic health data. A standard and valid frailty measure will ensure the consistency in the identification of frailty, which is important for researchers and clinicians to better understand the development of

frailty as well as to develop prevention and intervention strategies to improve the health outcomes of the older population.

8.2.2 Incorporating frailty assessment in the studies on safety and effectiveness of medicines in an older population

With the limited evidence from clinical trials on safety and effectiveness of medicine use in the older population, incorporating a standard and valid frailty assessment into large pharmacoepidemiological studies may improve the ability to understand the risks and benefits of medicine use in older populations. The use of administrative health databases has been shown to be a practical tool for monitoring and identifying adverse drug events [253, 254]. The large sample size of administrative health database provides an opportunity to design a robust study with sufficient power to better understand the direction in the association between frailty and medicine use; with a better identification and adjustment of confounding variables than in a smaller study. In addition, there is the ability for frailty assessment to be measured with a temporal sequence relevant to changes in medicine use. Further, large pharmacoepidemiological studies may also provide the opportunity to better evaluate the impact of the use of medicines that may be beneficial in frailty prevention.

Future studies on quality use of medicines could focus on evaluating the impact of using frailty assessment at the time of prescribing to tailor medicine prescribing based on frailty status. Studies to examine the impact of high risk medicines use on each criteria assessed by the frailty measures are also warranted. For example, an analysis on the impact of anticholinergic medicines use on the specific frailty criteria, including: mobility impairment, ability to perform activities of daily living, muscle weakness, and depression may assist in determining the contributory role of medicines to frailty development. This may provide valuable information, enabling safer and effective use of medicines in older populations.

8.3 Conclusion

This thesis aimed to develop a valid frailty measure suitable for use in the Australian health care system and subsequently use it to provide further insight into frailty and its association with medicine use in older people. The thesis resulted in the development of a valid measure tested within one data set, however, there is a need to develop a standardised and validated frailty measure that is applicable across different settings. In terms of the association between frailty and medicine use, the findings of this thesis confirmed previous research demonstrating an association between frailty and medicine use, however, there is still a need for further research to determine whether the presence of frailty causes the use of medicine or the use of medicine causes frailty in older people. Longitudinal studies assessing frailty at the time of prescribing with subsequent follow-up are required to provide a better evidence base for the direction of the association between frailty and medicine use. This thesis makes a contribution to knowledge on the validity of existing frailty measures in an older Australian population and also makes recommendations for future research to further evaluate the association between frailty and medicine use in large pharmacoepidemiological studies with robust study designs.

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Appendix A Statement of Authorship

Chapter 4: How common is frailty in older Australians?

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Imaina S. Widagdo

First author, contributed to the conception and design of the study, acquisition of data and analysis, interpretation of data analysis, and preparation of the manuscript.

Signature: Date:

Nicole L. Pratt

Contributed to the conception and design of the study, interpretation of data analysis, and revision of the manuscript

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Chapter 5: Predictive performance of four frailty measures in an older Australian population

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Chapter 6.1: Construct validity of four frailty measures in an older Australian population: A Rasch analysis

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Appendix B The list of assessment criteria of the 52 frailty measures

Type of frailty measure Self-report	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Screening letter (Barber et al., 1980)	√ Depend on someone for regular help Had day(s) unable to have a hot meal Health concern/difficulty Vision/hearing difficulty	-	√ Confined at home due to ill health Hospital in the last year	√ Live alone No relative to call for help	-	1/>: at risk – need assessment
Frail Elderly Functional Assessment Questionnaire (Gloth et al., 1995)	√ Able to walk, transfer out of bed, turn over in bed, wash dish, prepare hot dinner, manage money, use phone, eat by mouth, dress, bathe/shower, toilet, bedside commode, sit up, grasp, reach out past nose, take meds	-	-	-	-	Low score better function
Sherbrooke postal questionnaire (Hebert et al., 1996)	√ Need cane/walker/wheelchair See/ hear well	√ Memory problem	√ 3/> medications daily	√ Live alone	-	1/> OR did not return questionnaire: at risk for functional decline
Ten-item questionnaire (Gealy, 1997)	√ ADLs – eating, bathing, toileting, dressing, transfer, walking IADLs – use a phone, shopping, food preparation, housekeeping, laundry, mode transportation, ability/lack to self-medicate	-	-	-	-	Greater mean ADL/IADL score: greater frailty
ADL and self-reported health as frailty measure (Dayhoff et al., 1998)	√ ADLs Walking between rooms, moving around outdoors, using stairs, walking at least ¼ mile, using toilet, washing and bathing, dressing and undressing, getting in and out of bed, feeding, cutting toenails, cooking, light/heavy housework, carry heavy objects Self-rated health (excellent, good, fair, poor, terrible)	-	-	-	-	Frail: 21/> and fair/poor self-report health

