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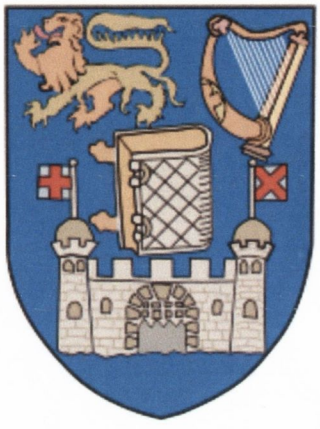
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Frailty in an Older Population: The Impact on Community-Dwelling Elders, Dementia Patients and Older Caregivers

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Doctor of Philosophy



December 2012

A thesis submitted to the National University of Ireland in fulfilment of the requirement for the degree of Doctor of Philosophy.

Research conducted at The Mercer's Institute for Research in Ageing, Trinity College School of Medicine, Faculty of Health Sciences, St James's Hospital
And
The TRIL (Technology Research for Independent Living) Centre, Trinity College School of Medicine, Faculty of Health Sciences.

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Acknowledgements

This research would not have been possible without the help and support of the many people I have been privileged to work with over the past number of years at the Mercer's Institute for Research in Ageing and the Technology Research for Independent Living Clinic both situated at St James's Hospital, Dublin. In particular, I wish to thank Professor Brian Lawlor for inspiring me to pursue a career in old age psychiatry and for , providing me with so many opportunities to advance my training. His guidance, dedication and expert supervision has enabled me to pursue this research and taught me what it is to be an old age psychiatrist. I would like to thank my colleague, Dr Damien Gallagher for his expertise and support on the Enhancing Care in Alzheimer's Disease Study. I would also like to thank Lisa Crosby for the significant contribution she made to our work and the caring approach she took with all of the participants in our studies. I would especially like to thank all of the staff at the Memory Clinic, Irene Bruce, Rachel Farley, Matthew Gibb, Dr Robert Coen, Dr Conal Cunningham, Dr David Robinson and Dr Kevin McCarroll who provided continuous advice and clinical support without which our research would never have happened. I would also like to acknowledge the work of Deirdre Ryan, Nicola Burke and Sophia Kilcullen on the ECAD study. I had the privilege of furthering my research by joining the Technology Research for Independent Living Clinic team. I would like to thank all of the staff at the TRIL Clinic for facilitating my work in such an enjoyable working environment. I would especially like to thank Clodagh Cunningham for her encouragement and for the caring manner in which she dealt with all of the participants attending the TRIL Clinic. I must also acknowledge the tremendous contribution of Professor Rose-Anne Kenny to my work; she provided excellent counsel and supervision, directing my research towards completion. I would

also like to thank Dr Chie Wei Fan for all of her advice and inexhaustible optimism which provided constant motivation

I wish to acknowledge the support of my family and close friends; in particular my loving husband Dr. Joseph Butler; without his inspiring drive, constant encouragement and loyal support I am quite sure I would never have reached my potential in either my academic or clinical career. I would like to thank my loving parents, Mairin and John and my siblings, Cormac, Sean, Darragh and Becca for their continuous words of encouragement and for having shown me the importance of kindness, understanding and empathy in my approach to life which I believe has provided a great foundation on which to build a career in psychiatry. I would also like to acknowledge the unwavering support of my husband's family Emily, Gerry, Gerard and Emer in all of my endeavours, and our friend Dr Roisin Dolan for being an excellent sounding board when any challenges arose and for her fantastic company on the many therapeutic weekends in Rossnowlagh. Many thanks also to my great friend Dr Mary Davoren for always being available for encouraging advice and great laughs when spirits were flagging.

Finally I would especially like to thank all of the participants of both the ECAD and TRIL studies. Without the generous contribution of their time and effort this work would not have been possible.

Funding

2010	Janssen Pharmaceuticals – Educational Grant
2010	GE Healthcare joins the funding body for the TRIL Clinic
2008	Elan Pharmaceuticals – Educational Grant
2007	TRIL Clinic is funded by Intel Corporation, the Industrial Development Agency (IDA) Ireland, with operational support from St James's Hospital Dublin.

The financial sponsors have played no role in the design, execution, analysis and interpretation of data or writing of any of the studies included in this thesis.

Awards

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2012	**Frailty and Quality of Life for People With Alzheimer's Dementia and Mild Cognitive Impairment** Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen R, Bruce I, Walsh JB, Cunningham C, Lawlor BA. The American Journal of Alzheimer's Disease and Other Dementias; In Press.
2012	**Depression: A Modifiable Factor in Fearful Older Fallers Transitioning to Frailty.** Ní Mhaoláin AM, Fan CW, Romero-Ortuno R, Cogan L, Cunningham C, Lawlor B, Kenny RA. International Journal of Geriatric Psychiatry; In Press.

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Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen R, Bruce I, Walsh JB, Cunningham C, Lawlor BA. Submitted to the Journal of the American Geriatric Society September 2012

2012 **The Impact of Frailty on Cognitive Performance in Independent Community Dwelling Older Adults.**
Ní Mhaoláin AM, Fan CW, Romero-Ortuno R, Cogan L, Cunningham C, Kenny RA, Lawlor B. Submitted to International Psychogeriatrics September 2012

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Papers under Review Resulting from Other Research related to Thesis

2012 **Preparedness for the Caregiving Role: A Protective Factor against Depression and the Desire to Institutionalise for our Older Caregivers.**
Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen R, Bruce I, Walsh JB, Cunningham C, Lawlor BA. Submitted to International Psychogeriatrics July 2012

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10th- 11th Nov 2011 Killarney, Ireland. **College of Psychiatry of Ireland Winter Conference**
The Impact of Frailty on Cognitive Performance in Independent Community Dwelling Older Adults.
Ní Mhaoláin AM, Fan CW, Romero-Ortuno R, Cogan L, Cunningham C, Kenny RA, Lawlor BA.
Oral Presentation

10th- 11th Nov 2011 Killarney, Ireland. **College of Psychiatry of Ireland Winter Conference**
Preparedness for the Caregiving Role: A Protective Factor against Depression and the Desire to Institutionalise for Our Older Caregivers.
Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen, RF, Walsh C, Cunningham CJ, Lawlor BA.
Poster Presentation

12th-14th Oct 2011 Brighton, UK. **British Geriatrics Society Autumn Meeting**
Preparedness for the Caregiving Role: A Protective Factor against Depression and the Desire to Institutionalise for Our Older Caregivers.
Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen, RF, Walsh C, Cunningham CJ, Lawlor BA.
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Oral Presentation

28th-30th Sep 2011 Malaga, Spain. **7th Congress of the European Union Geriatric Medicine Society**
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Oral Presentation

9th -10th Sep 2011
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18th-21st Mar 2011
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26th-29th Sep 2010
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Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen RF, Walsh C, Cunningham CJ, Lawlor BA.
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Ní Mhaoláin AM, Gallagher D, Crosby L, Ryan D, Lacey L, Coen RF, Walsh C, Cunningham CJ, Lawlor BA.
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19th Mar 2009
Dublin, Ireland.

Department of Medical Gerontology Trinity Research Day
Frailty in Alzheimer's Disease Patients and their Caregivers.
Ní Mhaoláin AM, Gallagher D, Lawlor BA.
Oral Presentation

Invited Lectures

18th Jan 2011

North Dublin Geriatric Meeting
Frailty in an Older Population: The Impact on Community Dwelling Elders and Dementia Patients.
Podium Presentation

8th April 2011

College of Psychiatry of Ireland Spring Academic Meeting
Frailty in an Older Population: The Psychological Impact on Community Dwelling Elders.
Podium Presentation

Summary

Frailty represents one of the greatest gerontological challenges faced by societies in coming years. Growing numbers of older citizens leads not only to increasing numbers of healthy elders, but also frail and disabled elders. Frailty incorporates multisystem alterations which lead to decreased mobility, reduced strength, and diminished responsiveness to external and internal stressors. Frailty research has thus far focused primarily on its association with medical factors and social, cognitive and psychological aspects have been largely neglected. These are key areas that require further evaluation. Within this study we aim to characterize frailty in three groups of older persons, independent community dwelling elders, cognitively impaired patients, and dementia caregivers. We explore the associations between frailty, cognition, mental health and psychological wellbeing within these groups.

Our findings suggest that older persons who are becoming increasingly physically frail could be considered psychologically frail with an increased likelihood of emotional disturbance, notably anxiety and depressive symptoms. Anxiety may be important in determining the link between frailty, social isolation and loneliness. We have also identified within our study population that depressive symptoms were associated with fear of falling in fallers at a transitional level of frailty and may be an important factor to consider to reduce fear of falling in this group. We have also attempted to identify how cognition and frailty may be related and found that global cognitive performance was poorer within both pre-frail and frail elderly and that the likelihood of having impaired executive functioning was increased fourfold in pre-frail or frail elders. We were able to characterize frailty in a group of cognitively impaired older adults and found that frailty was correlated with age and increasing

comorbid illness. We similarly found advancing frailty to be associated with poorer health related quality of life in cognitively impaired older persons as well as with increasing informal health care costs. Finally we identified perceived stress to be a key factor increasing the likelihood of both younger and older caregivers being at a transitionary stage of frailty.

Our findings add support to a multidimensional conceptualization of frailty to include important psychological and social correlates. Given the potential reversibility of frailty at an early stage our results to date contribute novel findings that may improve our ability to target vulnerable groups with preventative strategies and early treatment to minimize the risk of burgeoning frailty and mental health difficulties.

Chapter 1

Introduction

Part I: Frailty; An Overview

1.1 Background

The number of people aged over 65 will rise from 390 million now to 800 million by 2025 - reaching 10% of the total global population (WHO). Increased survival leads not only to increasing numbers of healthy elders, but also frail and disabled elders. The concept of frailty has been used as a reservoir for different problems that persons experience with aging. Frailty represents a major health problem that will lead to an increase in the use of health care by older persons. Frailty is considered to be a pathway to health decline and is described as a status of global impairment of physiological reserves involving multiple organ systems. It represents a complex biological phenomenon, and is often closely associated with pathology and disease. Frailty incorporates multisystem alterations which lead to decreased mobility, reduced strength, and diminished responsiveness to external and internal stressors.

The relentless path to old age, frailty, and death is one of the enigmas of medicine and over the last number of years there has been a surge of interest and focus on the area of frailty within the field of gerontology. Frailty is known to increase susceptibility to adverse outcomes for our older population and caring for frail older adults is a challenging process due to their complex medical, psychological and social needs. Researchers, policy makers, administrators and health care providers generally agree that frailty will have a significant impact on affected individuals, their families particularly those involved in care-giving, the health care system and society as a

whole. Frailty represents one of the greatest gerontological challenges faced by societies in coming years.

1.2 Defining Frailty

Frailty is a syndrome that many working in the field of gerontology have difficulty defining. It is a relatively new term that has emerged over the last 15 years with large research teams and trials trying to shed some light on its definition and potential interventions (CIFA, 2003; Ory, 1993). In the past the term frailty has often been used interchangeably with disability and chronic disease. However as our knowledge of frailty grows the importance of defining it as a separate clinical entity is becoming more apparent (Conroy, 2009). Historically frailty has been a term often used with differing definitions. Originally some authors connected it to what was described as "failure to thrive" in older adults a concept well known to paediatric medicine (Berkman *et al.*, 1989; Verdery, 1997). Similarly it was associated with disuse syndrome (Bortz, 1984). In the late 1980s descriptions of frail elderly people included those over the age of 65 dependent on others for activities of daily living and suffering from several diseases as well as " old debilitated individuals who cannot survive without the help from others" (Woodhouse, 1988).

By the early 1990s specific criteria began to be used in an attempt to pin down the concept of frailty. One specific definition required the presence of any of the following criteria: cerebrovascular accident, chronic and disabling illness, confusion, dependence in ADL's, depression, falls, impaired mobility, incontinence, malnutrition, polypharmacy, pressure sore, prolonged bed rest, restraints, sensory impairments, socio-economic or family problems.(Winograd, 1991) Similar groups

devised more stringent criteria in an attempt to define this elusive syndrome: older adults with at least four of the following characteristics: age >80 years, depression , balance and gait problems, rarely or never walk for exercise, use of sedatives, decreased shoulder strength, any lower extremity disability, decreased knee strength, and loss of near vision (Speechley, 1991).

The majority of these earlier definitions were ultimately seen as potentially flawed as they incorporated what many considered to be the adverse outcomes of frailty rather than the just the syndrome itself. Therefore within the more recent definitions of frailty, attempts have been made to exclude any adverse outcomes and to instead focus on aspects of impaired physiological functioning representative of frailty. There has been a move towards recognizing frailty as a multi-system decline, which is distinct from disease and disability but also intrinsically linked to these as both contributing factors and outcomes. Frailty has been described as a state of reduced physiologic reserve associated with increased susceptibility to disability (Buchner and Wagner, 1992). This susceptibility inherent to frailty has also been described as " a loss of capability to withstand minor environmental stresses" (Campbell and Buchner, 1997). Most current definitions of frailty emphasize this multisystem impairment and vulnerability.

A number of frailty models have arisen to define and operationalize frailty in a more specific and standardized manner. These models derive from distinctive theoretical views of how frailty develops and manifests itself in older adults. Strawbridge and colleagues developed a Functional Domains model of frailty in the Almeda County Study (ACS) (Strawbridge, 1998). They proposed an early frailty model based on

deficiencies in four domains of functioning (physical, nutritive, cognitive, and sensory). The model was the first to combine deficits across these domains into a single measure. Rockwood and colleagues went on to develop a Burden model of frailty based on the Canadian Study of Health and Aging (Rockwood *et al.*, 2005). It is a measure of the cumulative burden of symptoms, diseases, conditions and disability in the form of a frailty index. The accumulation of deficits within this index include but are not limited to conditions which are geriatric in nature. Another research group led by Linda Fried and her colleagues have developed what is known as the Biological Syndrome Model of frailty based on the Cardiovascular Health Study (CHS) (Fried, 1991). This model postulates frailty to be a ''biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems,'' and defines a frailty phenotype in terms of five components present in a hypothesized cycle of frailty, two of these components being defined in terms of physical performance measures (Fried *et al.*, 2004; Fried *et al.*, 2001).

Within the Burden Model of Frailty devised by Rockwood and colleagues frailty is defined by deficit accumulation. The simple theory behind this model is that as people age, they accumulate deficits that are eventually manifested as frailty, disease, or disability (Rockwood and Mitnitski, 2011). The model maintains consensus with other frailty definitions in that it is based on the understanding that frailty is an attribute of aged people who are at an increased risk of adverse health outcomes (including death) as a consequence of a diminished ability to respond to stress (Abellan van Kan *et al.*, 2008). This diminished ability to respond to stress is conceived of as a loss of redundancy, which arises as a consequence of the

accumulation of multiple deficits (Lally and Crome, 2007). This model counts a wide range of potential deficits from an array of health problems, which come in many forms; symptoms, signs, laboratory abnormalities, diseases, and disabilities. These features are clinically recognizable, and each represents an insult that has been insufficiently repaired and is referred to as a deficit (Rockwood and Mitnitski, 2011).

This definition of frailty takes the opposite approach of looking for a small number of essential features that people who are at risk have in common. Instead it counts deficits with little regard for their nature and uses the number or proportion of deficits to define their risk state. Therefore the more deficits occur, the more at risk an individual is and so the frailer they are. Deficit accumulation is indistinguishable from the loss of physiologic reserve because it is the basis for this loss. To standardize this counting of deficits an index is used within the context of a comprehensive geriatric assessment (Jones *et al.*, 2005; Jones *et al.*, 2004). The total number of items that can be used in a frailty index is considered to be 80, for example, assuming that the maximum number of diagnoses is 15 and the maximum number of medications is 20 (Rockwood and Mitnitski, 2011). The criteria for an item to be considered as a deficit are that the item needs to be acquired, age-associated, and associated with an adverse outcome and should not saturate too early. This frailty index mixes patient self-report with physician assessment and laboratory and other measurement data. The index has been robustly associated with decline in health status and mortality (Mitnitski *et al.*, 2006; Mitnitski *et al.*, 2007) The fundamental basis of this definition and method of measuring frailty is that is focuses on the 'big picture'; the complexity of frailty to include a multitude of medical and social needs to allow clinicians to provide more comprehensive treatment (Rockwood and Mitnitski, 2011).

Whilst the Frailty Index as defined by Rockwood is recognised as a sensitive predictor of adverse health outcomes due to its graded risk scale and robust clinical inferences with regard to the number and actual composition of the items in it; its use is for the most part specific to specialists in the field of geriatrics in the context of a full and comprehensive geriatric assessment. Its use can seem daunting to non geriatricians and it does not easily apply to all clinical settings. Accepting frailty as a heterogeneous phenomenon, an alternative approach to its definition and measurement has been to search for a specific number of deficits that people who are at risk have in common. This is the basis of the phenotypic or biological syndrome model of frailty originally described by Linda Fried and her colleagues, a definition which has been proposed and tested in Cardiovascular Health Study in the United States (Fried *et al.*, 2001).

In an attempt to standardize and operationalize the definition of frailty, Fried proposed a clinical phenotype of frailty as a well-defined syndrome with biologic underpinnings. The hypothesis being that the clinical manifestations of frailty are related in a mutually exacerbating cycle of negative energy balance, sarcopenia, and diminished strength and tolerance for exertion. This definition of frailty consists of the occurrence of at least 3 of the following 5 deficits in an individual: slow walking speed, impaired grip strength, a self-report of declining activity levels, unintended weight loss, or exhaustion. Classification is of frail (3 or more deficits), pre-frail (1 or 2 deficits), or robust (none of the deficits present) individuals (Fried *et al.*, 2001). These frailty characteristics serve as surrogates for the diminution in adaptive capacity. The phenotypic approach to frailty is the most widely studied approach, and in a variety of settings, this approach has been shown to correlate both with the risk of

adverse outcomes and with many important clinical parameters (Hubbard *et al.*, 2008; Leng *et al.*, 2007).

There is evidence to support this hypothesis of the frailty syndrome or phenotype as a self-perpetuating cycle of naturally progressing events that manifest with the clinical markers as described above (Buchner *et al.*, 1996; Evans, 1995; Leibel, 1995; Morley, 1997; Tseng *et al.*, 1995) Recent work has also confirmed that this proposed frailty phenotype conforms to the definition of a medical syndrome; i.e. " a group of signs and symptoms that occur together and characterize a particular abnormality". This work analyzed patterns of co-occurrence of the 5 frailty-defining criteria and identified patterns of criteria co-occurrence that support the syndrome definition such as manifestation in a critical mass and aggregation in a hierarchical order, as would occur in a cycle in which dysregulation in a sentinel system may trigger a cascade of alterations across other systems (Bandeen-Roche *et al.*, 2006). Further work using latent class analysis found 3 population subsets with similar profiles of frailty criteria co-occurrence; each criterion's prevalence increased progressively across the population subsets, indicating increase in frailty severity. These findings support the internal validity of the frailty criteria in characterizing frailty as a medical syndrome and provide justification to the current counting strategy for defining frailty categories (i.e., nonfrail, prefrail, and frail) (Bandeen-Roche *et al.*, 2006; Xue, 2011).