Type of frailty measure Self-report	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
1994 Frailty Measure (Strawbridge et al 1998, Ho et al 2002, Matthews et al 2004)	√ Physical functioning: Sudden loss of balance, arms/legs weakness, dizzy/faint when stand up quickly Nutritive functioning: Loss of appetite, unexplained weight loss Sensory: 3 items vision problem, 3 items hearing problem	√ Cognitive: difficulty paying attention, trouble finding word, difficulty remembering things, forgetting where put something	-	-	-	3/> in any item in each domain: difficulty Frail: difficulty in 2/> domain
The Vulnerable Elders Survey – VES (Saliba et al 2001)	√ Age Stooping, crouching, kneeling Reaching/extending arms above shoulder Writing, handling, grasping small objects Walking a ¼ mile Heavy housework Difficulty with: Shopping, managing money, light housework, bathing/showering, walking – with cane/walker is OK Self-rated health (excellent, very good, good, fair, poor)	-	-	-	-	3/>: Identify risk of death and functional decline
Groningen Frailty Indicator – GFI (Steverink et al 2001, Schuurmans et al 2004)	√ Mobility (use of aids: independent) Shopping, walking around, dressing and undressing, toilet Vision problem Hearing problem Nutrition: unintentional wt lost in the last 6 month Self-rated physical fitness (0-10)	√ Memory problem/dementia Psychosocial: Emptiness, missing people, feel abandoned, feel sad, fell anxious	√ 4/> medications	√	-	4/> moderately frail

Type of frailty measure Self-report	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Geriatric Functional Evaluation – GFE (Scarcella et al 2005)	√ Sight, hearing, mobility Diet Functional abilities	√ Disorientation Delirious psychosis Memory loss Energy and motivation Reasoning ability Hallucinations	√ Respiratory function Cardiovascular function Comorbidity	√ Community support Live alone or with friend/family/part-ner Economic situation	√ Housing condition (ground floor/ elevator)	<10: seriously non-self sufficient 10-50: partially self-sufficient >50: self-sufficient
The Swiss Interdisciplinary Longitudinal Study on the Oldest Old (SWILSO-O) frailty measure (Guilley et al 2008)	√ Sensory: reading, hearing one person, hearing several persons Mobility: difficulty going up and down stairs, moving around outside, walking 200m	√ Memory problems Energy: Tiredness Loss of appetite	√ Physical pain: limbs, head face	-	-	Frailty 2 of 5 domains
The Hebrew Rehabilitation Center for Aged Vulnerability Index and The VES (Kanauchi et al 2008)	√ Age Stooping, crouching, kneeling Reaching/extending arms above shoulder Writing, handling, grasping small objects Walking a ¼ mile Heavy housework Difficulty shopping Managing money Walking – with cane/walker is OK Light housework Bathing/showering Self-rated health (excellent, very good, good, fair, poor) HRCA: A: help in prep meals, taking out garbage, housework, walking up/down stairs, use walker/cane B: leave their residence, help in dressing, health impediments	√ HRCA A: identifying correct year	-	-	-	VES: 3/>: frail and HRCA A: 1/> and B: 1/>: frail Frail on either of the 2