Given the multiple definitions of frailty available there has been a move towards clinical consensus as to the criteria used to describe the frailty phenotype.In the absence of a gold standard an emerging consensus promotes the definition of frailty that focuses on the frailty phenotype as it is believed it can be usefully distinguished

from co-morbidity and from disability (Ferrucci, 2004). It is thought that early stages of this process may be clinically silent but that when the losses of reserve reach an aggregate threshold this leads to serious vulnerability.The syndrome may then become detectable by looking at clinical, functional,behavioural and biological markers. Others have resisted the ''frailty equals physical frailty'' approach, to the point of emphasizing not just cognitive and psychological aspects, but even social relationships in defining frailty.(Frieswijk *et al.*, 2004; Rockwood *et al.*, 1994) Despite these differences there is widespread agreement that if frailty is to be measured it must include reference to multisystem impairment and vulnerability, and that it can be expressed as a gradient. For the purposes of this review we have primarily focused on the biological syndrome of frailty, given it is by far the most widely studied approach and has been robustly validated across a number of settings.

1.3 Manifestation of the Frailty Criteria

Understanding the natural history of frailty development is vital in order to facilitate preclinical detection of at-risk individuals and to allow for potential intervention on those components that are first affected. An important longitudinal study hypothesized that the cycle of frailty could be initiated through any one of the clinical manifestations of the syndrome, which would likely precipitate the cycle culminating in the aggregation of all clinical manifestations (Xue *et al.*, 2008). Although there was heterogeneity in the initial manifestations of frailty this work did find evidence of a partially hierarchical order to the onset of frailty. Weakness as defined by impaired grip strength was identified as the most common first manifestation. This is consistent with other available literature that a decline in muscle strength often begins in midlife (Lindle *et al.*, 1997; Nair, 1995). The loss of this muscle mass and muscle quality is

also termed sarcopenia, which results from anatomic and biochemical changes in aging muscle.

Within this same study slowness and low physical activity were found to more often precede the frailty criteria of exhaustion and weight loss (Xue *et al.*, 2008). However should an individual develop exhaustion or weight loss as initial presenting symptoms they are more likely to become fully frail than those lacking the presence of any frailty criteria. In the same study it was found that independent of whichever criteria represented the entry point into the cycle of frailty, 80% of transitions to full-blown frailty involved adding the criteria of exhaustion and/or weight loss. Also, weight loss and exhaustion rarely developed alone but more often co-occurred with other manifestations of frailty.

These findings are consistent with known evidence that once depletion of a system has occurred, and compensatory mechanisms have been made redundant, the addition of new deficits to a system leads to failure of the whole organism (Bortz, 2002; Kitano, 2002). This raises the possibility that decreased energy production or increased use, as in wasting conditions, may be involved in the threshold transition in a final common pathway toward frailty (Xue, 2011). The singular occurrence of weakness may represent a clinically meaningful indicator of increasing vulnerability at a relatively early stage in the frailty process, when preventative intervention might be easiest to implement and may be most effective (Xue, 2011). By the time someone experiences aggregate manifestations of frailty it may be too late to implement frailty interventions. It is for this reason that identifying those at the earliest stage of frailty

or pre-frailty and understanding more about the factors associated with this early stage is of prime importance for frailty research moving forward.

1.4 Frailty a Dynamic Process

Frailty is described as having a continuum. The initial stage of frailty, in which patients demonstrate fewer than 3 of the characteristics diagnostic of frailty, is referred to as the pre-frail stage. Studies show that pre-frail elderly persons are more likely than non-frail elderly persons to develop the full syndrome (Fried *et al.*, 2001). The end stage of the frailty continuum is failure to thrive (Robertson and Montagnini, 2004). Elderly patients, with or without comorbidity, eventually reach an irreversible stage of functional decline, progressive apathy, and decreased appetite that ultimately ends in death. For this reason frailty is often misconstrued as a premorbid state defining the end of life with an inevitable trajectory to death. However there is evidence to suggest that frailty can be both static and dynamic.

Dynamic frailty is defined as a decline in the measurement of frailty markers over a 3-year period, with or without a diagnosis of frailty. Dynamic frailty, even when adjusted for age, education, disability, chronic disease, and static frailty markers, is associated with an increased mortality (Puts *et al.*, 2005a). This evidence therefore points us to the fact that there are stages of frailty transition that may have potential for intervention. Epidemiologic data on transitions between frailty states (i.e., nonfrail, prefrail, frail) were first reported in an important longitudinal study, where older persons not only transitioned from states of non-frail, pre-frail to frail but also moved in the reverse with about one-third of all 18 months transitions occurring from states of greater frailty to states of less frailty (Gill *et al.*, 2006). The likelihood

however of transitioning from a stage of full frailty to non-frailty was extremely rare. These findings highlight the importance of a focus in frailty research on early identification and intervention to optimise the chances of prevention or amelioration of full-blown frailty.

1.5 Prevalence of Frailty and its Clinical Significance

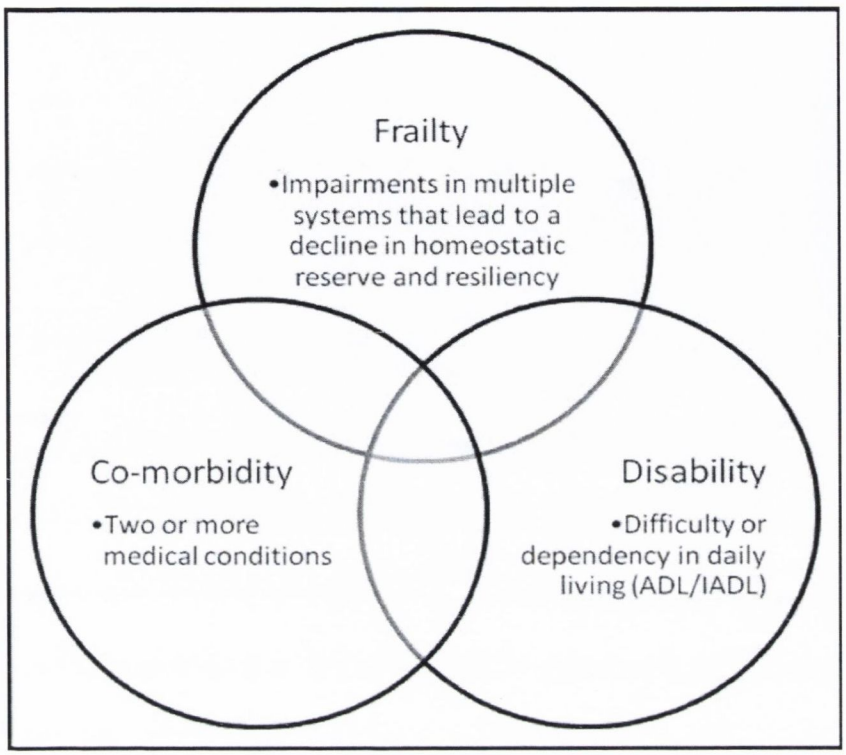
The number of people aged over 65 worldwide is rising rapidly, the fastest growing segment of this population are those over the age of 85 years. The incidence of frailty increases with age and will become more prevalent as our population continues to grow old (Klein et al., 2005). Studies conducted in the US indicate that the incidence of frailty increases with age ranging from 7% to 32% (Wilson, 2004). Researchers have demonstrated that even when individuals with acute and chronic medical conditions were excluded, 7% of the population aged more than 65 years and 20-40% of the population aged more than 80 years were frail (Fried *et al.*, 2004). There appears to be a higher prevalence in women than men and in the US it has been identified that, African Americans are more than twice as likely to be frail than Caucasians (Fried *et al.*, 2001).

Similar age trends and gender differences have been reported for older adult populations in European and Latin American countries. A recent survey of 7510 community-dwelling older adults in 10 European countries found that the prevalence of frailty ranged from 5.8% in Switzerland to 27% in Spain, with an overall prevalence of 17% and was higher in southern than in northern Europe, consistent with an unexplained north-south health risk gradient previously reported in the same population (Santos-Eggimann et al., 2009). According to a survey of 7334 older adults who were 60 years or older living in 5 large Latin American and Caribbean

cities, the prevalence of frailty varied from 30% to 48% in women and from 21% to 35% in men, which was much higher than their American and European counterparts. In the context of the US Cardiovascular Health Study the prevalence of pre-frailty in those over the age of 65 years was estimated to be 46% (Fried *et al.*, 2001). The 4-year incidence of frailty in the elderly has been identified as 7% (Fried *et al.*, 2001); a similar study in the Hispanic population showed the 7-year incidence to be 7.9% (Gill *et al.*, 2006).

Why is frailty important? In the past the term frailty has often been used interchangeably with disability and chronic disease. However as our knowledge of frailty grows the importance of defining it as a separate clinical entity is becoming more apparent (Conroy, 2009). There has been a move towards recognizing frailty as a multi-system decline, which is distinct from disease and disability but yet intrinsically linked to these as both contributing factor and possible outcome Figure 1.1. Disability, defined as the inability to perform activities of daily living (ADL), instrumental activities of daily living (IADL), or difficulty with mobility, does not affect the body across multiple organ systems (Fried *et al.*, 2004). Among frail elderly persons, only 60% have difficulty completing IADL, and 27% cannot complete ADL; furthermore, only 28% of disabled elderly persons are frail (Fried *et al.*, 2001). Even when adjustments are made for disability and comorbidity, elderly persons with a diagnosis of frailty continue to have a higher mortality rate (Puts *et al.*, 2005a). Although disability may contribute to frailty and vice versa, the two diagnoses are distinct from each other.

Figure 1.1 Frailty, Disability and Co-morbidity



The emerging consensus promotes the definition of frailty that focuses on physical frailty as it is believed it can be usefully distinguished from co-morbidity and from disability (Ferrucci, 2004). After adjustment for age, race, sex, smoking, and comorbid illness, frail patients have 1.2- to 2.5-fold increase in their risk for falls, decreased mobility, worsening ADL, institutionalization, and death (Fried *et al.*, 2001). A separate, cross-sectional observational study reported that frail patients had a significantly increased risk of cardiovascular disease, hypertension, cancer, and death, even after adjusting for chronic conditions (Klein *et al.*, 2005). When compared with non frail individuals the intermediate group of pre-frail persons are also at increased risk of developing all five index components of the phenotype as well as adverse outcomes such as falls, disability, institutionalization and death (Buchner and Wagner, 1992; Campbell and Buchner, 1997; Fried *et al.*, 2004; Hogan, 2003; Rockwood *et al.*, 2000). More importantly it is at the pre-frail stage that investigators believe the frailty syndrome may be reversed.

As the elderly population continues to grow, the impact of frailty will be felt throughout families and pervade our economic, health care, and social systems. By recognizing the frailty syndrome and suggesting lifestyle changes and interventions, physicians may help patients prevent co-morbidities and slow health decline in later life. Therefore, the development and evaluation of interventions designed to prevent or ameliorate frailty should remain as one of the top priorities in frailty research.

1.6 Causal Pathways to Frailty

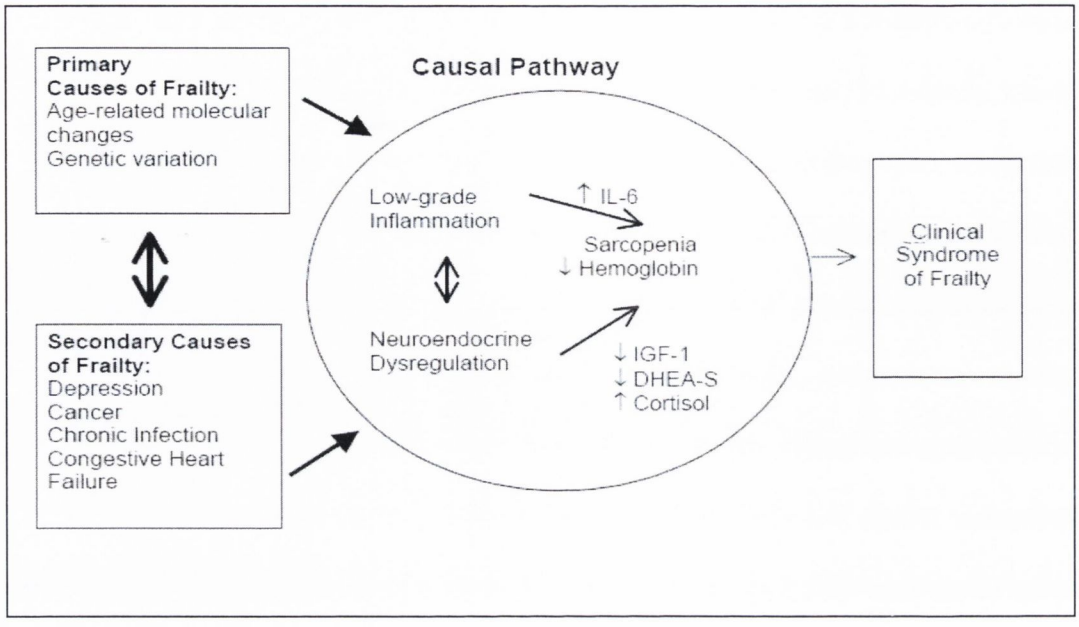
There are many causes of frailty suggested,all of which result from an accumulation of deficits that interact in a downward spiral. A hypothetical model of the proposed

causal pathway to frailty is well described by Walston and Fried (Figure 1.2). This model hypothesises that both primary and secondary drivers of frailty exist. Primary drivers consist of age related molecular changes and genetic variation between individuals. Secondary drivers are thought to be physical, psychological and environmental factors. Ultimately these drivers lead to low grade inflammation and neuroendocrine dysregulation leading to an increase in pro-inflammatory cytokines such as interleukin-6 (IL-6) and c-reactive protein (CRP), hypercortisolemia and subsequent reduction in insulin-like growth factor (IGF-1), all of which result in sarcopenia which is known to be a major contributor to the clinical syndrome of frailty (Cappola, 2003; Cohen, 1997; 2003; Ferrucci et al., 1999; Leng, 2004; Taaffe, 2000). The causal mechanisms which lead to this dyregulation of inflammatory cytokines and drive towards sarcopenia are varied, including oxidative stress, dysregulation of hormones, malnutrition, physical inactivity, and muscle apoptosis (Dirks *et al.*, 2006; Marcell, 2003) These factors associated with a pro-inflammatory state and sarcopenia are all hypothesized to contribute to frailty through interactive pathways at multiple temporal and spatial scales (Fried *et al.*, 2005). There is a vast array of work exploring these causative drivers of frailty and a number of principle aetiologies and core associations are detailed below.

1.6.1 Frailty and its Relationship with Ageing

Ageing is a complex phenomenon that can be difficult to define at its different levels. It can be conceptualized as a process of decline and deterioration of functional properties at the cellular, tissue, and organ level. It is a breakdown in maintenance of specific molecular structures and pathways, a loss of homeostasis, and a failure in homeodynamics (Lloyd *et al.*, 2001). Individuals vary a great deal in the onset of the

Figure 1.2 Causal Pathways to Frailty



Hypothetical causal pathways towards frailty Walston & Fried 2003, Chapter 9 Frailty and its implications for Care, Geriatric Palliative Care; 93-109 Oxford University Press.

aging process and the rate and extent of its progression. Differences in the manifestations of aging reflect differences in functional capacity. Functional capacity is a direct measure of the ability of cells, tissues, and organ systems to operate properly/optimally and is influenced by genes and environment (Lloyd *et al.*, 2001). Aging presents itself to a greater or lesser degree from ''successful'' aging to ''pathological'' aging depending on the reserve functions of the different physiological systems, their resilience and the consequent appearance of disease (Fulop *et al.*, 2010). Frailty may be considered to reflect an intermediate, but distinct state between these two extremes, where a certain reversibility of pathological processes may still exist (Bortz, 2002). This would imply that although aging predisposes to frailty, not all elderly are frail and suggests common, but not identical, pathways between aging and frailty (Bergman *et al.*, 2007; Schuurmans *et al.*, 2004). This opens up the possibility that frailty can be amenable at least to some extent to interventions (De Lepeleire *et al.*, 2009).

Mechanisms of homeodynamic maintenance in ageing include DNA repair and synthesis; the detection and clearance of defective proteins, lipids, organelles and cells; and the defence against pathogens and injury. The physiologic theories of ageing relate to a breakdown of these mechanisms such as DNA damage, mitochondrial damage, critical telomere length and oxidative stress, which trigger cellular responses such as apoptosis, senescence and repair and the induction of immune activation and inflammation (Chen *et al.*, 1995; Marshall and Watson, 1997; Nabeshi *et al.*, 2006; Ozawa, 1997; Ramasamy *et al.*, 2005; Roos and Kaina, 2006; von Zglinicki, 2000). Whilst the widely-used 5-item frailty criteria used for screening for frailty represents composite outcomes of multiple organ systems, other surrogate

endpoint markers of frailty have been identified which confirm the multiple systems that are dysregulated in this syndrome. These include elevated cytokines and chemokines (De Martinis *et al.*, 2006; Leng *et al.*, 2002; Qu *et al.*, 2009) reduced insulin-like growth factor 1(IGF-I), dehydroepiandrosterone sulfate, and leptin (Hubbard *et al.*, 2008); perturbed neutrophil, monocyte, and white blood cell distribution (Leng *et al.*, 2009; Leng *et al.*, 2007). This multisystem dysregulation which defines frailty yielding decreased physiologic reserves and increased vulnerability to stressors has commonality to that of aging where there is loss of molecular/cellular functional properties yielding decreased adaptability to internal/external stress and increased vulnerability to disease and mortality (Fedarko, 2011). Both have a basis in loss of homeostasis, although with aging, the failure in homeodynamics is global, whereas with frailty, the failure is around energy metabolism and neuromuscular changes.

In characterized frail elderly populations, the observed changes in functional performance and biomarker distribution are distinct from the corresponding age-related changes observed in non-frail individuals (Bandeen-Roche *et al.*, 2006; Fried *et al.*, 2004; Fried *et al.*, 2001; Walston, 2002). Despite this distinction the underlying processes of ageing and frailty remain very much interlinked. An example would be the sentinel homeodynamic cellular response of apoptosis, which is known to have pathophysiologic consequences for aging. Too much apoptosis can yield tissue degeneration (Adams *et al.*, 1996), whereas too little apoptosis allows dysfunctional cells to accumulate or differentiated immune cells to persist (Gupta, 2005). Evidence suggests that sarcopenia is apoptosis-driven (Marzetti and Leeuwenburgh, 2006). Interestingly the pro-inflammatory marker interleukin 6 (IL-6) seems to be protective

against apoptosis (Biffl *et al.*, 1996) and its serum levels are known to increase with not only increasing age but also with increasing frailty (Giuliani *et al.*, 2001; Yao *et al.*, 2011) indicating a common apoptosis driven pro-inflammatory response underlying both processes..

In many ways the relationship between frailty and ageing is impossible to tease apart, they are co-existent. The beginning of the "frailty cycle" consists of the accumulation of a lack of physical exercise, inadequate nutrition, unhealthy environment, injuries, disease, drugs, in combination with the ageing process. These interconnected factors lead to chronic undernutrition, consolidated by age-related changes, contributing to the loss of bone and skeletal muscle mass. Muscle weakness develops through the accumulation of metabolic debris and DNA alteration occurs. Sarcopenia results with a loss of reserve capacity and an increased sense of effort for any given exercise intensity. As the perception of exercise effort increases, older individuals become more likely to avoid exercise. A vicious cycle then begins; as regular physical activity decreases with age, there is a down-regulation of physiological systems as they adapt to reduced exercise and stress levels. With age, the decline in general function of cardiovascular and skeletal muscle reserves, as well as a reduction in maximum oxygen volume, then contribute to an increased perception of effort required for a particular task compared to that required when younger (Guilley, 2005) .If tasks are perceived as more difficult, the likelihood of avoidance of physical effort is increased, and as more occasions of physical effort are avoided, exercise performance continues to decline, contributing to additional physiological decrements in functional reserve capacity, leading to more sarcopenia, which increases restriction of physical

activity.(Janssen, 2002; Morley, 2008) A vicious cycle ensues in which ageing and frailty have both played key instigating roles.