Type of frailty measure Self-report	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
The Brief Risk Identification of Geriatric Health Tool (BRIGHT) questionnaire (Kerse et al 2008)	√ In the last 3 months Help around indoors Had tripped/fallen Sob walking across room Help with bathe/shower Help with grooming Help with dressing Help with housework Need help filling questionnaire Self-rated health (yes/no)	√ Bothered with feeling down/depressed/hope-less Difficulties making decision Memory problems	-	-	-	3/> Case finding disabilities
PRISMA-7 (Raiche et al 2008, Hebert et al 2009) Modified Sherbrook	√ Age >85yo Male Health limits activity Help regularly Regularly use a cane, a walker or a wheelchair	-	√ Stay at home due to health problems	√ Someone to count on	-	3/> To identify for moderate/severe disabilities
The Tilburg Frailty Indicator (Gobbens et al 2010)	√ Unintentional weight loss in last 6mo Diff walking Diff maintaining balance Poor hearing Poor vision Lack of strength Tired Self-rated health (yes/no)	√ Memory problem Feeling down in last month Feeling nervous in last month Cope with problems well	-	√ Live alone Miss people around Enough support	-	Max score 15 – highest level of frailty
Self-rated health as frailty measure (Hoogendijk et al 2013)	√ Self-rated health: 0 to 10	-	-	-	-	Score of 6/<
FiND questionnaire (Cesari et al 2014)	√ A. Diff walking 400m B. Diff climbing stairs C. Unintentional weight loss >4.5kg in the last year D. Exhaustion E. Physical activity	-	-	-	-	A+B >:1 – disabled A+B : 0 and CDE : 1/> - frail A-E : 0 - robust

Type of frailty measure Physical assessment	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Albuquerque Falls Study (AFS) frailty measure (Vellas et al 1997)	√ One-leg balance	-	-	-	-	Ability to stand on 1 leg unsupported for 5 seconds – predict falls and injurious falls
Modified Physical Performance Test – MPPT (Brown et al 2000, Villareal et al 2003)	√ Lift a 7lb book Put on and take off a coat Pick up penny Chair rise Turn 360' 50-ft walk One flight of stairs 4 flight of stairs Progressive Romberg test (balance test)	-	-	-	-	4pt per item 32-36: not frail 25-32: mild frailty 17-24: mod frailty
Short physical frailty measure (Gill et al 2002)	√ >10sec on rapid gait test Chair stand	-	-	-	-	1: moderately frail 2: severely frail
Beaver Dam Eye Study frailty index (Klein et al 2003)	√ Gait time (3.37/> women or 2.19/> in men) Peak expiratory flow rate Handgrip strength – dominant hand Chair stand	-	-	-	-	1 point each item - frailty score
Grip strength as frailty marker (Syddall et al 2003)	√ Grip strength – harpenden dynamometer	-	-	-	-	Single marker of frailty
Modified Beaver Dam Eye Study frailty index (Klein et al 2005)	√ Gait time (3.37/> women or 2.19/> in men) Peak expiratory flow rate Handgrip strength – dominant hand Chair stand Visual impairment	-	-	-	-	1-2: mild 3: moderate 4-5: severe
Short Physical Performance Battery (SPPB) frailty score (Bandinelli et al 2006)	√ Gait speed Repeated chair rises Standing balance	-	-	-	-	Score ≤9 : frail

Type of frailty measure	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Physical assessment						
Balance Performance Oriented Mobility Assessment (BPOMA) and Get-Up-and-Go test (Opasich et al 2010)	√ BPOMA Get-Up-and-Go	-	-	-	-	BPOMA >19 and GUG 10s/<: non-frail BPOMA 19/<and GUG >10s: moderate frail BPOMA 9/< and GUG >10s: severe frail
Timed Up-and-Go test (Savva et al 2013)	√ TUG test	-	-	-	-	>16s: frail
Mixed						
YHAP-EPESE frailty measure (Speechley and Tinetti 1991)	√ Age >80 Balance and gait abnormality Infrequent walking for exercise Decrease shoulder strengths Decrease knee strengths Lower limb disability Near vision loss Vigorous descriptor (opposite of frail descriptor)	√ depressed	√ Sedatives use	-	-	4/> frail descriptor And 1/0 vigorous item
Rapid clinical screening (Winograd et al 1991) – hospital	√ ADLs Falls Impaired mobility Malnutrition Prolonged bed rest Restraints Sensory impairment	√ Confusion Depression	√ CVA Chronic disabling illness Incontinence Polypharmacy Pressure site *Dementia *Terminal illness	√ Socioeconomic/ family problems	-	Independent: no help in all ADL Frail meet any 1 of the criteria except * Severe: Severe dementia and ADL dependence Terminal illness
Modified Functional Independence Measure – FIM (Carlson et al 1998) Hospital	√ 1-7 scoring Feeding , hygiene, bathing, toileting, dressing, mobility	√ Communication	-	-	-	Decrease at least 1point : poor functional homeostasis No change/increase : good