Facets of senescence, apoptosis, and repair response have yet to be carefully studied in the setting of frailty. It may be expected that the patterns observed in normal aging between these different cellular and systemic responses would be further perturbed or accelerated in the syndrome of frailty. Future investigations targeting these areas will provide the data necessary to test these hypotheses related to the biology of aging and its close relationship with frailty (Fedarko, 2011).

1.6.2 Frailty and Inflammation

The finding that systemic low-level inflammation is strongly associated with frailty is consistent with the consensus that inflammation is associated with aging and chronic age-related diseases too (Franceschi *et al.*, 2000). It has been hypothesised that some of this inflammation may be a failure of the immune system to be properly regulated during the aging process, resulting in a continued, albeit low, level of effect over time (Buchner and Wagner, 1992; Hamerman, 1999). Age associated altered immunological profiles and dysregulated immune responses, loosely termed ''immunosenescence,'' may themselves contribute to pathology in addition to amplifying inflammatory processes (Fulop *et al.*, 2010). The physiological characteristics of frailty such as low muscle strength, exhaustion, reduced physical activity and unintentional weight loss can all be at least partially explained by increased levels of inflammatory mediators, especially by the increase of Interleukin-6 (IL-6). This cytokine, together with its surrogate, C-reactive protein (CRP), is one

of the most studied inflammatory parameters which is possibly causally related to the frailty syndrome (Fulop *et al.*, 2010).

Frailty associated inflammation can be categorized into heightened inflammation and alterations in innate and adaptive immunity. The heightened inflammatory state seems to play an important role, either directly or through adverse influence on intermediary pathophysiologic processes, in the pathogenesis of frailty. Alterations in innate and adaptive immunity trigger heightened inflammation as well as produce increased susceptibility to infections in frail older adults (Yao *et al.*, 2011). The aging immune system is characterized by a low-grade, chronic, systemic inflammatory state, so-called 'Inflammaging' (Franceschi *et al.*, 2000). This inflammatory phenotype is marked by the presence of elevated inflammatory molecules and is associated with increased morbidity and mortality in older adults (De Martinis *et al.*, 2006).As mentioned previously CRP and IL-6 are well known inflammatory molecules associated with the aging immune system. Similarly elevated levels of white blood cell (WBC) counts are also an important cellular marker of systemic inflammation.

Recent studies have provided a large body of evidence that suggests a heightened inflammatory state in frail older adults as marked by further increases in the levels of these molecular and cellular inflammatory markers compared with that observed in nonfrail, robust, older individuals (Hage and Szalai, 2007; Leng *et al.*, 2002; Leng *et al.*, 2009; Leng *et al.*, 2007; Leng *et al.*, 2004b; Puts *et al.*, 2005b; Walston, 2002; Walston *et al.*, 2008; Yao *et al.*, 2011). Increases in IL-6 levels are associated with several pathophysiologic processes, including atherosclerosis, osteoporosis, and sarcopenia, and with functional decline, disability, and all-cause mortality in older

adults (Ershler, 1993).In addition, increased IL-6 levels are associated with lower muscle mass and strength even in well-functioning older men and women (Reuben *et al.*, 2002).

1.6.3 Frailty and Age-Related Disease Processes

A large body of the literature, most rapidly accumulated in the past few years, suggests that frail older adults manifest multisystem dysregulation, including that in the musculoskeletal, immune, endocrine, hematologic, and cardiovascular systems, to name a few (Fried *et al.*, 2009; Leng *et al.*, 2008). It is not surprising therefore that frailty is also closely related to many age-related diseases. Whilst acute illness and injury may be abrupt and potentially reversible they still represent potential contributing factors to emerging frailty. Toxins, infections, injuries and malignancy may all provoke frailty. Similarly chronic illness plays a contributing role in particular due to its ability to prevent and diminish involvement in physical exercise and participation in activities of daily living (Bortz, 1982; Toth, 2000). Frailty and chronic diseases are prime modulators of a person's health trajectory in later life. An understanding of the presence or absence of frailty and chronic diseases constitutes a basic representation of physiologic reserves in old age (Weiss, 2011).

The duration of frailty is not long in comparison with most diseases. In 1.5 years, 12.9% to 23.0% of people with frailty will recover to a prefrail state, whereas 13.1% to 20.1% will die (Gill et al., 2006). Thus, the time spent frail is also less than time spent disabled, because of higher risk of mortality (Thorpe et al., 2009). Given the prevalence and duration, it follows that a small minority of people who have multimorbidity, several chronic diseases simultaneously, are frail. In the

Cardiovascular Health Study, only 9.7% of the older adults with multiple co-morbid illnesses were frail, whereas 67.7% of frail adults had multiple chronic illnesses (Fried *et al.*, 2001).The mean number of chronic diseases experienced by a frail older adult is 2.1, compared with 1.4 among non frail older adults (Hirsch *et al.*, 2006). These findings suggest that frailty is either (1) not caused by mechanisms that are shared with chronic diseases; (2) may be caused by mechanisms that are shared with chronic diseases once the diseases have reached a severe or advanced state; or (3) may be caused by specific interactions between disease related physiologic impairments that occur less frequently than single diseases, but is unlikely to be caused by 1 or 2 disease pathways alone, except in the case of (2) (Weiss, 2011).

Chronic diseases associated with frailty in published cohort studies of older adults using the biological syndrome model as the standardized measure of frailty include; hypertension, chronic kidney disease, osteoarthritis, depressive symptoms, coronary heart disease, diabetes mellitus, chronic lower respiratory tract disease, myocardial infarction, rheumatoid arthritis, stroke, peripheral arterial disease, congestive heart failure (Cesari *et al.*, 2006; Chaves *et al.*, 2005; Fried *et al.*, 2001; Fried *et al.*, 2009; Thorpe *et al.*, 2009; Woods *et al.*, 2005). Despite these associations no single disease-frailty association seems to be markedly stronger than the rest. Many diseases may converge to cause a single prominent frailty symptom or sign, or a single disease that is severe may cause multiple diverging symptoms and signs of frailty. Whilst there appears to be a clear association between frailty and certain chronic disease states frailty does not appear to be disease specific (Fried and Walston, 2003).

Frailty meets criteria for a geriatric syndrome because it does not fit within a discrete

disease definition category, but is substantially prevalent and involves several organ systems (Bandeen-Roche *et al.*, 2006; Inouye *et al.*, 2007). Unlike many conventional medical disease syndromes, frailty is likely to have multiple potential triggers, or points of entry, some of which correspond closely (Weiss, 2011). Physiologic inefficiencies become manifest in frailty, often in the presence of chronic disease complicated by malnutrition. As a consequence, frail older adults may perform less external work to avoid spending more out of a smaller pool of internal resources. Stress imposed on frail older adults can strengthen this negative feedback on activity, and lead to disuse and to worsening of chronic disease states (Bortz, 1986).

Current treatments older adults receive for chronic disease may not take the absence or presence of frailty into account which may impact on the effects of care received. An incomplete or distorted understanding of frailty in the context of disease states on the part of health care providers may lead to suboptimal therapeutic care. The motivation for understanding frailty and chronic disease states is to reverse it, improving energy efficiency in older individuals through appropriate therapies that augment compensatory strategies. It is an imperative to target treatment among frail older adults because a treatment administered in the wrong physiologic context can contribute to a rearrangement of interactions among physiologic systems that may not be helpful (Weiss, 2011). Frailty holds the promise as a treatment effect modifier that identifies a vulnerable subset in whom treatment may be more or less efficacious (Faber *et al.*, 2006). The objective of geriatric medicine is to continually improve the outcomes of older adults even when affected by diseases and frailty that may accompany later life. Frailty is highly predictive of adverse health outcomes and understanding the associations between frailty and specific disease states can inform

the next generation of research models evaluating frailty as an emergent property in the complex adaptive system of ageing (Weiss, 2011).

1.6.4 Frailty and Hormones:

Age-dependent declines in a number of hormones have been implicated in the causation of frailty in the elderly—particularly via their effects on muscle mass and bone density.

1.6.4.1 Testosterone

In men, aging is associated with substantial mean decreases in bioavailable testosterone and dehydroepiandrosterone (DHEA) (Kahonen, 2000; Leifke et al., 2000). The fall in testosterone levels which accompanies male aging is associated with a decline in muscle mass and strength, bone mineral density and cognition as well as a number of symptoms of frailty such as fatigue (Baumgartner, 1999; Matsumoto, 2002). Low testosterone has also been associated with hip fracture and poor function in older persons (Haren, 2002; Perry, 2000). Testosterone replacement has been shown to increase muscle mass in males, improve cognition in some human studies and in elderly men following hospitalization improve functioning (Bakhshi et al., 2000; Cherrier, 2001; Kenny, 2001; 2004; Snyder, 1999). On the whole evidence suggests that low testosterone plays a role in the development of frailty in males however it is not yet clear whether the same can be said for females (Bhasin, 2003; Morley *et al.*, 1997).

1.6.4.2 Dehydroepiandrosterone (DHEA)

DHEA acts as a precursor for sex hormones. Similar to testosterone and estradiol its levels decrease with age (Morley, 2004). Changes in regulation of these hormones

secondary to aging or disease states are likely to accelerate the decline in muscle strength and mass in older adults with physical frailty (Morley et al., 2001). Previous studies have associated it with reduced muscle mass (Valenti, 2004). Serum levels of the sex hormone dehydroepiandrosterone sulfate (DHEA-S) and IGF-1, a signalling target of GH, are significantly lower in frail than non-frail older women (Leng *et al.*, 2004a). Unfortunately subsequent studies looking at its replacement in older persons have had disappointing results (Baulieu, 2000; Percheren et al., 2003).

1.6.4.3 Growth Hormone and Insulin-like Growth Factor-I (IGF-1)

Serum levels of GH and IGF-1 decline progressively during aging (Johannsson, 2000). In aging and severe GH deficiency, muscle mass and strength are decreased along with loss of bone mass (osteopenia), with increased risk of fracture (Lissett, 2000). Furthermore, lower serum IGF-1 level is associated with progressive disability, poor muscle strength, slow walking speed, and increased mortality in the WHAS, suggesting a potential role for GH-IGF-1 somatotropic axis dysregulation in the development of frailty (Cappola *et al.*, 2001; Cappola *et al.*, 2003). Unfortunately replacement of growth hormone in older persons has failed to produce any positive effects in frail elderly and has been associated with many adverse effects (Harman, 2003; 2004). .

1.6.4.4 Thyroid

There is little evidence to suggest that thyroid hormone changes associated with aging have a direct link to the pathogenesis of frailty. However hypo and hyperthyroidism are associated with a decline in muscle strength and cognitive dysfunction and so may indirectly contribute to frailty (Morley, 2003).

1.6.5 Frailty, Lifestyle and Environment

How a person interacts with the environment and makes decisions play major roles in modulating the development and course of frailty or diseases. Physiologic frailty may be unobservable outside a specific context made up of environmental features and behaviour moulded by that environment, and therefore a full measure of frailty would require a matrix comprising physiologic reserves and parameters for interactions with the environment and personal choices (Weiss, 2011). Among these, a poor nutritional state has been strongly implicated by consistent findings that show an increased risk for malnutrition and frailty (Semba *et al.*, 2006). Nutritional factors both anorexia and obesity have been identified as potential contributors to frailty (Morley, 2001; Villareal, 2004). Sedentary lifestyles may contribute to these nutritional drivers and act as a driver itself (Blair, 1995).

Weight loss is a hallmark of the frailty syndrome.(Morley, 2002) One of the main phenotypic characteristics of frailty is 'shrinking', defined by muscle and total body mass wasting (Fried, 1991). In the majority of frailty definitions nutrition forms part of the frailty criteria. With aging there is a physiological anorexia that occurs to offset the decline in physical activity (Morley, 1997). There is also a decrease in fundal compliance due to a decline in nitric oxide generation in response to food stimulus (Sun, 1998). This ultimately leads to a more rapid antral filling and earlier satiety (Rayner, 2000; Sturm, 2004). There is also an increase in cholecystokinin, a satiating hormone in older persons in part due to decreased clearance (MacIntosh, 2001). Considering frailty as a wasting syndrome, its relation to obesity has remained unclear for a long time. Recent evidence however has associated overweight persons with pre-frailty and obesity with both pre-frailty and frailty (Blaum *et al.*, 2005).

Therefore, both undernutrition and obesity should be viewed as potential markers or signs of frailty (Villareal *et al.*, 2004).

It is thought that the multisystem dysregulations associated with frailty become clinically apparent when unmasked by stressors (Buchner and Wagner, 1992; Buchner, 1992). Frailty research has thusfar focused primarily on medical factors and psychosocial environmental aspects have been largely neglected (Hogan, 2003; Markle-Reid and Browne, 2003). However more recent studies have identified some psychological factors such as positive affect which may be associated with a reduced risk of frailty in older adults as well as social factors such as loneliness and isolation which may be associated with an increased risk of frailty (Ostir et al., 2004; Rockwood et al., 2004). A study based in China found that social factors, such as limited contact with relatives, blue-collar occupations, and absence of religious or community activities, were more likely to be seen in the frail elderly (Woo *et al.*, 2005).

1.6.6 Other Markers of Frailty

Given the clear links between frailty, age, chronic disease, nutritional and environmental factors; many demographic and neuroendocrine factors have been identified as potential markers for frailty alongside the criteria as defined in the Cardiovascular Health Study. Demographic markers include female sex, African-American race, lower education level, lower income, chronic illness and disability (Fried *et al.*, 2001; Hirsch *et al.*, 2006). Even with the exclusion of patients with diabetes or cardiovascular disease, frail patients have been shown to have increased C-reactive protein (CRP) and fibrinogen (Walston, 2002). CRP has been shown to activate the inflammation and clotting cascade, including d-dimer and factor VIII, as

well as circulating interleukin-6, all of which have been found to be elevated in frail older adults (Leng et al., 2002). Glucose intolerance has also been identified in association with frailty, where both fasting and post-prandial glucose and insulin levels have been found to be elevated in frail patients (Morley et al., 2005). These findings are not surprising given that glucose intolerance has been linked with sarcopenia and hyperinsulinemia has also been associated with leptin resistance and appetite suppression (Ahmed et al., 2007). Insulin-like growth factor (IGF-1) which stimulates growth hormone release, regulating cell growth and development is often found to be decreased in patients with diabetes or malnutrition. Serum levels of IGF-1 have been shown to be significantly lower in frail individuals also (Leng *et al.*, 2004a).

Cortisol and vitamin D have also been associated with frailty in older adults , the loss of stringent regulation of the hypothalamic-pituitary-adrenal axis is hypothesized to cause an age-related increase in cortisol production, which leads to decreased skeletal muscle mass and strength (Walston and Fried, 2003). This hypothesis is supported by recent epidemiologic evidence that demonstrates a positive association between higher levels of evening cortisol, 24-hour mean cortisol, and blunted diurnal variation of cortisol, with the frailty burden and clinical presentation observed in frail older women in the WHAS (Varadhan *et al.*, 2008). Low 25, hydroxyvitamin D level has also been shown prospectively to be associated with prevalent and incident frailty, particularly in older men (Puts *et al.*, 2005b; Shardell *et al.*, 2009). As the biological underpinnings of frailty continue to emerge, the "translational" potential for the health provider will perhaps be the ability to use serum markers to identify frailty more precisely (Hamerman, 1999).

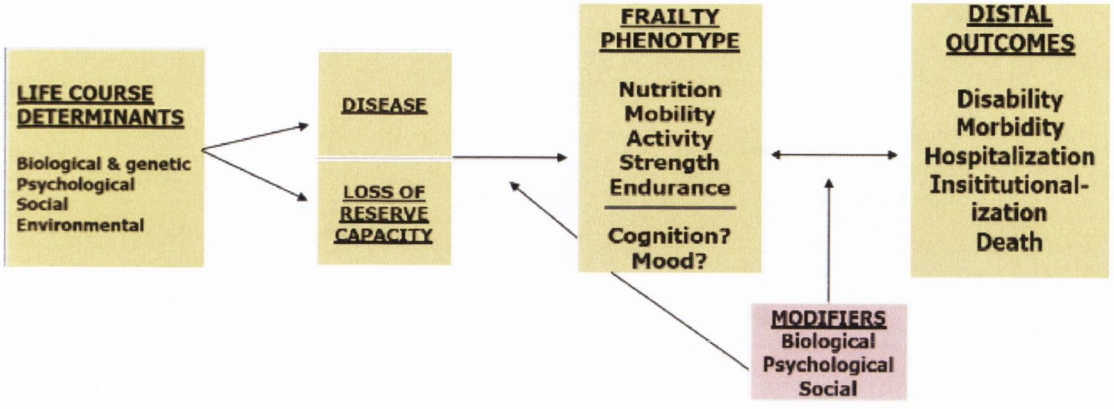
1.7 Treatment and Intervention in Frailty

With better characterization of the frailty syndrome and its pathopsyiology, including the dysregulation in musculoskeletal, neuroendocrine and immune systems, research can increasingly focus on treatments and interventions. To date curative treatments have not been identified, however increasingly our knowledge of interventions to improve clinical outcomes is expanding. We know frail elders suffer increased adverse clinical outcomes, such as acute illness, falls, disability, institutionalization and death (Fried *et al.*, 2001). Given the high morbidity and mortality secondary to frailty, increased awareness of this syndrome, its early diagnosis, and therefore, timely implementation of beneficial interventions or modifiers will be essential in improving health outcomes in affected older adults Figure 1.3 (Ko, 2011). To date a growing evidence-base in this area has shown us that exercise intervention and geriatric interdisciplinary assessment and treatment models can improve outcomes in a frailer population.

1.7.1 Exercise Intervention

Evidence suggests that a structured exercise programme enhances functional performance across the frailty spectrum, although its effect in the most severely frail patients may be limited. The benefits include increased mobility, enhanced performance of activities of daily living, improved gait, fewer falls, increased bone mineral density, and improvements in general well-being (Daley and Spinks, 2000; Keysor, 2003; Spirduso and Cronin, 2001). In a recent systematic review, Chin and

Figure 1.3 Working Framework of Frailty



colleagues examined 20 randomized controlled trials published from 1995 to 2007 that evaluated the effects of 23 different exercise training programs on physical performance in older people with varying degrees of frailty (Chin A Paw et al., 2008). Most of these interventions were facility-based, group-exercise programs composed of resistance training; balance training; or multicomponent training, including resistance, endurance, balance, and flexibility exercises. Fourteen trials demonstrated a beneficial effect of exercise on functional performance; five of the studies that did not show significant benefit of exercise were performed in a highly frail population, suggesting that the degree of frailty may play a role in dictating effectiveness of exercise programs. Despite these positive outcomes, specific guidelines of exercise programs (type, intensity, frequency, and duration) for frail, older adults have not yet been established (Ko, 2011). Even though the perfect prescription for exercise in frail older adults is not yet known, promisingly, studies have shown benefit from programs of resistance training on as few as 2 days per week and has been shown to be a well tolerated intervention for older adults (Hunter *et al.*, 2004; Lang *et al.*, 2010).

1.7.2 Hormonal Intervention

Given the decline in circulating levels of sex steroids, DHEA-S, vitamin D, and IGF-1 are associated with frailty, their supplementation is a potential intervention to improve muscle mass and strength, in the hope of improving function (Espinoza and Walston, 2005). However, to date, the efficacy of hormonal replacement therapy in treating frailty has not been established. The effect of testosterone replacement on functional performance in older adults has yielded mixed results (Ottenbacher *et al.*, 2006; Page *et al.*, 2005; Sattler *et al.*, 2009; Storer *et al.*, 2008). Similarly although vitamin D replacement in older adults with deficiency increases muscle strength and function its

efficacy in frailty intervention has not been reported (Bischoff-Ferrari *et al.*, 2009a; Bischoff-Ferrari *et al.*, 2009b). Hormone therapy is not currently recommended for the clinical management of frail older adults in the absence of clear clinical deficiencies (Ko, 2011).

1.7.3 Anti-inflammatory Intervention

New methods of inhibiting inflammatory effects of cytokines are forthcoming, in particular by blocking cytokines themselves or cytokine receptors, especially those for tumour necrosis factor-alpha, interleukin-1, and interleukin-6 (Xing and Wang, 2000). These treatments may have a moderating effect on emerging frailty in the future. Although substantial evidence supports the relationship between chronic IL-6 elevation and frailty-related outcomes, including muscle mass decline, disability, and mortality, pharmacologic treatments aimed at reducing inflammation in frail, older adults have not yet been developed (Ko, 2011).

1.7.4 Comprehensive Geriatric Assessment and Treatment

Evidence suggests that once an elderly patient has been identified as frail, the risk of adverse outcomes may be reduced via a comprehensive geriatric assessment with the development and implementation of an interdisciplinary treatment plan (Walston and Fried, 2003). The overall objectives of this intervention are to improve physical and psychological function, reduce hospitalization and long-term care placement, improve quality of life, and decrease early mortality in older adults (Urdangarin, 2000). This is achieved through patient assessment by an interdisciplinary assessment and care team. Medical history, physical examination and relevant psychosocial and environmental data is collected and informs the formulation of treatment goals and management

plans developed with the direct participation of the patient and caregiver. This geriatrician-led interdisciplinary team approach has been shown to improve functional status, reduce acute care hospital days and readmission, and lower mortality rate for frail older patients in both an outpatient and acute care setting (Eng *et al.*, 1997; Landefeld *et al.*, 1995; Rubenstein *et al.*, 1984; Weaver *et al.*, 2008).

1.7.5 Screening for Frailty

Frailty represents the complex and cumulative expression of altered homeostatic responses to multiple stresses. Physicians who are not familiar with the clinical care of frail, older adults may not easily recognize frailty in its early stage. The health provider continues to play an important role in encouraging older persons to accept personal health practices— especially exercise, which provides overall systemic benefits—as a way of life. Assessment tools that can predict the risk of functional decline, disability, and frailty and instruments that can be easily administered during routine physician visits by non-geriatricians should be used as screening tools for frailty (Corapi *et al.*, 2006). Clinicians should also consider diseases and disease processes that we know to be associated with frailty. Providing opportunity to screen vulnerable clinical populations for this syndrome and also ensuring overlapping diseases can be ruled out in frail patients.

Once a frail, older adult is identified, the patient should be initiated on exercise intervention and referred for geriatrics-focused interdisciplinary management (Ko, 2011). In an increasingly frail patient, caregivers could implement structured resistance training programs at home or through community resources such as day care centres that provide exercise therapy or long-term care facilities that could also

emphasis restorative physical therapy. In an acutely ill frail older adult, inpatient management should be delivered through an interdisciplinary team approach with the implementation of a comprehensive geriatric assessment. Interventions emerging from further research into the complex arena of frailty and the resultant advocacy of appropriate health practices may ultimately promote secondary or primary preventive measures for frailty that will provide both individual and societal benefit.

Part II Our Focus; Frailty in Older Populations

1.8 Frailty in Community-Dwelling Elderly

Researchers have demonstrated that even when individuals with acute and chronic medical conditions were excluded, 7% of the population aged more than 65 years and 20-40% of the population aged more than 80 years were frail (Fried *et al.*, 2004). Frailty research has thusfar focused primarily on its association with medical factors and social, cognitive and psychological aspects have been largely neglected (Hogan, 2003). These are key areas that require further evaluation. Approximately one in four patients treated in the community have severe emotional problems, predominantly anxiety and/or depression (Ansseau, 2004). Other psychological factors common to community dwelling elderly are those associated with falls. Fear of falling is one of the most common fears amongst the community-dwelling aged, where it is experienced by approximately half of the population and is suggested to be as serious a health problem as falls themselves (Howland *et al.*, 1993; Murphy *et al.*, 2002; Wilson, 2005; Zijlstra, 2007). A cost-effective way to improve detection of psychological health problems is to pay special attention to and facilitate early identification of elderly at risk of mental health deterioration (Smit *et al.*, 2007; Smit *et al.*, 2006). Knowledge of health-related variables that may be associated with

emotional disturbance improves our ability to target vulnerable groups with preventative strategies and early treatment to minimize the risk of burgeoning mental health difficulties. Frailty may represent an important physical health-related variable that to date has not been fully evaluated in relation to cognition, psychological wellbeing or mental health. Identifying any association between frailty and elderly who are cognitively or emotionally vulnerable is worthwhile not least due to already known adverse health outcomes. Another factor to consider is the potential reversibility of frailty at an early stage (Fried, 2004). If it is associated with deteriorating psychological health then it may represent a key target for intervention.

1.9 Frailty in the Cognitively Impaired Older Person

The prevalence of dementia is rising; currently it affects 24.3 million people worldwide. Alzheimer's dementia (AD), occurring in middle or late life accounts for 50 – 60% of all cases (Boyle *et al.*, 2010). Frailty as a distinct physiologic syndrome can be delineated from co morbidity and is known to contribute to significant health decline disability and mortality. In the Alzhemier patient it may significantly influence the burden of illness associated with this disease. The frailty syndrome has not yet been investigated in full within an AD patient cohort.Although the clinical hallmark of AD is progressive loss of memory and other cognitive abilities, several studies have shown that persons with AD also exhibit changes in mobility and body composition suggesting that many older persons with AD may be frail (Cronin-Stubbs *et al.*, 1997; Scarmeas *et al.*, 2005). Recent work indicates that core components of frailty, including impaired grip strength, slowed gait, and low body mass index (BMI), predict subsequent development of dementia (Rosano *et al.*, 2005; Stewart *et al.*, 2005; Wang *et al.*, 2006). Similarly physical frailty has been associated with

incident mild cognitive impairment and Alzheimer disease in community dwelling elders (Boyle *et al.*, 2010). To date there remains a paucity of literature available on frailty in the context of dementia and MCI. Given the belief that early intervention in the frailty pathway may lead to reversal of the syndrome, frailty may represent an important target in our attempts to minimize poorer outcomes for Alzheimer patients.It would seem appropriate to invest expertise and effort now to identify the association between frailty and cognitive and functional impairment in AD.

1.10 Frailty in the Dementia Caregiver

Approximately three-quarters of people with dementia live at home and traditionally the state only intervenes when family care is absent or breaks down (O'Shea and O'Reilly, 1999). Caregivers represent a valuable and frequently neglected resource that bear more than the simple financial burden of caring for patients with dementia. Providing care for a relative with any disability is accompanied by a considerable emotional, psychological and physical cost. In some caregiver studies nearly half meet diagnostic criteria for depression, many with no history of depression prior to assumption of the care giving role (Clyburn *et al.*, 2000).Informal caregivers report higher levels of anxiety and use psychotropic medication more frequently. Caregivers are also known to engage in fewer protective health behaviours, and are at increased risk of illness and mortality (Clipp and George, 1990; Schulz, 1999; Vitaliano, 1990; 1996; 2003). It is thought that the multisystem dysregulations associated with frailty become clinically apparent when unmasked by stressors. Recent studies have found elevated plasma levels of the biological markers associated with frailty such as IL-6 and CRP to be linked with the effects of Alzheimer caregiving stress and age (Clyburn *et al.*, 2000). Despite this, to date no study has looked at the clinical frailty

phenotype as a whole within dementia caregivers. Previously identified primary stressors in caregiving such as severity of care recipient cognitive impairment, level of help required for daily living and patient neuropsychiatric symptoms may be associated with emerging frailty in caregivers. Secondary stressors associated with dementia caregiving such as relationship quality, loneliness and isolation may also have an association. Further research examining the role of psychological factors within the continuum of frailty in dementia caregivers would be beneficial.

1.11 Objectives

The overall objective of this project is to characterize frailty in three groups of older persons, independent community dwelling elders, cognitively impaired patients, and dementia caregivers. We wish to investigate the prevalence, correlates and impact of frailty within these three groups.

This work will focus in particular on the following:

1) To expand on the current knowledge of the cognitive and psychological associations of frailty in a group of independent community dwelling elder

   We will focus on four key areas

   - Frailty and cognition
   - Psychological frailty
   - Frailty and fear of falling
   - Frailty, loneliness and social isolation

2) To characterize frailty in a sample of patients with a diagnosis of possible/probable Alzheimer's disease of varying severity and investigate the

association between frailty markers and clinical characteristics of these patients.

We will focus on three key areas

- Determinants of frailty in the cognitively impaired
- Frailty and quality of life for cognitively impaired patients
- Frailty as a driver of increasing economic cost and resource utilization in the context of cognitive impairment

3) To investigate the presence of the clinical frailty phenotype in a sample of primary caregivers. Establishing a detailed clinical picture of both patient and caregiver related drivers of carer frailty.

We will focus on three key areas

- The role of frailty in the dynamics of the carer-patient relationship
- Caregiver stress, burden and the frailty phenotype
- Caregiver loneliness, isolation and frailty

Chapter 2

Methodology

2.1 Experimental Design:

This work was conducted as a cross-sectional, observational study.

2.2 Patient Cohort

Participants were recruited in the course of the Enhancing Care in Alzheimer's Disease (ECAD) study and the Technology Research for Independent Living (TRIL) Clinic both of which took place in a university teaching hospital in Dublin. Through the ECAD study, 115 patients with a diagnosis of cognitive impairment were recruited along with 107 of their primary caregivers. A primary caregiver was defined as the individual who consistently assumed responsibility for any care provision required for the individual with cognitive impairment. This was a convienient sample recruited consecutively from a pool of 180 patients who attended the Memory Clinic over a six month period.

The Memory Clinic is a cognitive studies clinic attached to the Mercer's Institute for Research in Ageing in St James's University Hospital, Dublin, Ireland. Referrals to the memory clinic are primarily from general practitioners, medicine for the elderly or neurology services for the purposes of a multidisciplinary clinical assessment including full neuropsychological assessment in the context of queried cognitive change. A large proportion of the referrals would be from within Dublin and its surrounding areas, however referrals are accepted from all services countrywide if deemed appropriate. Those excluded from our study either refused to participate, were not diagnosed with cognitive impairment, fulfilled exclusion criteria or lived

outside of Dublin or its bordering counties which made the home-based assessment process too impractical to complete.

The Technology Research for Independent Living Clinic was launched in 2008. Its purpose was to provide multiexpertise research focusing on the older individual, recognising the interplay between systems for wellbeing, physical, cognition, perceptual and social domains. An overarching goal of this research clinic was to develop a deeper understanding of risk factors for health decline in ageing across the domains of falls, cognition, social and mental health functioning. The purpose of which, was to contribute new information facilitating the development of home based technologies that might assist the provision of personalised healthcare, greater independence and quality of life within the home environment.

A media campaign was launched in 2008 to encourage participant referrals to the clinic, which provided access to a comprehensive geriatric assessment for adults over the age of 60. Those recruited were done so consecutively over a 12 month period and represented a convienient sample of older adults. Seventy percent were self-referrals from all over Ireland who responded to reading material about the TRIL clinic in national publications. The remaining 30% were referred from general practioners primarily within the catchement area of St James's Hospital which is a large settled area of Dublin with a relatively high proportion of older community dwellers, as well as from the outpatient and emergency department of St James's hospital itself.

2.2.1 Community-Dwelling Elderly

624 community dwelling elders were recruited through the TRIL Clinic which offered an outpatient clinical service to community-dwelling people aged >60 years in the form of a comprehensive geriatric assessment incorporating the use of technologies to measure risk factors for falls, cognitive decline, mental health and social connectedness.

2.2.2 Cognitively Impaired Older Persons

115 participants with cognitive impairment were recruited through the ECAD Study. They were identified from referrals to the Memory Clinic as described above Inclusion criteria required these participants to have received a diagnosis of probable or possible AD or amnestic mild cognitive impairment (MCI) of suspected AD aetiology and to be age > 50 years. Patients were excluded if they had co-morbid illness, which was a significant independent cause of disability (e.g. Parkinson's disease or dense hemiplegia or previous CVA).

2.2.3 Primary Caregivers

107 primary caregivers were recruited for the purposes of the study. They were identified through the Memory Clinic at St James's Hospital as described above. Inclusion criteria required that their care-recipients all had a dementia or cognitive impairment diagnosis. Exclusion criteria required that the caregivers did not have any history of cognitive impairment themselves.

2.3 Participant Assessment

Subjects were assessed in two ways. They were either visited in their own home for assessment by a researcher on two separate occasions or they received a comprehensive geriatric assessment through the TRIL research clinic within the hospital setting. It was felt home visits were more appropriate for those patients with cognitive impairment to provide a comfortable and familiar environment for them for the purposes of assessment. Similarly due to the nature of their responsibilities caregivers often favoured a home assessment as it facilitated their participation in the study as they did not have to leave the home for an extended period. Due to the duration of the assessments, they were carried out over two home visits to ensure participant fatigue did not impair the process.

Community dwelling elders were assessed through the TRIL centre in St James's Hospital, a clinical research unit that facilitates the recruitment of participants for the purposes of various research projects. This facility provides a rapid-access, comprehensive assessment of older people to include (i) identification of falls risk factors and physical assessment (ii) assessment of cognition and (ii) interviews on social connection and emotional health of the older person. Given that we were assessing older persons who may be frail; this clinic lent itself to the assessment process as it is designed as a one-site seamless, integrated clinic that allowed for complete evaluation in a comfortable environment.

2.4 Frailty and Biophysical Measurements

Frailty was measured using the proposed clinical phenotype of frailty described by Fried and collegues. This is a well-defined syndrome with biologic underpinnings

validated in the context of the Cardiovascular Health Study (Fried *et al.*, 2001). The operational definition of this biological syndrome model is a condition consisting of five phenotypic criteria indicating compromised energetics, namely, low grip strength, low energy, slowed walking speed, low physical activity and unintentional weight loss (Table 2.1). A prefrail stage in which one or two criteria are present, identifies a subset at high risk of progressing to frailty and are known as pre-frail or intermediately frail (Table 2.2).

2.5 Questionnaires and Psychosocial Measures

Sociodemographic and medical details were collected as part of a structured questionnaire. Psychosocial measurements, frailty markers and biophysical measurements were also taken for all participants.

2.5.1. Community-dwelling Elderly Assessment

2.5.1.1 Cognitive Assessment

Community-dwelling elderly received a complete battery of standard neuropsychological tests (Table 2.3)

Table 2.1 The Biological Syndrome Model of Frailty

CHARACTERISTIC OF FRAILTY	CRITERIA
Shrinking (unintentional sarcopenia)	Any reported unintentional weight loss in previous year asked as " In the last year, have you lost weight unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion or BMI < 18.5kg/m^2
Weakness	Grip Strength, was measured using a hand held dynamometer. Three attempts were recorded for both hands and an average grip strength obtained for both left and right hands. The highest average was then taken as the study participant grip strength and stratified by gender and body mass index (BMI) quartiles as shown below: *Men* *Cutoff for grip strength (Kg)* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21

Poor endurance, exhaustion	Exhaustion [2 Items from Center for Epidemiologic Studies Depression Scale CESD]. Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion. (Radloff, 1977)
Slowness	A clear and unobstructed distance of 15 feet was measured out and marked within the participant home or inpatient assessment unit. The time taken to walk 15 feet from a standing position (the participant was informed to walk at their normal walking pace) was then measured and stratified by gender and height. *Men* — *Cutoff for 15 feet* Height ≤173 cm — ≥7 sec (≤65.3cm/sec) Height >173 cm — ≥6 sec (≤76.2cm/sec) *Women* Height ≤159 cm — ≥7 sec (≤65.3cm/sec) Height >159 cm — ≥6 sec (≤76.2cm/sec)
Low Activity	Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender.(Folsom *et al.*, 1986). Frailty in Males: <383 Kcals/week Frailty in Females: <270 Kcals/week

Table 2.2 Classification of Frailty Groups

CHARACTERISATION OF FRAILTY:	
Non-frail or robust	0 criterion present
Pre-frail	1-2 criterion present
Frail	3-5 criterion present

Table 2.3 Neuropsychological Test Battery

Category	Test
Dementia Screening	Mini Mental State Examination (Folstein *et al.*, 1975)
Mood – Anxiety	Hospital Anxiety and Depression Scale - Anxiety Subscale (Zigmond and Snaith, 1983)
Mood – Depression	Centre for Epidemiological Studies Depression Scale- 8 item (Carpenter *et al.*, 1998)
Verbal Memory	Word Recall, immediate and delayed (subtests from Wechsler Memory Scale 3rd Ed. WMS-III) (Taylor and Heaton, 2001)
Visual Memory	Visual Reproduction I (subtest from WMS-III)
Prospective Memory (working memory and conceptualization)	Hidden Belongings and Remembering and appointment task (RBMT-E) (Shinagawa *et al.*, 2010)
Language - Executive function	Animal Fluency Test
Language - Comprehension	Understanding written instructions test
Executive Function	Forward & backward digit span (WAIS-III) Similarities test (WAIS-III) (Johansson and Wressle, 2010)
Attention	SART (Sustained Attention Response Task) (Seli *et al.*, 2011)

2.5.1.2 Psychosocial Assessment

A quantitative assessment was conducted on a wide range of psychosocial measures in our cohort of healthy older people including a subset of fallers & non-fallers who attended the clinical research facility in the TRIL center. These assessments allow analysis of the relationship between baseline measures of social network, personality, physical frailty and mental health measures. Psychosocial measures used include:

1. *Centre for Epidemiological Studies Depression Scale (CESD)* (Radloff, 1977)

The CES-D scale and its abbreviated versions is a short self-report scale designed to measure depressive symptomatology in the general population. The items of the scale are symptoms associated with depression which have been used in previously validated longer scales. The scale has been tested in household interview surveys and in psychiatric settings. It has been found to have very high internal consistency and adequate test- retest repeatability. Validity has been established by patterns of correlations with other self-report measures, by correlations with clinical ratings of depression, and by relationships with other variables which support its construct validity. Reliability, validity, and factor structure have been similar across a wide variety of demographic characteristics in the general population samples tested.