Type of frailty measure	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Mixed						
The Zutphen Study frailty measure (Chin A Paw et al 1999)	√ Self-reported physical activity <210min/wk (lowest quartile) measured weight loss 1985 and 1990	-	-	-	-	Frail : both
CSHA rules based definition (Rockwood et al 1999)	√ Self-reported functional status (Older Americans Resources and Services Activities of Daily Living Scale)	√ Clinical assessment for cognitive impairment w/o dementia	√ Clinical assessment for dementia (DSM:III-R criteria4) Incontinence	-	-	0: walk w/o help, perform basic ADL (eating, dressing, bathing, bed transfers), continent, no cog impairment 1: bladder incontinence only 2: 1 (2 if incontinent) or more of needing help with mobility/ADL, has CIND, or has bowel/bladder incontinence 3: 2 (3 if incontinent) or more of dependent for transfer or 1/> ADL, incontinence of bowel/bladder, and dementia
Frailty Phenotype (Fried et al 2001)	√ >10lbs unintentional wt loss in the last year Grip strength Self-report exhaustion Slow walking time Low physical activity	-	-	-	-	Frail: 3/> Pre-frail: 1/2
Frailty Index (Mitnitski et al 2001, Mitnistki et al 2002)	√ Nutrition IADL/ADL Vision/hearing	√ Depression symptoms	√ Comorbidities	-	-	92 items FI: 0 - 1

Type of frailty measure Mixed	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Physical frailty measure (Binder et al 2002)	√ 50-foot walk Put on and off lab coat Pick up penny Chair stand Lift 7lb book to shelf Climbing one flight of stairs Standing balance Climbing up and down 4 flight of stairs 360' turn Self-report ADL VO2 peak	-	-	-	-	Mild-mod frailty: 2/3 – MPPT score 18-32, VO2 peak 10-18 and self-report diff 1 BADL or 3 IADLs
Frailty Index from a standardised Comprehensive Geriatric Assessment – FI-CGA (Jones et al 2004)	√ Communication (vision, hearing, speech) Mobility Balance Bowel function Bladder function IADLs ADLs Nutrition	√ Mood and motivation	√ Cog status (no cog impairment to dementia)	√ Social resources	-	Each: 0-no prob 1 minor 1 major 0-7: mild frailty 7-13: moderate frailty 13/>: severe frailty
CSHA Geriatric Status Scale (Rockwood et al 2004)	√ IADL	√ Modified MMSE score Neuropsychological test battery	-	-	-	Mild (mild cog imp, s/r one IADL, modified MMSE >77) Moderate/severe (mild dementia/moderate dementia, IADL)

Type of frailty measure	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Mixed						
Frailty Staging System (Cacciatore et al 2005 based on Lachs et al 1990)	√ Disability – ADL/IADL Mobility – test (touch back of head, pick up spoon, rise from chair then walk 10ft then return sit) Visual – test Hearing – test Nutrition – weight measured	√ Cognitive function	√ Urinary incontinence	√ Help in emergency available	√ Stairs Rugs/bathtub/lighting	each function domain:0/1 vis impair (3 and 4) cog impair MMSE <24 low social support (4) 3 classes of frailty 0/1: class 1 2/3: class 2 4-7: class 3
French EPIDOS study frailty measure (Carriere et al 2005)	√ Time since baseline evaluation Age x time since baseline Gait speed Time to complete 5 chair stand Balance: time to stand in tandem position Measured BMI Grip strength Physical activity MET – self-report Self-rated health (very good, good, bad, very bad)	√ Fear of falling	-	√ Education level	-	Calculated score for Higher score higher risk of IADL (any 1)
Static and dynamic frailty index (Puts et al 2005)	√ Measured weight Peak expiratory flow (mini wright flow meter) Vision capacity Hearing Physical activity – LASA questionnaire	√ Cognitive function – MMSE Sense of mastery Depressive symp - CESD	√ urinary incontinence	-	-	Frailty: 3/> Static frailty : low functioning at T2 Dynamic : relevant decline between T1 and T2
The Edmonton Frail Scale (Rolfson et al 2006)	√ Self-rated health (excellent, very good, good, fair, poor) How many of these activities you need help – meal prep, shopping, transportation, telephone, housekeeping, laundry, managing money, taking meds Weight loss TUG test	√ Clock drawing test Often feel sad/depressed	√ Hospitalisation in the past year – how many times 5/> regular medicines use compliant on meds urinary incontinence	√ Help available	-	Score 0-17

Type of frailty measure	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Mixed						
Marigliano–Cacciafesta polypathological scale – MCPS (Amici et al 2008, Amici et al 2011)	√ Sight/hearing Metabolism/nutrition – MNA score/BMI, diabetes/severe malnutrition	√ Cognitive state and mood (GDS/MMSE)	√ Neurological disorder Cardiopathy (NYHA) Respiratory disorder Renal disease Pain Peripheral vascular disease Cancer Gastrointestinal disorder	-	-	Slight polypathology <15 15-24: medium 25-49: medium-severe 50-74: severe >75: very severe
Simplified frailty phenotype (Ensrud et al 2008, Kiely et al 2009)	√ Weight loss – in 2year measured (un/intentional) Chair rise 5 times Energy		-	-	-	2/>: frail 1: pre-frail 0: robust
Prognostic frailty score (Ravaglia et al 2008)	√ Age 80/> Male Low physical activity Calf circumference Sensory deficit IADLs– phone, travel, money, taking medications Tinetti gait and balance test	√ Pessimism about self-health	√ Comorbidity	-	-	3/>: frail 0: non-frail
Frailty phenotype with cognitive impairment (Avila-Funes et al 2009)	√ Weight loss recent and unintentional of 3kg/> or BMI <21 Exhaustion Slow walking test Weakness – chair rise Physical activity	√ MMSE Isaacs Set Test – verbal fluency and speed of verbal production Lowest quartile in both test : cog impaired	-	-	-	3/> +/- cog. impair: Frail

Type of frailty measure Mixed	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Modified 5 indicators (Hubbard et al 2009)	√ Weight loss >5kg in last year Grip strength 16kg/< TUG 17s/> FEV1 30%/<	√ MMSE 24/<	-	-	--	3/>: frail 1 /2: pre-frail 0: fit
FRAIL scale (Hyde et al 2010)	√ Fatigue: feel worn out/tired? have lot of energy? Resistance: limited ability to climb stairs Ambulation: limited ability to walk 100m Loss of weight >5% Between W1 and W2 (measured) or Between W2 and W3 (self -report)	√ Illness: depression/anxiety disorder, Alzheimer's or other dementia	√ Illness >5: arthritis, diabetes, angina/myocardial infarction,hypertension, stroke, asthma, chronic bronchitis, emphysema, osteoporosis, colorectal cancer, skin cancer, leg ulcers	-	-	3/>: Frail
Survey of Health, Ageing and Retirement in Europe (SHARE) frailty index (Romero-Ortuno et al 2010)	√ Exhaustion: too little energy in the last month to do what you want Weight loss: appetite loss, eating less than usual Weakness: measured grip strength dynamometer Slowness: difficulty walking 100 m due to health problems in the last 3 month OR climbing 1 flight of stairs without resting Low activity: how often engaged in activity that need low/mod level of energy – gardening, cleaning car, walking 1 >than once a week - 2 -3 -4 (never)	-	-	-		Web-based tool Latent Gold to classify frailty into 3 class – non, pre and frail

Type of frailty measure	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
Mixed						
EASY-Care (Olde-Rikkert et al 2013) Personal details (10 items) Medical history 7 domains –Seeing, hearing, communication (4 items) –Self management (13 items) –Mobility (8 items) –Safety (5 items) –Finances (3 items) –Prevention (7 items) –Mental health and wellbeing (9 items) Summary outcome and scores Qualitative summary of needs and priorities (worded) Independence score 0–100 Falls risk score 0–8 Risk of breakdown in care score 0–12 Needs and priorities older person Needs carer Components of the care and welfare action plan Consent to information sharing	√ Seeing, hearing, speech problem, can use phone Grooming, dress, wash hands and face, use bath/shower, do housework, prepare meal, feed self, mouth/teeth problem, take own meds, use toilet/ commode Transfer from bed to chair, feet problems, get around indoors, manage stairs, falls in the last 12mo, can walk outside, go shopping Take regular exercise, shortness of breath during normal active, concern about weight Able to pursue leisure activity, self-rated health (excellent, very good, good, fair, poor)	√ Feel safe inside home Feel safe outside Ever feel threatened/harassed by anyone Feel lonely, recent loss/bereavement, trouble sleeping in last month, bothered by feeling down, depressed/hopeless, little interest or pleasure in things, concern with memory loss/forgetfulness	√ Skin problems – ulcer/pressure sores, incontinence bowel, urine Blood pressure check regularly, up-to-date with vaccine, pain in the last month	√ Difficulty getting public services – to health care providers Feel discriminated Anyone for help Happy with accommodation Able to manage money/financial affairs Like to have advice on financial allowance/ benefits Smoke, drink too much	-	Nurse identify needs for assessment
Clinician's judgment						
Subjective Frailty Score (Gerdhem et al 2003)	√ Individual general health and impression within 15s from first sight and transfer to arbitrary score 1-100	-	-	-	-	1: not rail 100: very frail By 2 nurses and 2 physiotherapists