2. *Hospital Anxiety and Depression Scale –Anxiety Subscale* (HADS-A) (Zigmond and Snaith, 1983)

The HADS is a self-assessment scale developed and found to be a reliable instrument for detecting states of depression and anxiety in the setting of hospital medical outpatient clinics. The anxiety and depressive subscales are also valid measures of severity of emotional disorder.

3. *Eysenck Personality Inventory (EPI)* (Eysenck and Eysenck, 1964)

Personality was measured using the Eysenck Personality Inventory-Revised (EPI-R), a 48 item personality questionnaire, which measures two important personality dimensions, extroversion–introversion and neuroticism-stability. The EPI-R has been shown to have good internal consistency, test-retest reliability, and concurrent validity particularly for the measurement of extraversion and neuroticism (Sato, 2005).

4. *The Geriatric Adverse Life Events Scale (GALES)* (Devanand *et al.*, 2002)

The GALES includes a checklist of 26 adverse life events. The participant reports the number of life events experienced in the past year

5. *Social Network Typology* (Wenger *et al.*, 1996)

Social networks were assessed using the Practitioner Assessment of Network Type Schedule developed by Wenger. The schedule classifies social network into one of five types; the family dependent support network; the locally integrated support network; the local self-contained support network; the wider community-focused support network; the private restricted support network.

6. *De Jong Loneliness Scale* (de Jong-Gierveld and van Tilburg, 2008)

The De Jong Gierveld Loneliness Scale can be used as either a one-dimensional loneliness scale, or to distinguish between social and emotional loneliness. The loneliness subscales for emotional and social loneliness have proved to be valid and reliable measurement instruments for these phenomena in mind. For use in large surveys a shorter 6-item version of the De Jong Gierveld scale was constructed in such a way that the threefold application of the original scale (an overall loneliness scale as well as emotional and social subscales) was still guaranteed.

7. *Modified Falls Efficacy Scale (MFES)* (Tinetti *et al.*, 1990)

The Modified Falls Efficacy Scale is a one-page form, consisting of 14 questions each related to a particular activity (for example getting dressed, taking a bath, crossing roads etc). Unlike the original Falls Efficacy Scale (developed by Tinetti et al, 1990), this scale includes a greater range of outdoor activities when compared to the original Falls Efficacy Scale. The questions aim to determine how confidently clients feel they are able to undertake each activity on a scale of 0 (not confident at all) to 10 (completely confident). This scale has excellent reliability, is correlated with measures of balance and gait and predicts future falls and decline in functional capacity Most importantly, the scale has proven sensitive to change in fears following clinical interventions (Hill *et al.*, 1996).

2.5.2 Cognitively Impaired Older Persons

A diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders-Revised IV (DSM-R IV) edition (APA, 1994). Probable or possible AD was diagnosed according to the NINCDS-ADRDA criteria (McKhann *et al.*, 1984). Mild cognitive impairment was diagnosed according to international consensus criteria (Winblad *et al.*, 2004). Diagnoses were made by team consensus (neuropsychologist and consultant geriatrician or psychiatrist) in a memory clinic following neuropsychological assessment together with relevant haematological and neuroimaging investigations. Diagnoses were reviewed and MMSE conducted at the time of recruitment to the study (Folstein *et al.*, 1975). Measures of cognitive status, functional status and dependency as well as neuropsychiatric symptoms were collected on the patients using standardized clinical measures. A full and comprehensive assessment also took place at baseline using standardized clinical

measure of costs and resource utilization specific for dementia as well as standardized quality of life measures.

2.5.2.1 Psychosocial Assessment

1. *Mini Mental State Exam – (MMSE) as a measure of cognitive function* (Folstein *et al.*, 1975)

2. *Clinical Dementia Rating Scale – (CDR) as a measure of stage of dementia* (Morris *et al.*, 1997)

Severity of illness was assessed using the Washington University Clinical Dementia Rating Scale (CDR) a well-validated, global assessment instrument that yields both global and sum of boxes (SOB) scores.(Hughes *et al.*, 1982) The CDR-SOB score is considered a more detailed quantitative general index than the global score and provides more information in patients with mild dementia. The CDR is obtained through semi structured interviews of patients and informants, on 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale, the CDR-SOB score is obtained by summing each of the domain box scores.

3. *Disability Assessment for Dementia – (DAD) as a measure of activities of daily living* (Gelinas *et al.*, 1999)

Patient function was assessed with the Disability Assessment for Dementia scale (DAD). The DAD is a well-validated, multi-item instrument that assesses 10 activities of daily living and includes 6 instrumental activities of daily living (IADLs) (telephoning, performing housework/leisure activities, preparing meals, taking

medications, going on an outing and managing finance/correspondence) and 4 basic activities of daily living (BADLs) (dressing, eating, hygiene and continence). The DAD is based on an interview with the caregiver whereby the caregiver is asked to rate the patient's actual performance on observed activities of daily living over the preceding two weeks. Higher scores reflect greater ability to give a potential maximum score of 40 points (23 for IADLs and 17 for BADLs).

4. *Neuropsychiatric Inventory – (NPI) as a measure of neuropsychiatric symptoms of dementia* (Cummings *et al.*, 1994)

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI). This is a structured interview completed with the caregiver during which the caregiver is questioned regarding the occurrence of neuropsychiatric symptoms including: delusions, hallucinations, agitation, depression, anxiety, euphoria/elation, apathy, disinhibition, irritability/lability, aberrant motor behaviour, night time behaviour and appetite change. The frequency and severity of each symptom is recorded and may be multiplied to give a possible maximum score of 12 per symptom or 144 for all symptoms combined.

5. *Dependence Scale – as a measure of patient dependency* (Stern *et al.*, 1994)

The Dependence scale is a 13 item measure which is administered to a knowledgeable caregiver and asks questions regarding varying levels of dependence from mild (e.g. "does the patient need frequent help finding misplaced objects?") to moderate (e.g. "does the patient need to be watched when awake?") and severe (e.g. "does the patient have to be fed?"). A dependence score may be derived by summing the 13 items to give a possible maximum score of 15 with greater scores indicating

more dependence. In addition a six level ranking of dependence may be determined from level 0 to 5 with level 5 indicating the greatest level of dependence.

6. *Resource Utilisation in Dementia – (RUD-Lite) as a measure of costs of dementia care* (Wimo and Winblad, 2003)

The RUD instrument was developed for cost-effectiveness studies in dementia care. It includes a subset of resources considered significant in dementia that are reflective of a multinational perspective and maintain a societal viewpoint of resulting costs. The RUD instrument has been used in several studies, both cost of illness and evaluation studies in several countries. It has proven to be a powerful and comprehensive instrument. The RUD and the shorter version the RUD-Lite assess both formal and informal resource use and are administered as an interview with the primary caregiver about the patient's living situations.

7. *Quality of Life – (DEMQoL-Proxy)* (Smith *et al.*, 2005)

Quality of life was measured using the 31-item DEMQOL-proxy which is a structured interview completed with the caregiver during which they are questioned regarding five domains of HR-QOL. These include: daily activities and looking after yourself, health and well-being, cognitive functioning, social relationships and self-concept. The DEMQOL-Proxy has been shown to be comparable to the best available proxy measure in mild, moderate and severe dementia. It has been validated in the UK in a large sample of people with dementia and their carers and demonstrates good acceptability and internal consistency.

2.5.3. Caregivers

A battery of psychosocial questionnaires were administered to assess the patient-carer dyad looking specifically at carer burden and stress, the quality of relationship between patient and carer, loneliness, social supports and the desire to institutionalise.

2.5.3.1 Psychosocial Assessment

1. *Caregiver Burden - Zarit 22 item* (Zarit *et al.*, 1980)

Caregiver burden was measured with the Zarit Burden inventory which is a 22 item self-report instrument where caregivers rate the frequency with which they experience certain stressful aspects of caregiving on a scale from 0 (never) to 4 (nearly always). Responses to the individual items are summed with higher scores indicating a higher degree of burden to give a possible maximum score of 88.

2. *Caregiver Stress - Perceived Stress Scale -10 item* (Cohen *et al.*, 1983)

The 10 item Perceived Stress Scale measures the degree to which situations in one's life are appraised as stressful. Responses are on a five-point Likert type format range from never to very often. Item responses are summed. Total scores range from 0 to 40; a high score indicates greater perceived stress. Past research has reported good reliability and construct validity for this scale (Ramírez and Hernández, 2007).

Examples of items on the PSS10 include questions asking respondents how often they felt nervous and stressed; how often they felt difficulties piling so high that they could not overcome them; and how often they felt they were on top of things.

3. *Caregiver Resilience Scale (CRS)- Shortened version* (Wilks and Croom, 2008)

The Caregiver Resilience Scale is a shortened, 15-item questionnaire containing

positive self-descriptions relating to the characteristic of psychological resilience. Responses are on a seven point Likert type format range from strongly disagree to strongly agree. Overall mean scores range from 1 to 7; a higher mean indicates greater overall perceived resilience. Past studies have reported solid reliability for this scale. Examples of items include the following: 'I usually manage one way or another'; 'I can usually look at a situation in a number of ways'; and 'My belief in myself gets me through hard times.'

4. *Eysenck Personality Inventory (EPI)* (Eysenck and Eysenck, 1964)

5. *Coping style -Brief COPE* (Carver, 1997)

The Brief COPE scale is a 28-item self-report measure of both adaptive and maladaptive coping skills. The Brief COPE scale was designed to assess a broad range of coping responses among adults for all diseases. It contains 28 items and is rated using a four-point likert scale, ranging from "I haven't been doing this at all" (score one) to "I have been doing this a lot" (score four). A higher score represents greater coping strategies used by the respondents. In total, 14 dimensions are covered by this scale. These are self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion and self-blame. This scale has established reliability and validity across numerous studies.

6. *Social network - Lubben 6-item* (Lubben and Gironda, 2004)

The Lubben Social Network Scale–6 (LSNS-6) is a six-item, self-report scale to assess social isolation in older adults (aged 65 years old and above) by measuring

perceived social support received by family and friends. The LSNS takes about 5–10 minutes to complete and assesses the size, closeness, and frequency of contacts of a respondent's social network (including both kin/family and non-related individuals). The LSNS has been used in both practice and research settings and has been used primarily with older adults from a range of settings including the community, hospitals, adult day care centres, assisted living facilities and doctors' offices. The scale has also been used with specific elderly populations such as elderly diagnosed with breast cancer, myocardial infarctions and depressed elderly

7. *De Jong Loneliness Scale* (de Jong-Gierveld and van Tilburg, 2008)

The De Jong Gierveld Loneliness Scale can be used as either a one-dimensional loneliness scale, or to distinguish between social and emotional loneliness. The loneliness subscales for emotional and social loneliness have proved to be valid and reliable measurement instruments for these phenomena. For use in large surveys a shorter 6-item version of the De Jong Gierveld scale was constructed in such a way that the threefold application of the original scale (an overall loneliness scale as well as emotional and social subscales) was still guaranteed.

8. *Relationship with relative and preparedness for caregiving - Mutuality scale from the Family Care Inventory* (Schumacher *et al.*, 2007)

The Family Caregiving Inventory is composed of two structured interview instruments-one for the caregiver and one for the care receiver. Interviews with the caregiver and care receiver require approximately 2 hours and 1 hour, respectively, to complete. Measures of seven predictor variables (mutuality as perceived by the caregiver, preparedness for caregiving, gender of the caregiver, being a spouse

versus non-spouse caregiver, degree of cognitive and physical impairment of the care receiver, amount of direct care) and nine measures of caregiver role strain are included in the inventory. For the purposes of this study we completed both the mutuality and preparedness scale only.

9. *Positive Caregiving Beliefs –PAC Scale* (Tarlow *et al.*, 2004)

The nine-item Positive Aspects of Caregiving Scale presents statements about a caregiver's mental or affective state in the context of the caregiving experience. Responses are provided on a 5-point *agree/disagree* scale and are designed to assess the perception of benefits within the caregiving context, such as feeling useful, feeling appreciated, and finding meaning. Higher scores represent more positive appraisals. The PAC scale represents a unique construct distinguishable from well-being, negative affect, and social support.

10. *The Desire to Institutionalise Scale - DIS* (Morycz, 1985)

The DIS is a seven-item self-report inventory that quantifies stages in considering nursing home placement, ranging from discussion with family or friends about care recipient placement to actually applying for placement. An overall desire to institutionalize score can be calculated based on caregiver responses (e.g., a caregiver who has never discussed or obtained information about care recipient placement would yield a score of 0; one who has completed a nursing home application might obtain the highest score of 7).

2.6 Ethical Concerns

Local ethics approval was obtained for all parts of this study.

TRIL Clinic:

(SJH/ AMNCH Research Ethics Committee approval reference number 2007/06/13)

ECAD Study:

(SJH/ AMNCH Research Ethics Committee approval reference number 2008/08/09)

2.6.1 Capacity

Capacity was assessed for all participants and informed written consent to partake was obtained from all subjects. In circumstances where a participant lacked capacity to give consent secondary to their dementia diagnosis or cognitive impairment this was discussed with a family member who had capacity to consent by proxy for the individual. Verbal assent was obtained in all cases. Participants were informed that they may withdraw consent at any time and that refusal to participate did not effect any existing treatment.

2.6.2 Good Clinical Practice

All researchers involved in the programme engaged with the Irish Clinical Research Network (ICRIN) and were instructed and trained in Good Clinical Practice and good research practice to encompass the Declaration of Helsinki and Investigator Responsibilities. Researchers underwent training in the administration and scoring of all standardised instruments outlined in the methods section.

2.7 Sample Size

Studies on frailty have shown that over the age of 65 prevelance of frailty ranges from 7% to 40% (Fried *et al.*, 2001). For the purposes of this study we wished to calculate the sample size needed to be 95% sure that at least 20 research participants in each

group (patients, community dwelling elderly and caregivers) would be classified fully frail. With a mean prevalence of 23.5% and 20 as the minimum number of frail patients required then with a confidence interval of 95% an estimated appropriate sample size would be 115 participants. Given our plan was to investigate the presence of both frail and pre-frail criterion in our cohort of patient it is anticipated that a minimum of 100 patients would need to be assessed in each of our three groups, community-dwelling elderly, cognitively impaired patients and caregivers to enable us to detect varying levels of frailty in all groups.

2.8 Statistical Analysis

The collected data were analysed using the SPSS 16.0 statistical package program. Frailty was included in all analysis as an ordinal variable with six categories from 0 to 5 unless otherwise stated. Correlation or bivariate analysis for parametric data was performed using Pearson's correlation coefficient and for non-parametric data using the Spearman correlation coefficient. Chi square-tests; fisher's exact test and linear by linear association test were used for comparing categorical variables. The difference between variable means was compared using student t test, one-way analysis of variance (ANOVA) and three-way factorial ANOVA as appropriate.

Linear relationships for continuous outcome variables were explored with sequential or hierarchical multiple regression models, where the order of entering explanatory variables was determined by the strength of the bivariate correlation with the outcome variable. When each new variable was entered, the variance contributed by the variable, possible collinearity with other variables and the influence of the variable on the model were assessed. Odds ratio was used to describe the magnitude of

associations between categorical variables. Logistic regression was then used to calculate the effect of identified risk factors as independent odds ratios with the effects of other confounders removed. The same sequential method described for multiple linear regression was used for logistic regression, with variables being added to a model one at a time in order of the magnitude of the chi-square association, starting with the largest estimate. At each step changes to the model were examined to assess for collinearity and instability.

For testing mediation the Baron and Kenny (1986) method was conducted through a series of regressions and statistical significance of the mediation was computed using the Sobel (1982) test which can be interpreted as an index of the strength of the mediation. The critical value for significance in all analyses was $p<0.05$. The majority of data was collected using face to face interview which meant that the number of missing values throughout the data set was small (<5%) and any missing values which did occur were randomly scattered throughout the data set. For this reason the default option of the statistical package used to analyse the data was applied, which meant that in specific analyses, cases with missing values were omitted. The main effect of this process would be to reduce statistical power. Therefore in any analysis where there was missing data omitted, a post –hoc power analysis was completed and is shown in the results section of the data chapters.

Chapter 3

The Psychological Consequences of Frailty

3.1 Introduction

Mental health in the elderly is gaining increased momentum owing to the ageing of populations and the increasing demographic importance of elderly people. Approximately one in four patients treated in the community have severe emotional problems, predominantly anxiety and/or depression (Ansseau, 2004). These are treatable conditions but are often under detected or under treated despite their adverse consequences (Olafsdottir *et al.*, 2001; Volkers *et al.*, 2004). A cost-effective way to improve detection of mental health problems is to pay special attention to and facilitate early identification of elderly at risk of mental health deterioration (Smit *et al.*, 2007; Smit *et al.*, 2006). Knowledge of the factors associated with emotional disturbance may help us to focus on the persons at risk and also create intervention programmes. Well established risk factors for depression and anxiety include female gender, somatic illness, cognitive impairment, functional impairment, lack or loss of close social contacts, and a history of depression (Vink, 2008). A number of studies have also identified links between chronic diseases, the medically unwell and mental disorders (Jones *et al.*, 2004). Awareness of health-related variables that may be associated with increased risk of anxiety or depression improves our ability to target vulnerable groups with preventative strategies and early treatment to minimize the risk of burgeoning mental health difficulties. Frailty may represent an important physical health-related variable that to date has not been fully evaluated in relation to psychological wellbeing or mental health.

3.1.1 Frailty, Disability and Co-morbidity

A remarkable finding in frailty is that not all frail elderly experience the same symptoms and that frailty can be present in the absence of specific diseases, but more likely in combination with or as a consequence of co-morbidity (Fried *et al.*, 2004; Fulop *et al.*, 2010).This means that frailty is not identical to co-morbidity. Disability represents one of the main consequences of frailty; however frail elderly with the same number of co-morbidities can suffer from very different levels of disability (Fried *et al.*, 2004). The reason for this is that disability is also influenced by factors other than biological or physiological factors, for example personal characteristics including psychological state, emotional state and coping style. There is also an interaction with the physical and social environment, which can stimulate or hinder participation in activities. Therefore, in the last few years, frailty is acknowledged to be not only a biological or physiological state, but also a multidimensional concept (Walston *et al.*, 2006).Frailty research has thusfar focused primarily on its association with medical factors and social and psychological aspects have been somewhat neglected (Hogan, 2003). Within the literature there is reference to the 'well-established' relationship between frailty and psychological factors (de Vries *et al.*, 2011), however studies focusing primarily on the relationship between frailty and mental health are in fact lacking.

3.1.2 Measuring Frailty

A recent systematic review identified 20 frailty instruments within the current literature that have been devised to measure frailty within a broad context given the lack of agreement about a definition of frailty and the current disparity in perspectives about how best to conceptualize it. These instruments include self-report

questionnaires, interviews, performance tests or a combination of all. The instruments differ substantially in the way they operationalize frailty factors. Despite the heterogeneity of the instruments what is most surprising is that only five pay attention to factors from within the psychological and social domains of health. Those instruments that do include some reference to or measurement of psychological and/or social health, are generally instruments that approach the assessment of frailty as an age-associated accumulation of deficits (Mitnitski *et al.*, 2001). They give an estimate of frailty through a procedure of counting deficits across a whole range of health problems, which come in many forms, symptoms, signs, laboratory abnormalities, diseases and disabilities (Searle *et al.*, 2008). The higher the deficit count, the frailer the individual and the higher likelihood of adverse health outcomes.