Type of frailty measure Clinician's judgment	Physical	Psychological	Medical	Social	Environmental	Frailty criteria
CSHA Clinical Global Impression of Change in Physical Frailty Scale – CSHA Clinical Scale (Studenski et al 2004, Rockwood et al 2005)	√ Appearance: Grooming, posture, personal hygiene Strength: Grip, chair rise, manual muscle tests Balance: Falls, fear of falling, balance exam Nutrition: Weight, albumin, cholesterol Stamina; Self-report energy and fatigue, recent physical activity Mobility: Walking, transfer, stairs, asst devices ADL: Basic, instrumental, advance, ability to travel outside home Perceived health: Patient/other opinion of health	√ Emotional status: Depression, anxiety	√ Healthcare utilization: Hospitalisation, home care, freq. of doc visit Medical complexity: Number, severity of diagnoses, stability of conditions, number, complexity of medications	√ Social status: Roles, interaction with others, life events, living situation,	-	Amount of change from baseline (6month/>): 1 to 7 1 : marked worsening 7: marked improvement
General Practitioner's clinical judgment (Hoogendijk et al 2013)	√	√		√		Loss of resources and increasing risk of adverse health outcomes: frailty
Polypharmacy as frailty measure (Hoogendijk et al 2013)			√			5/> medications in the last 6 months: frail
The Gerontopole Frailty Screening Tool – GFST (Vellas et al 2013) Patient aged 65/> without both ADL 5/> and current acute disease	√ Unintentional weight loss in last 3 months Been more fatigued in the last 3 months Increase difficulty in mobility for the last 3 months Present with slow gait speed (>4s to walk 4m)	√ Complained of memory problems?		√ Live alone		GP If yes to any one/more Do you think your pt is frail?

Appendix C Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

This guidance document is sourced in full from the United States (US) National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort)

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 5 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be

applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Appendix D Chapter 5: Supplementary data

List of 39 variables included to construct the Frailty Index

Frailty index	Scoring
Live alone	Yes = 1; No = 0
Self-rated health	- Poor = 1 - Fair = 0.75 - Good = 0.5 - Very good = 0.25 - Excellent = 0
Arthritis	Yes = 1; No = 0
Asthma	Yes = 1; No = 0
History of heart attack	Yes = 1; No = 0
Hypertension	Yes = 1; No = 0
Migraine	Yes = 1; No = 0
Parkinson's disease	Yes = 1; No = 0
History of stroke	Yes = 1; No = 0
Thyroid disease	Yes = 1; No = 0
Ear, nose, throat problem	Yes = 1; No = 0
Mental disorder	Yes = 1; No = 0
Genito-urinary problem	Yes = 1; No = 0
Diabetes	Yes = 1; No = 0
Cancer	Yes = 1; No = 0
Chest pain	Yes = 1; No = 0
Constipation	Yes = 1; No = 0
Dental problem	Yes = 1; No = 0
Sleep problem	- Rarely/never = 0 - Sometimes = 0.5 - Often/almost always = 1
Spinal problem	Yes = 1; No = 0
Hearing difficulty	Yes = 1; No = 0
Eye trouble	Yes = 1; No = 0
Skin problem	Yes = 1; No = 0
Hands shaking problem	- No difficulty at all or a little difficulty = 0 - Some/ a lot of difficulty or just unable to do = 1
Stooping/crouching/kneeling problem	- No difficulty at all or a little difficulty = 0 - Some/ a lot of difficulty or just unable to do = 1
Difficulty with bathing	Yes = 1; No = 0
Difficulty with personal grooming	Yes = 1; No = 0
Difficulty with dressing	Yes = 1; No = 0
Difficulty with eating	Yes = 1; No = 0
Difficulty with toileting	Yes = 1; No = 0
Difficulty with going out	Yes = 1; No = 0
Difficulty with moving around	Yes = 1; No = 0
Difficulty with laundry/linen	Yes = 1; No = 0
Difficulty with housework	Yes = 1; No = 0
Difficulty with preparing meal	Yes = 1; No = 0
Difficulty with using telephone	Yes = 1; No = 0
Difficulty with managing money	Yes = 1; No = 0
Difficulty with using public transport	Yes = 1; No = 0
Difficulty with shopping	Yes = 1; No = 0

The predictive performance of frailty index at different cut-off points (N= 2087)

Cut-off points	% frail	Odds ratio (95%CI)	Sensitivity	Specificity	PPV	NPV	LR	AUC
Death at wave 3								
≥0.1	75	1.9 (1.4 – 2.6)	83.8	26.8	18.5	89.3	1.14	0.55
≥0.15	49.11	2.5 (1.9 – 3.2)	67.6	54.6	22.8	89.5	1.49	0.61
≥0.2	27.89	2.8 (2.2 – 3.6)	47.1	75.9	28.0	87.8	1.95	0.62
≥0.25	17.54	3.2 (2.4 – 4.1)	34.4	85.8	32.5	86.8	2.42	0.60
≥0.3	9.2	3.7 (2.7 – 5.1)	21.4	93.2	38.5	85.6	3.15	0.57
Hospitalisation								
≥0.1	75	1.6 (1.3 – 2.1)	79.7	29.3	33.2	76.7	1.13	0.55
≥0.15	49.11	1.7 (1.4 – 2.2)	56.5	57.5	36.9	75.0	1.33	0.57
≥0.2	27.89	1.9 (1.5 – 2.4)	34.1	78.4	40.9	73.0	1.58	0.56
≥0.25	17.54	2.3 (1.7 – 3.0)	23.8	88.1	46.7	72.4	1.99	0.56
≥0.3	9.2	2.2 (1.5 – 3.1)	11.9	94.1	46.9	70.8	2.02	0.53
Nursing home admission								
≥0.1	75	2.6 (0.9 – 7.4)	87.1	27.7	2.32	99.1	1.20	0.57
≥0.15	49.11	5.2 (2.1 – 12.8)	80.7	55.5	3.5	99.3	1.81	0.68
≥0.2	27.89	3.9 (1.9 – 8.0)	54.8	76.3	4.4	98.9	2.31	0.66
≥0.25	17.54	3.3 (1.6 – 7.0)	35.5	85.8	4.7	98.5	2.50	0.61
≥0.3	9.2	3.9 (1.6 – 9.2)	22.6	93.0	5.9	98.4	3.23	0.58
Fall								
≥0.1	75	1.4 (1.0 – 1.9)	78.5	27.5	17.2	87.0	1.08	0.53
≥0.15	49.11	1.8 (1.4 – 2.4)	59.3	55.6	20.4	87.7	1.34	0.57
≥0.2	27.89	2.7 (2.1 – 3.6)	43.3	78.0	27.4	87.8	1.97	0.61
≥0.25	17.54	2.7 (2.0 – 3.7)	28.9	87.0	29.9	86.5	2.22	0.58
≥0.3	9.2	2.8 (1.9 – 4.1)	15.6	93.8	32.3	85.3	2.52	0.55
Any outcomes								
≥0.1	75	1.9 (1.5 – 2.3)	81.1	30.1	49.2	65.7	1.16	0.56
≥0.15	49.11	2.2 (1.9 – 2.7)	59.9	59.9	55.4	64.1	1.49	0.59
≥0.2	27.89	2.8 (2.3 – 3.4)	38.9	81.4	63.6	61.5	2.09	0.60
≥0.25	17.54	3.4 (2.7 – 4.3)	26.8	90.3	69.7	59.7	2.76	0.59
≥0.3	9.2	3.8 (2.7 – 5.4)	14.9	95.6	73.9	57.4	3.39	0.55