The psychological factors included in these frailty indexes for the most part assess depression and presence of depressive symptoms, only two instruments include any reference to anxiety, assessing it as presence of anxiety or 'nervousness' without any direct measure of the extent of anxious symptomatology (Schuurmans *et al.*, 2004; Studenski *et al.*, 2004) In fact very little is available in the current literature evaluating frailty and anxiety in older adults. Only one study has quantified health anxiety specifically and its association with frailty in a small sample of community-dwelling elders, with a call for further studies investigating the association between frailty and more generalized anxiety in older populations (Bourgault-Fagnou and Hadjistavropoulos, 2009). A further study identified a higher risk of odds for psychiatric illness, chiefly self-reported depression with each additional deficit-defining frailty, again using a measure of frailty that represented the accumulation of

multiple, interacting illnesses, impairments and disabilities (Andrew and Rockwood, 2007).

Within the literature however, there is an increasing focus on the phenotypic definition of frailty as measured by the biological syndrome described by Fried. As described previously there is increasing consensus that this frailty phenotype is a definable clinical state that exhibits associations consistent with a syndromal presentation (Bandeen-Roche *et al.*, 2006; Buchner *et al.*, 1996; Evans, 1995; Fleg and Lakatta, 1988; Leibel, 1995; Morley, 1997; Tseng *et al.*, 1995). This 5-item phenotype is then particularly appealing for use in a clinical setting as it provides us with an easily applied theoretical framework that facilitates the investigation of mechanisms underlying the development of frailty. This is an easier process to identify frailty when compared to the application of the all encompassing frailty indices that can contain upward of 30 – 70 items (Rockwood *et al.*, 2005).

The use of this frailty phenotype to assess and measure frailty provides us with evidence of frailty as a medical syndrome. A medical syndrome is defined as "a group of signs and symptoms that occur together and characterize a particular abnormality." This allows us to characterize frailty in individual older adults in a way that supports early assessment and screening for the syndrome. Therefore this phenotypic approach to frailty as measured using the biological syndrome is the most widely studied approach in a variety of settings. It seems necessary then as frailty research progresses to better understand the strength of association between emotional health disturbance and phenotypic frailty as measured by the biological syndrome.

3.1.3 Frailty, Depression, Anxiety and Loneliness

To date the biological syndrome of frailty has been associated with increased depressive symptomatology in those not using antidepressant medications (Fried *et al.*, 2001). However no further studies have specifically evaluated the association between depression and the frailty syndrome controlling for other known psychosocial risk factors such as loneliness, adverse life events, functional limitations and comorbid somatic illnesses. More surprisingly, to date, to the best of our knowledge no studies have specifically investigated the association between generalized anxiety in older adults and the frailty phenotype in any capacity. Clarifying any association between the frailty phenotype and elderly who are emotionally vulnerable is worthwhile not least due to the known adverse health outcomes linked to both. Understanding the points of onset of frailty and/or emotional disturbance is vital for early identification of at-risk individuals and intervention on those components that are first affected, when reversal may be possible. An important factor to consider is the potential reversibility of frailty at an early stage (Strawbridge *et al.*, 1998). If its association with deteriorating mental health persists even in presence of other known risk factors for emotional disturbance then it may represent a key target for intervention that we are under utilizing.

However it is not just anxiety and depression that may have important links to frailty in old age. Social and environmental factors that represent key influences on psychological health may also play a role in the emergence of frailty in our older populations. It is known that environmental factors do influence the decline of wellbeing and frailty (Golden *et al.*, 2009). Loneliness is the subjective experience of isolation. Loneliness can independently affect mood and wellbeing in the elderly,

underlying a very significant proportion of depressed mood (Stek *et al.*, 2005). As well as the more apparent connection between loneliness and psychological and psychiatric morbidity, loneliness has also shown to be a risk factor for deteriorating physical health (Lubben and Gironda, 2003). Poor social support networks have been found to significantly influence both mental and physical health in the elderly (de Jong-Gierveld, 1987). Loneliness is a pervasive issue among older adults who often face a loss of committed intimate relationships (Rockwood *et al.*, 2004). Emerging frailty may play an important role in compounding the effect of social isolation and loneliness further contributing to psychological health decline and increased vulnerability. In fact social isolation has been already been associated with incident frailty in community dwelling elders (Fried *et al.*, 2001).

3.2 Summary of Aims

Primary aims of this study were to (i) characterize the frailty phenotype in a group of community dwelling elderly and to evaluate the relationship if any, between frailty and emotional disturbance as reflected by quantified depression and anxiety symptoms within the group, (ii) to investigate the strength of any association identified between frailty and emotional disturbance in the presence of other well-established risk factors for anxiety and depression in an older population, and (iii) to evaluate the relationship between established frailty, loneliness and social isolation in old age.

3.3 Results

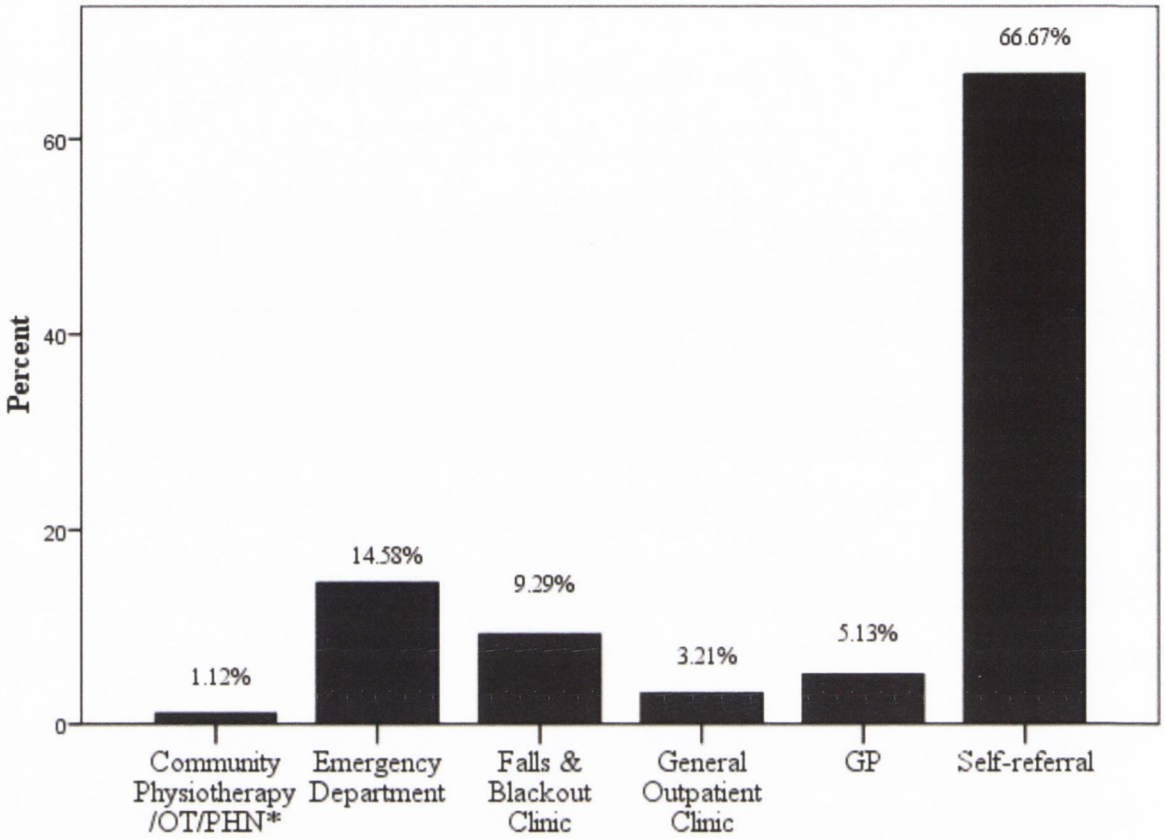
3.3.1 Population Demographics and Characteristics

A convenient sample of 624 community dwelling older people was recruited and all participants received a comprehensive geriatric assessment to include frailty and a psychosocial assessment through the TRIL (Technology Research for Independent Living) Clinic. The referral sources for recruitment are depicted in Figure 3.1, a large proportion of the study participants were self-referrals. Figure 3.2 shows the mean age of the cohort which was 73.1 years (Standard deviation 7.48). Figure 3.3 depicts the breakdown of men and women that participated in the study with almost two thirds being female. Almost half of our participants had a partner with whom they lived, just over 29% were widowed and almost 5% were separated or divorced. (Figure 3.4) This translated to over one third of participants living alone. (Figure 3.5) The majority of our study participants lived within an urban setting and were retired. (Figure 3.6 & 3.7) Our sample included a range of socioeconomic groups as per the census classification. (Figure 3.8)

3.3.2 Characterization of the Frailty Syndrome

Frailty was measured using the Biological Syndrome Model which was originally described by Fried using five frailty criteria (Cigolle *et al.*, 2009). Our only adaptation to these criteria being the definition of weight loss which was assessed objectively as BMI of less than 18.5 kg/m^2, rather than a subjective report of weight loss of more than 10 pounds. This was reflective of similar adaptations for the weight loss criterion from other large population based studies validating the biological syndrome model of frailty (Radloff, 1977). Exhaustion was determined by two questions from the Center for Epidemiologic Studies Depression Scale (CES-D), " I felt that everything I did

Figure 3.1: Referral Sources of Participants



* OT = Occupational Therapy, PHN = Public Health Nurse

Figure 3.2: Histogram of Age Distribution in Participant Cohort

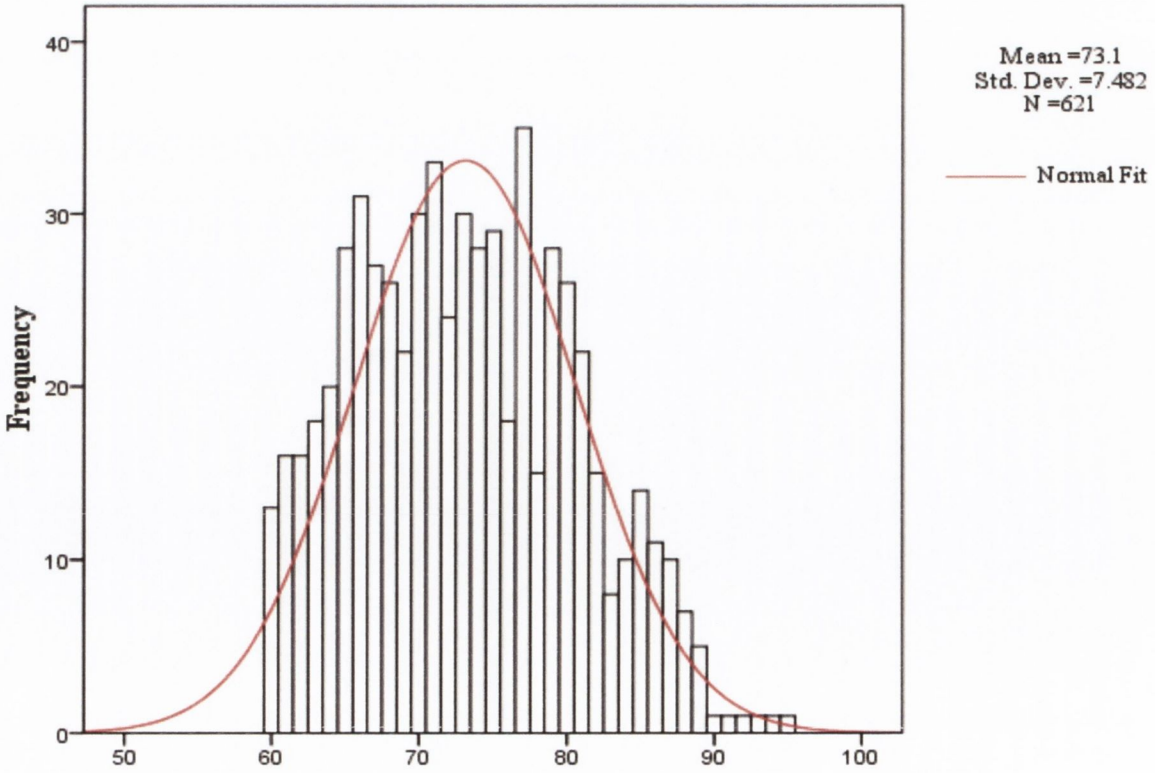


Figure 3.3: Pie Chart of Sex Distribution in Participant Cohort

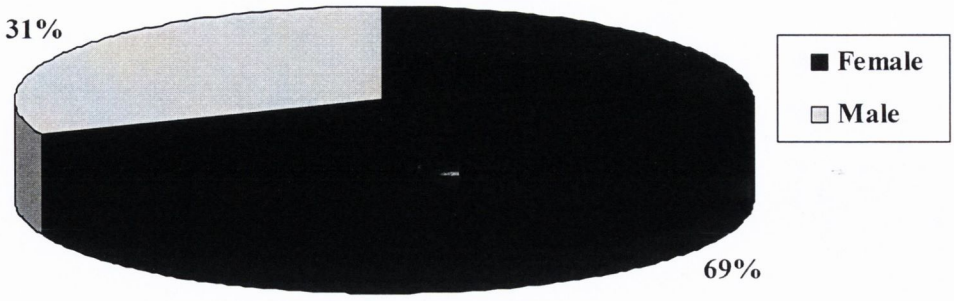


Figure 3.4: Marital Status of Cohort

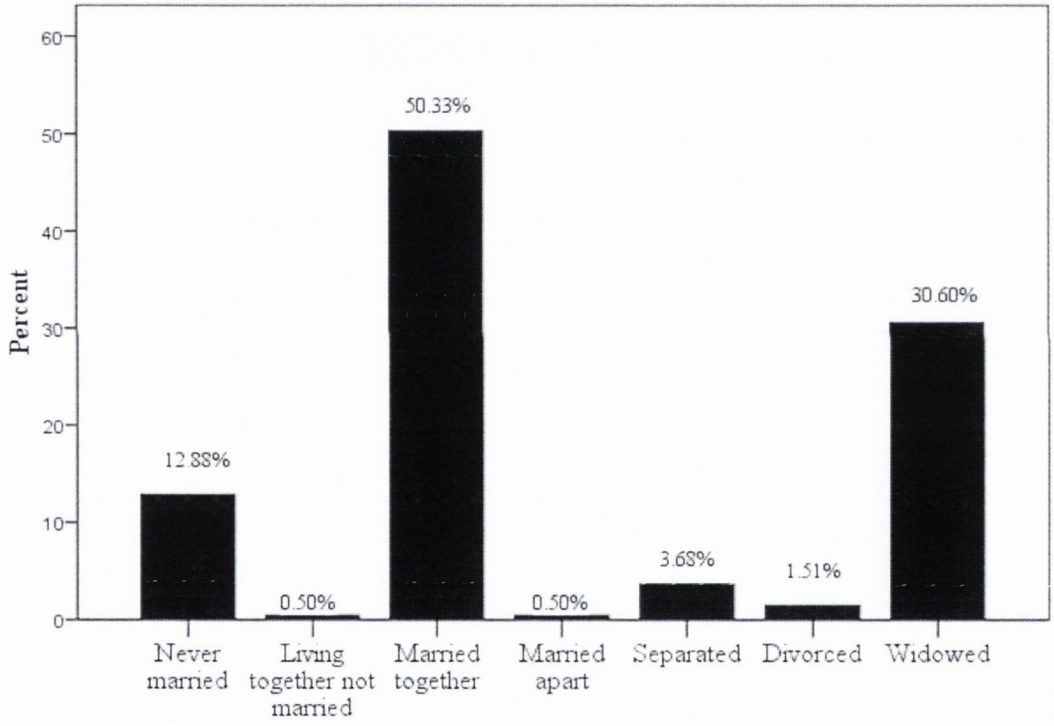


Figure 3.5: Living Status of Participant Cohort

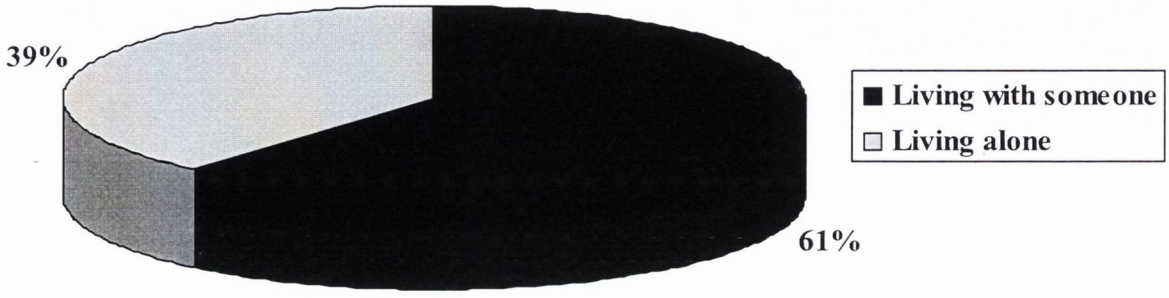


Figure 3.6: Residential area of Participant Cohort

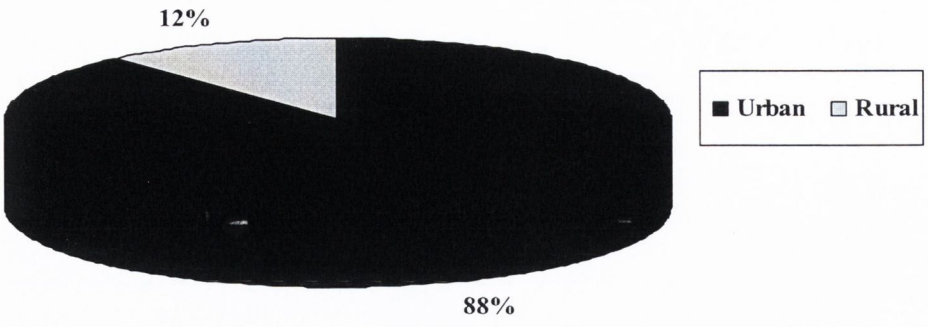


Figure 3.7: Work Status of Participant Cohort

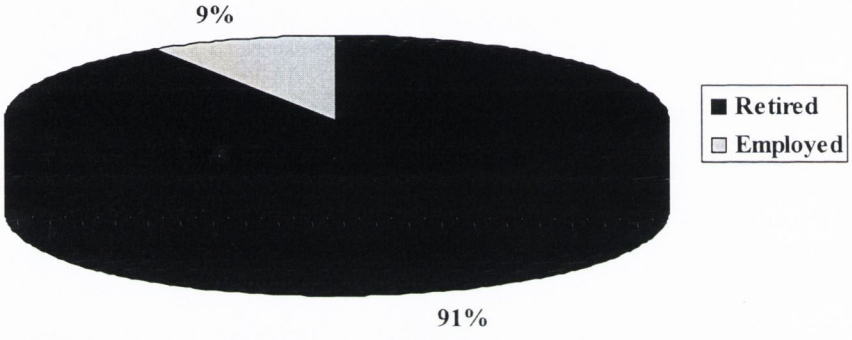
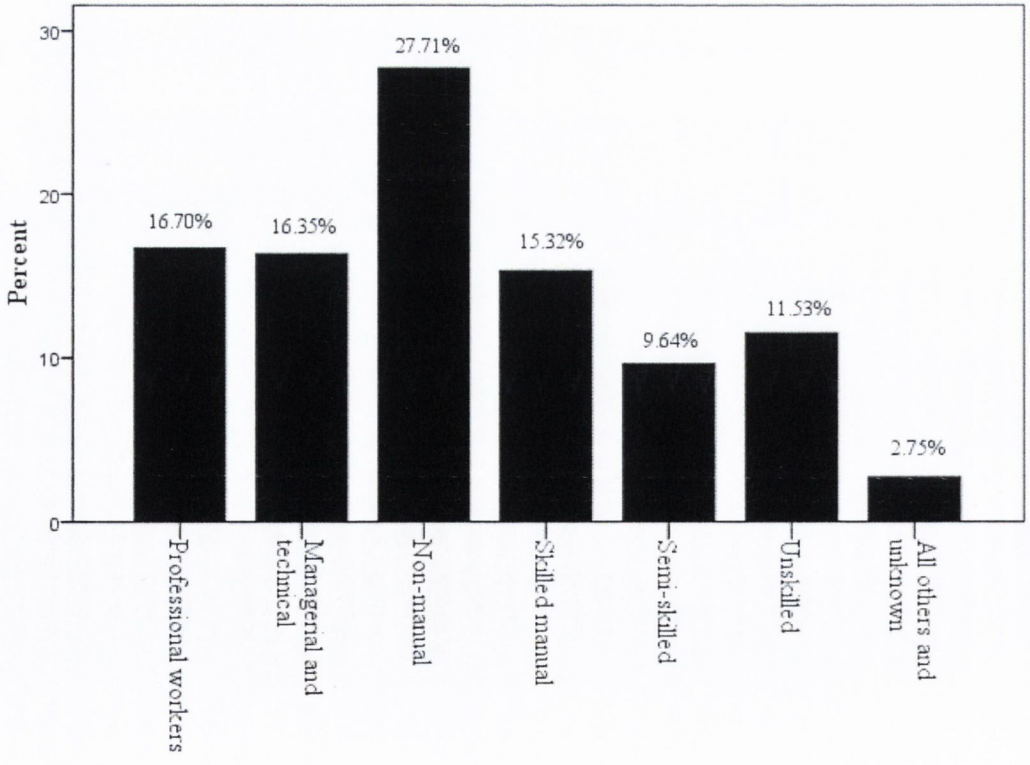