% frail: proportion of frail participants; CI: confidence interval; sensitivity: probability of persons with outcome who are classified as frail; specificity: probability of persons without outcome who are classified as non-frail; PPV: probability that a person has the outcome if he/she was identified as frail; NPV:probability that a person has no outcome if he/she was identified as non-frail; Likelihood Ratio (LR): [sensitivity/100-specificity] – how much more likely is a person with the outcome to be classified as frail than those without the outcome; AUC: area under the curve;

Comparison of predictive performance of four frailty measures in predicting adverse outcomes using complete data (N= 1113)

Frailty measure	% outcome (frail/non-frail*)	Odds ratio – OR (95% CI)	Sensitivity	Specificity	PPV	NPV	LR	AUC (dichotomised model)	AUC (full model)†
Death at wave 3 (N= 112)									
Frailty phenotype	19.7/9.4	2.4 (1.3-4.4)	12.5	94.3	19.7	90.6	2.19	0.53	0.58
Simplified frailty phenotype	26.1/9.7	3.3 (1.3-8.5)	5.4	98.3	26.1	90.3	3.17	0.52	0.55
Frailty index	20.9/8.5	2.8 (1.8-4.5)	25.9	89	20.8	91.5	2.35	0.58	0.64
Prognostic frailty score	15.7/5.6	3.2 (2.1-4.7)	68.8	58.6	15.7	94.4	1.66	0.64	0.64
Hospitalisation (N= 274)									
Frailty phenotype	29.6/28	1.1 (0.6-1.9)	5.8	94.6	29.6	71.9	1.07	0.50	0.52
Simplified frailty phenotype	58.8/27.6	3.8 (1.4-9.9)	3.7	99	58.8	72.4	3.7	0.51	0.52
Frailty index	41.4/26.4	1.9 (1.3-2.9)	16.8	90.7	41.4	73.6	1.81	0.54	0.58
Prognostic frailty score	35.6/22.6	1.9 (1.4-2.5)	53.7	62	35.6	77.4	1.41	0.58	0.58
Nursing home admission (N= 12)									
Frailty phenotype	3.9/1.1	3.6 (0.8-16.8)	16.7	94.7	3.9	98.9	3.15	0.56	0.64
Simplified frailty phenotype	5.9/1.2	5.3 (0.6-43.4)	8.3	98.3	5.9	98.8	4.88	0.53	0.59
Frailty index	2.8/1.1	2.6 (0.7-9.9)	25	88.8	2.8	98.9	2.23	0.57	0.59
Prognostic frailty score	1.9/0.7	2.8 (0.8-9.3)	66.7	58.3	1.9	99.3	1.59	0.63	0.63
Fall (N= 134)									
Frailty phenotype	7.4/14.1	0.5 (0.2-1.4)	2.9	94.1	7.4	85.9	0.49	0.52	0.58
Simplified frailty phenotype	17.7/13.7	1.4 (0.4-4.8)	2.2	98.3	17.7	86.3	1.29	0.50	0.51
Frailty index	21.6/12.8	1.9 (1.1-3.1)	17.9	89.6	21.6	87.3	1.72	0.54	0.59
Prognostic frailty score	15.5/12.5	1.3 (0.9-1.9)	47.8	58.5	15.5	87.5	1.15	0.53	0.53
Any outcomes (N= 446)									
Frailty phenotype	40.9/40	1.0 (0.6-1.7)	6.5	93.7	40.9	59.9	1.03	0.50	0.54
Simplified frailty phenotype	69.6/39.5	3.5 (1.4-8.6)	3.6	98.9	69.6	60.6	3.27	0.51	0.54
Frailty index	58.9/37.4	2.4 (1.7-3.5)	18.4	91.5	58.9	62.6	2.16	0.55	0.61
Prognostic frailty score	49.1/32.9	1.96 (1.5-2.5)	54.0	62.5	49.1	67.0	1.44	0.58	0.58

* non-frail group from frailty phenotype and simplified frailty phenotype analysis were combined with pre-frail group; † full model includes multi-level or continuous version of the frailty measure; %outcome: proportion of outcome among frail and non-frail group; CI: confidence interval; sensitivity: probability of persons with outcome who are classified as frail; specificity: probability of persons without outcome who are classified as non-frail; PPV: probability that a person has the outcome if he/she was identified as frail; NPV:probability that a person has no outcome if he/she was identified as non-frail; Likelihood Ratio (LR): [sensitivity/100-specificity] – how much more likely is a person with the outcome to be classified as frail than those without the outcome; AUC: area under the curve