Figure 3.8: Social Class (Census Classification) of Participants



was an effort", "I could not get going"(Fried *et al.*, 2001). Slowness was defined in terms of usual pace walking speed and weakness was assessed using grip strength, both dependent on gender, BMI and using the cut points as per the Cardiovascular Health Study (Taylor *et al.*, 1978). Low activity was defined by kilocalories expended per week, dependent on responses to selected items from the Minnesota Leisure Time Activity Questionnaire (Fried *et al.*, 2001). Frailty scores ranged from 0 indicating robust with no frailty criteria present to 5 representing complete frailty. Categorization of these scores determines those with 0-1 criterion present as non-frail and those with 2 frailty criteria to be intermediately or pre-frail and those with 3 or more criteria to be fully frail (Folstein, 1975). Exclusion criteria for the analysis of frailty and emotional disturbance were a diagnosis of Parkinson's disease, dementia and/or a history of previous stroke.

568 participants were suitable for the characterization of frailty and analysis of emotional disturbance as 57 fulfilled exclusion criteria. On application of the Fried frailty criteria 283 (49.8%) could be classified as robust or non-frail, 247 (43.5%) as being pre-frail and 38 (6.7%) as completely frail (Figure 3.9). There was a trend towards significance in frailty dependent on female gender (χ^2, $p = .052$). Figure 3.10 depicts a means plot showing that there was a significant difference in mean age between the groups with the frailer groups being older (One-way ANOVA, $p < .001$). Figure 3.11 also shows there was a higher burden of co-morbidity within the frailer groups as measured by the AACI (One-way ANOVA, $p < .001$).

Figure 3.9: Characterization of Frailty in the Cohort

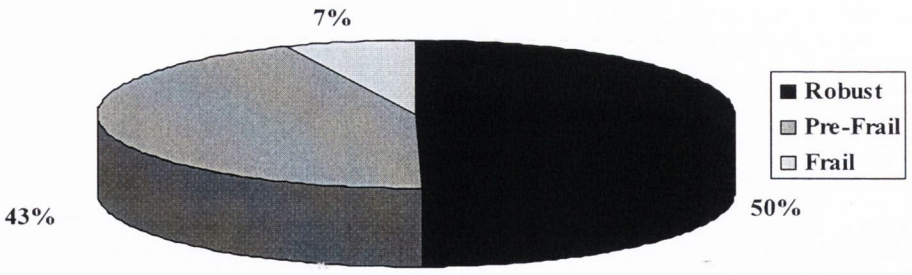


Figure 3.10: Means Plot showing Age between Frailty Groups

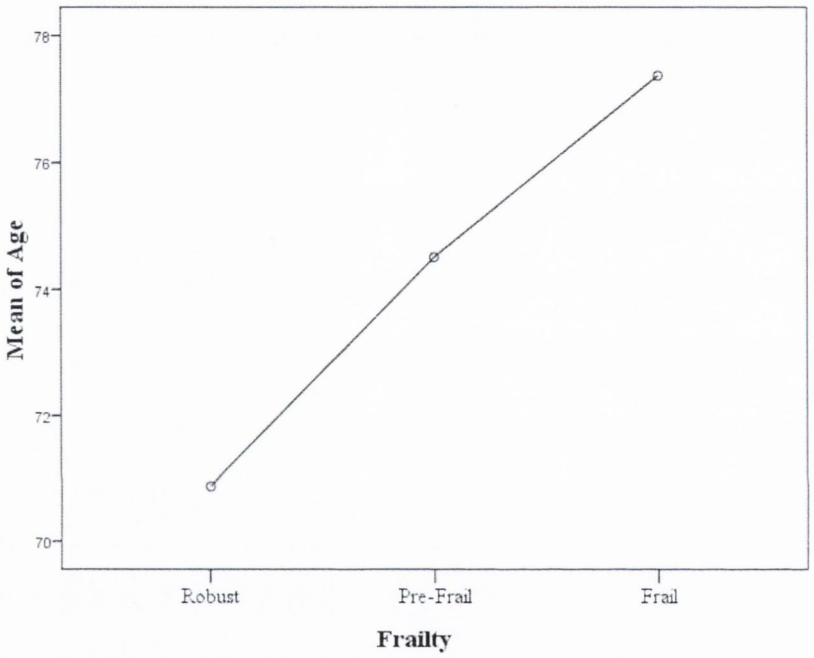


Figure 3.11: Means Plot showing Co-morbidity Scores between Frailty Groups



3.3.3 The Relationship between Frailty and Depression

Given that subjective exhaustion is measured as a frailty criterion using the same CES-D scale we utilized to assess depression it was felt to be a potential confounder in our analysis of the relationship between depression and frailty. We therefore used a modified frailty index when investigating any association between frailty and depressive symptoms using the CESD-8. This modified frailty index omitted the "exhaustion" criterion for frailty and consisted solely of the four other frailty criteria, cut-offs for determining pre-frailty and frailty remained the same. The effect of utilizing a modified version of the frailty index to exclude exhaustion would have only been to underestimate the extent of frailty within the group. We were able to maintain the cut-offs for determining pre-frailty and frailty as it is merely the cumulative presence of two or more of any of the frailty criteria that determine the pre-frail or frail syndrome.

Using the modified frailty index where the criteria of exhaustion was excluded to facilitate analysis of the CESD, 309 (49.5%) were classified as robust, 289 (46.3% were classified as pre-frail and 26 (4.2%) were completely frail (Figure 3.12). There was no significant difference in gender across the modified frailty groups ((χ^2, $p = .574$). The significant difference in mean age between groups with the frailer groups being older was maintained (One-way ANOVA, $p < .001$), as was the higher burden of co-morbidity within the frailer groups (One-way ANOVA, $p < .001$). The mean CESD-8 scores reflective of depressive symptoms experienced by the participants were significantly higher in both pre-frail and frail participants when compared to robust (Figure 3.13: One-way ANOVA $p < .001$) Using the already established cut-off for the CESD-8 of a score of 4 or more, pre-frail and frail subjects were more

likely to have case-level depression when compared to those who were robust or not-frail (Figure 3.14, χ^2: Linear-by-linear association test, $p < .001$)

To ascertain if frailty was independently associated with anxiety or depression scores, we conducted linear regression analysis to include known risk factors of anxiety and depression in the elderly. Hierarchical linear regression models were constructed to include frailty and adjust for potential confounding factors in the analysis. The independent variables entered into the regression models were based on known predictors of anxiety and depression in an older population. We included, age, gender and cognition as measured by the MMSE.(Baron and Kenny, 1986) To include an objective measure of history of depression and/or anxiety we examined the prevalence of psychotropic medication use. Any patient currently prescribed an antidepressant regardless of class was grouped as having a history of depressive or anxiety disorder. We also included measures of functioning, adverse life events and subjective loneliness as well as a measure of current co-morbid illness. We set the critical value for significance in all analysis at $p<0.05$. In an optimal predictor model, increasing frailty retained a significant association with higher depression scores along with loneliness and adverse life events (Table 3.1).

3.3.4 The Relationship between Frailty and Anxiety

The mean total HADS-A score reflective of anxiety symptoms within the participant cohort were significantly higher in both pre-frail and frail participants when compared to robust (Figure 3.15: One-way ANOVA $p < .001$).We used the established cut-off points for the HADS-A to identify borderline case-level anxiety and probable case-level anxiety. Both pre-frail and frail elders were more likely to have both borderline

Figure 3.12: Characterization of Frailty (Exhaustion excluded) in the Cohort

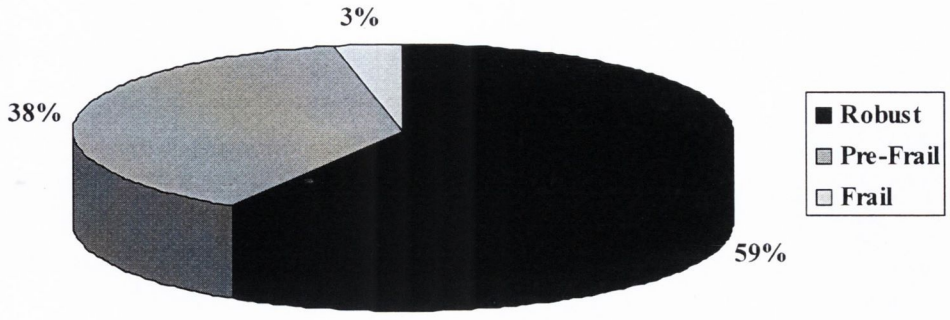


Figure 3.13: Means Plot showing Depression Scores across Frailty groups

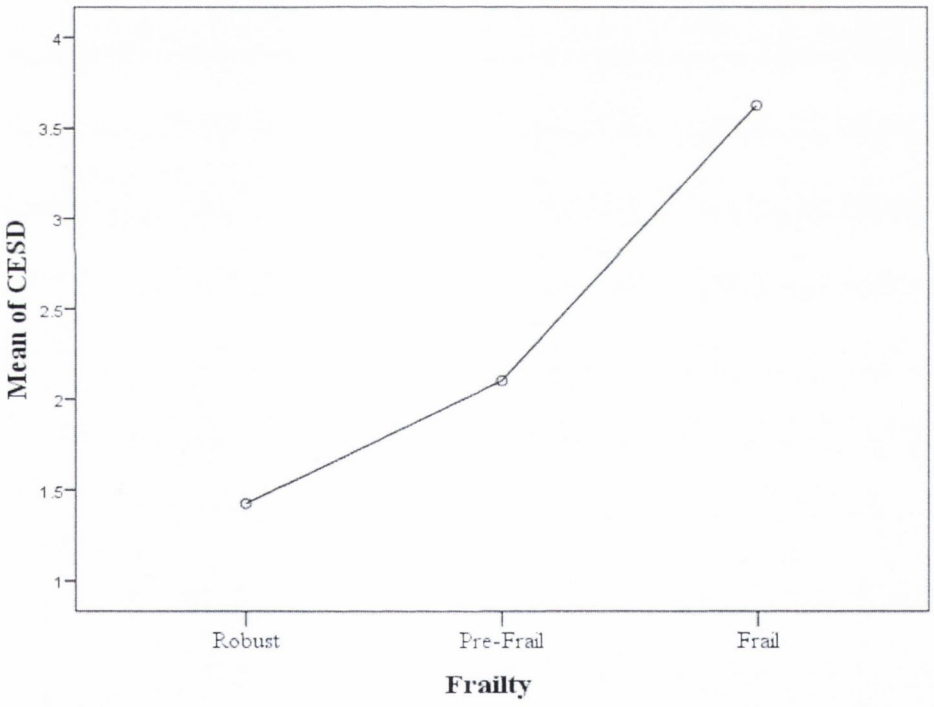


Figure 3.14: Probable Case-Level Depression according to Frailty Group

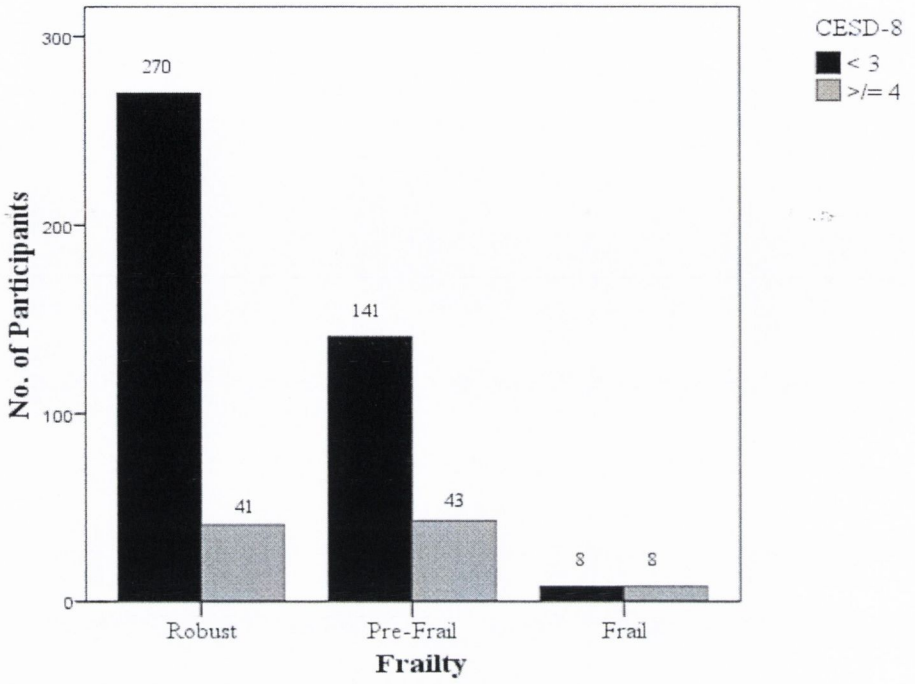


Table 3.1: Regression Model of Risk Factors for Depression including Frailty

	Beta	+/-SE	Significance
CESD Depression Score *(R^2=.238)*			
Age	.004	.013	p = .789
Gender	.137	.165	p = .409
MMSE[a]	-.016	.037	p = .655
Loneliness [b]	**.477**	**.065**	**p < .001***
Frailty	**.278**	**.106**	**p = .009***
Antidepressant Use	.267	.244	p = .274
Independence in ADLs [c]	-.040	.036	p = .268
No. of adverse life events [d]	**.161**	**.050**	**p = .001***
Co-morbidities [e]	.062	.032	p = .052

* Statistically significant p < .001
[a] Cognition as measured by the Mini Mental State Examination
[b] de Jong Loneliness Scale
[c] Lawton Instrumental Activities Scale
[d] Geriatric Adverse Life Events Scale
[e] Age-Adjusted Charleson Comorbidity Index

and case-level anxiety when compared to their more robust counterparts (Figure 3.16 χ^2: Linear-by-linear association test, $p < .014$, Figure 3.17 χ^2: Linear-by-linear association test, $p < .014$ respectively). To ascertain if frailty was independently associated with anxiety controlling for other known risk factors for emotional disturbance, we conducted hierarchical linear regression analysis to include the same risk factors for anxiety and depression in the elderly as described in the previous section. Frailty, loneliness and a history of depressive or anxiety disorder requiring pharmacotherapy retained their association with higher HADS-A scores reflective of increased anxiety in the optimal predictive model (Table 3.2).

3.3.5 The Relationship between Frailty, Loneliness and Social Isolation

In this study we also attempted to evaluate the relationship between frailty, subjective loneliness and social isolation. Loneliness was measured using the de Jong Gierveld short-item loneliness scale which captures two subjective aspects of loneliness, both social loneliness and emotional loneliness. Social isolation is an objective measure of poor social integration without subjective appraisal. We assessed social integration using the Lubben Social Network Scale Expanded -18 items (LSNS-18). This scale measures the level of perceived support received from family, friends and neighbours and was specifically designed for use in older persons. Lower scores indicate increasing social isolation.

The mean loneliness score, with higher scores reflective of increased total loneliness were significantly higher in both pre-frail and frail groups (Figure 3.18: One-way ANOVA $p = .002$) When this was broken down into the component parts of social and emotional loneliness, only emotionally loneliness was significantly different with

Figure 3.15 Means plot showing Anxiety Scores across Frailty Groups

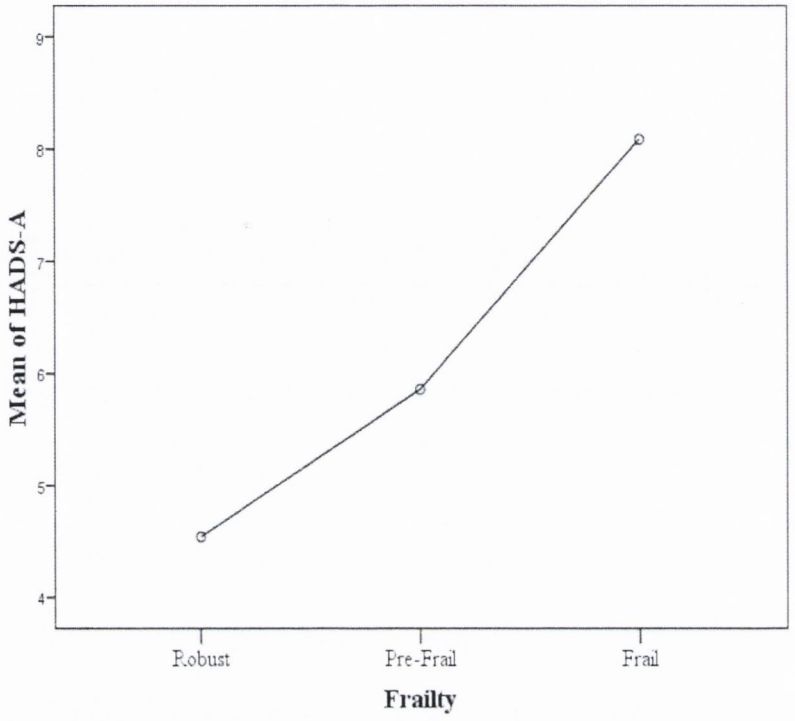


Figure 3.16 Borderline Case-Level Anxiety according to Frailty Group

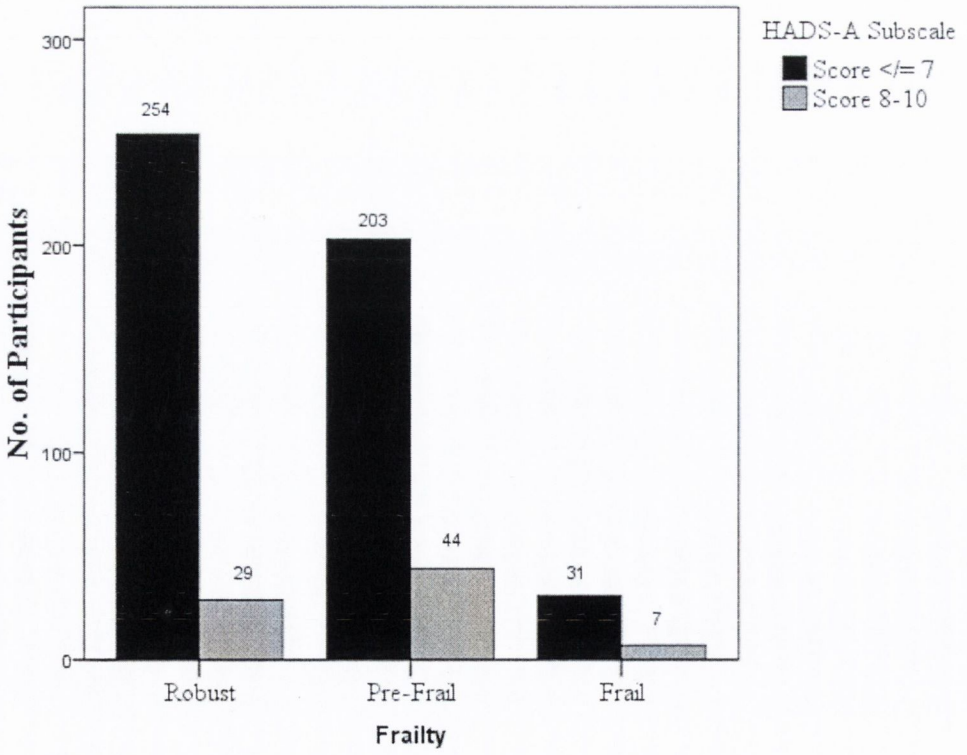


Figure 3.17 Borderline Case-Level Anxiety according to Frailty Group

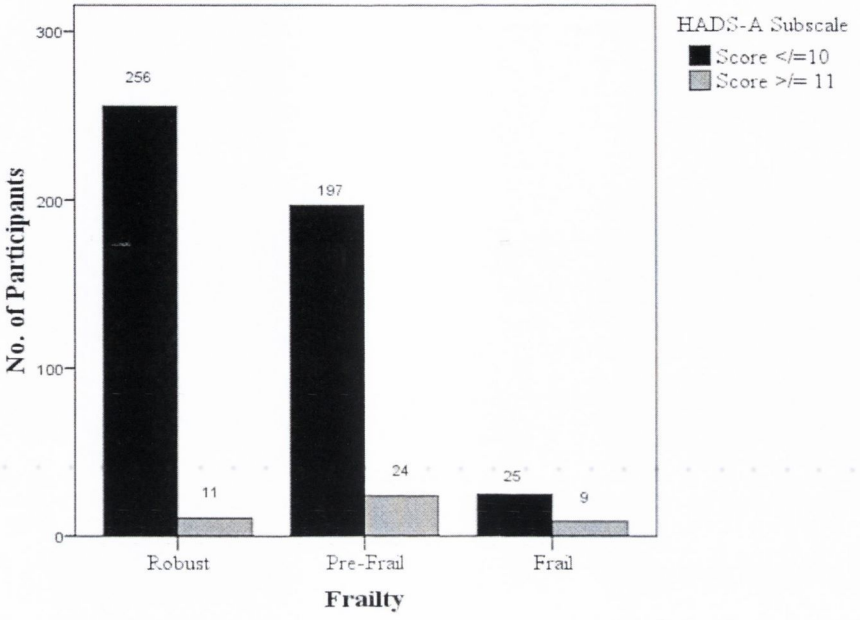


Table 3.2 Regression Model of Risk Factors for Anxiety including Frailty

	Beta	+/-SE	Significance
HADS Anxiety Score *(R^2 =.230)*			
Age	-.040	.024	p = .099
Gender	.186	.299	p = .585
MMSE[a]	-.074	.067	p = .267
Loneliness [b]	**.905**	**.098**	**p < .001***
Frailty	**.774**	**.160**	**p < .001***
Antidepressant Use	**1.32**	**.437**	**p = .003***
Independence in ADLs [c]	.085	.065	p = .191
No. of adverse life events [d]	.101	.089	p = .25
Co-morbidities [e]	.019	.057	p = .741

* Statistically significant p < .05
[a] Cognition as measured by the Mini Mental State Examination
[b] de Jong Loneliness Scale
[c] Lawton Instrumental Activities Scale
[d] Geriatric Adverse Life Events Scale
[e] Age-Adjusted Charleson Comorbidity Index

higher scores across frailty groups (One-way ANOVA, $p < .001$). Social loneliness scores were not significantly different across the three groups (One-way ANOVA, $p < .372$). Mean LSNS-18 scores were significantly lower across both pre-frail and frail groups however, with lower scores reflective of increasing social isolation (Figure 3.19: One-way ANOVA $p < .001$).

3.3.6 Supplementary Mediation Analysis: The Influence of Anxiety on the Relationship between Frailty, Social Isolation and Loneliness.

We have identified a relationship between frailty, social isolation and loneliness. Our previous findings indicate a close association between anxiety and depression and frailty. The relationship between depression, loneliness and social isolation has already been well-established in the literature. The cumulative effect of frailty and depression would of course influence emerging loneliness and loss of social networks given the already known influence of depression on these factors. Our results suggest however that anxiety is also an important variable closely associated with the biological syndrome of frailty. We were interested in establishing whether anxious symptoms had any influence on the relationship between frailty and loneliness and social isolation. If so anxiety may represent an important target in any interventions to address loneliness and isolation in frail older adults.

We were interested in examining whether anxiety would mediate the already established relationship between frailty and both loneliness and social isolation. That is, might frailty be related to loneliness and social isolation because it is related to anxiety which is also related to loneliness and social isolation? Following the recommendations of Baron and Kenny (1986) for testing mediation, this analysis was

Figure 3.18 Means Plot showing Loneliness Scores across Frailty Groups

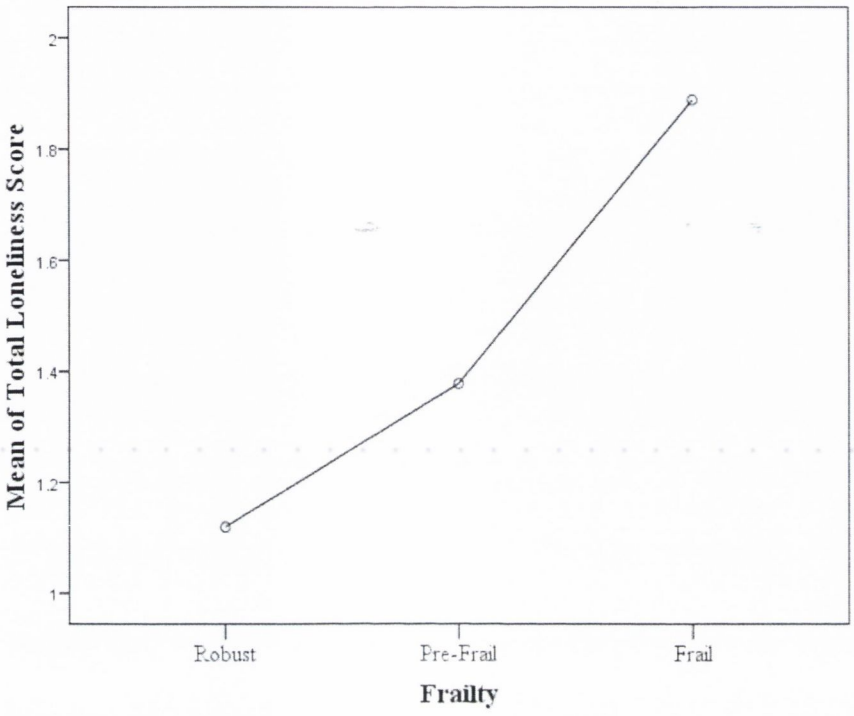
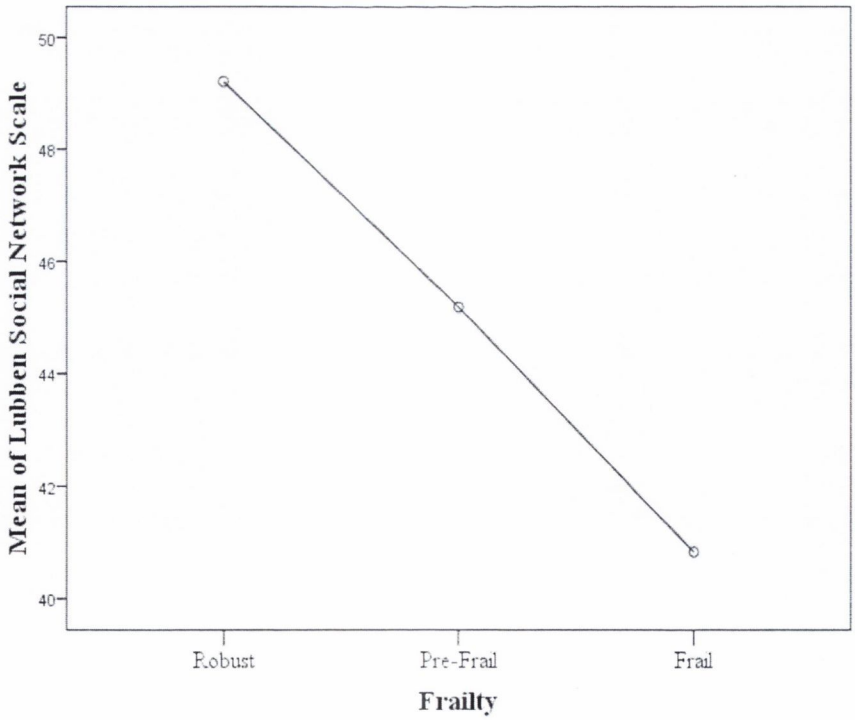


Figure 3.19 Means Plot showing Social Network Scores across Frailty Groups



conducted through a series of regressions (Sobel, 1982). First, the dependent variable (i.e. loneliness/social isolation) was regressed on the independent variable (i.e. frailty); second, the mediator (i.e. anxiety) was regressed on the independent variable (i.e. frailty); third, the dependent variable (i.e. loneliness/social isolation) were each simultaneously regressed on both the independent variable (i.e. frailty) and on the mediator (i.e., anxiety); and fourth, the results of the last regression equation (step 3) were examined. Mediation is indicated when, in step 3, a previously significant relationship between the dependent (i.e. frailty) and independent variable (i.e. loneliness/social isolation) decreases. Perfect mediation holds if, on step 3, the relationship between the dependent variable (i.e. loneliness/social isolation) and the independent variable (i.e. frailty) becomes zero, suggesting that the independent variable (i.e. frailty) only impacts the dependent variable (i.e. loneliness/social isolation) through its effects on the mediator variable (i.e. anxiety). In contrast, partial mediation is indicated on step 3 by a significant decrease in the effect of the independent variable on the dependent variable. The statistical significance of the mediation can be computed using the Sobel (1982) test to assess the indirect effect of the independent variable (i.e. frailty) on the dependent variable (i.e. loneliness/social isolation) through the mediator variable (i.e. anxiety) (Andrew and Rockwood, 2007). Sobel's test can be interpreted as an index of the strength of the mediation. The results of the mediation analysis appear in Tables 3.3 & 3.4. Examination of the mediation effects revealed that anxiety fully mediated the relationship between frailty and both loneliness and social isolation. That is, the direct effect of frailty on either loneliness or social isolation, while controlling for the effect of anxiety, was no longer significant. This was corroborated by the significant mediation effect as measured by the Sobel test ($p < .001$).

Table 3.3 Summary of regression results: Testing the Mediating Effects of Anxiety on the Relationship between Frailty and Social Isolation

Equation	β	SEβ	t	p	R2	Significance of mediation (sobel test)
1. Frailty → Social Isolation	-0.130	2.176	-3.01	0.003*	0.017	
2. Anxiety → Frailty	0.203	0.662	4.74	0.000**	0.041	
3. Frailty and Anxiety → Social Isolation						
						z = 2.83*
Social Isolation						
Frailty	-0.089	2.333	-1.98	0.048		
Anxiety	-0.141	0.159	-3.14	0.002*	0.033	

* Statistically significant p = < 0.05, ** p < 0.001, β = Beta, SEβ = Standard Error

Table 3.4 Summary of regression results:
Testing the Mediating Effects of Anxiety on the Relationship between Frailty and Loneliness

Equation	β	SEβ	t	p	R2	Significance of mediation (sobel test)
1. Frailty → Loneliness	0.121	0.163	2.79	0.005*	0.015	
2. Anxiety → Frailty	0.203	0.662	4.74	0.000**	0.041	
3. Frailty and Anxiety → Loneliness						
						z = 4.14**
Loneliness						
Frailty	0.060	0.232	1.43	0.154		
Anxiety	0.345	0.016	8.15	<0.001**	0.131	

* Statistically significant p = < 0.05, ** p < 0.001

3.4 Summary of Findings

Little previous research has systematically examined anxiety and depression and their association with the biological syndrome model of frailty using well validated psychological measures. One previous study looked at self-reported psychiatric illness in older people and found that for each additional deficit defining frailty, odds of psychiatric illness increased (Woods *et al.*, 2005). A further large epidemiological study also identified a relationship between depressive symptoms and incident frailty (Bourgault-Fagnou and Hadjistavropoulos, 2009). There is an even greater paucity of literature evaluating the relationship between frailty and quantified levels of anxiety in older persons. Health anxiety only has been associated with frailty in a small sample of community-dwelling elders, with a call for further studies investigating the association between frailty and more generalized anxiety.

We have found that frail elders experience more symptoms of anxiety and depression than those who are robust. Both pre-frail and frail older persons were an at-risk population more likely to have borderline and case-level anxiety and probable case-level depression. When linear regression models were constructed our findings were consistent, frailty had a strong association with higher scores on both anxiety and depression scales even when other risk factors were accounted for. Our findings suggest that older persons who are becoming increasingly frail according to the frailty phenotype could also be considered psychologically frail with an increased likelihood of emotional disturbance.

We have also identified an association between increasing frailty, loneliness and increasing social isolation. However on further investigation, a supplementary

mediation analysis revealed that in fact generalized anxiety which we identified as a novel psychological factor associated with frailty fully mediated this relationship between frailty and both loneliness and social isolation. This indicates that it may in fact be the psychological factors associated with frailty that are important in determining the link with social isolation and loneliness and so represent key targets in any interventions for frail and socially vulnerable elderly.

Chapter 4

Frailty and Fear of Falling in Older Fallers

4.1 Introduction

Falls represent a serious problem for community-dwelling older people with approximately one third falling annually, resulting in restricted activities of daily living, loss of confidence and independence. They are the primary cause of injury-related death and the third leading cause of poor health, hospitalization and disability (Tinetti and Speechley, 1989). A single fall in an older person may result in fear of falling, one of the most common fears amongst the community-dwelling aged, where it is experienced by approximately half of the population (Friedman *et al.*, 2002). It is suggested to be as serious a health problem as falls themselves (Zijlstra *et al.*, 2007). Of those older adults reporting fear of falling up to 40% also report activity avoidance due to fearfulness. This leads to restriction of activities, reduced physical fitness and increased risk for future falls, mortality, morbidity and premature nursing home admission (Cumming *et al.*, 2000). This underlies the need to study fear of falling and its correlates to enable identification of fearful and avoidant older people and facilitate recommendation of prevention strategies.

4.1.1 Older Fallers and Fear of Falling

Approximately 30–40% of falls are preventable, the most effective strategy being a multifactor approach targeting various risk factors for falling simultaneously in selected or unselected populations (Davison *et al.*, 2005). Most fall prevention trials have been targeted at reducing the physical risk factors of falling, such as poor balance, impaired muscle strength or the harmful side-effects of medication. Fall-related psychological factors have gained less attention (Decullier *et al.*, 2010).

Factors independently related to fear of falling are understudied, yet to identify the appropriate population for prevention strategies knowledge of these factors is important (Kannus *et al.*, 2005). Psychological risk factors for falling may go unrecognized and be omitted from falls prevention interventions, hampering the success of such programmes.

Fallers are a heterogeneous group; there are different faller profiles. Assessing fallers within such profiles could be helpful to develop new dedicated fall prevention programs (Fried et al., 2004). Frailty as a multidimensional construct representing an age-related reduction in physiologic reserve and resistance to stressors; is widely recognized to be associated with adverse health outcomes including falls (Fried *et al.*, 2001). The clinical correlates of frailty manifest as increased vulnerablilty, impaired capability to withstand intrinsic and environmental stressors and limited capacity to maintain physiological and psychosocial homeostasis. A frailty phenotype has been operationalized, based on the presence of a critical mass of core "frail" elements, with the core entities being weakness, poor endurance, weight loss, low physical activity and slow gait speed (Fried *et al.*, 2001). This phenotype represents the biological syndrome of frailty. It is clear that frailer fallers therefore would differ significantly in physical performance when compared to other types of fallers given the presence of this biological syndrome, however they may also differ psychologically. Understanding the psychological correlates of fear of falling in a group of fallers transitioning to frailty when compared to non-frail fallers may help us identify which kind of intervention may be effective in reducing or preventing fear of falling in this vulnerable group of older people.

4.2 Summary of Aims

Primary aims of this study were to (i) characterize the frailty phenotype in a group of community dwelling older fallers and to evaluate the relationship if any, between frailty and fear of falling as reflected by a measure of falls efficacy within the group, (ii) to evaluate the difference if any in psychological factors associated with fear of falling within those fallers transitioning to frailty when compared to the fallers that could be considered physically robust or non-frail

4.3 Results

4.3.1 Population Demographics and Characteristics

Within the convienient sample of 624 community dwelling older people recruited and through the TRIL (Technology Research for Independent Living) Clinic, 301 were included in the analysis of this study as 'older fallers'. To be defined an older faller there had to be a minimum of one self-reported fall in the preceding 12 months and the person was of age > 60 years. A fall was defined as 'An unexpected loss of balance resulting in coming to rest on the floor, the ground or an object below knee level.' (Lach *et al.*, 1991).

Only 24% of the faller group were male Figure 4.1. The mean age of fallers was 75.1 years (Standard deviation 7.43) Figure 4.2. The population characteristics of the 301 older fallers are displayed in Table 4.1. Almost half of the faller population lived alone, mean MMSE within the group reflective of global cognition was 26.7 (+/- 3). Mean Timed up and Go Test was consistant with that expected of a group of fallers at 11.8 (+/- 5.7). Persons who require more than 10 seconds for this test are thought to have limited physical mobility, be at risk for falls, and may require assistance for other mobility tasks. Mean balance score within the group was high but with a large

Figure 4.1 Pie Chart of Sex Distribution in Older Faller Cohort

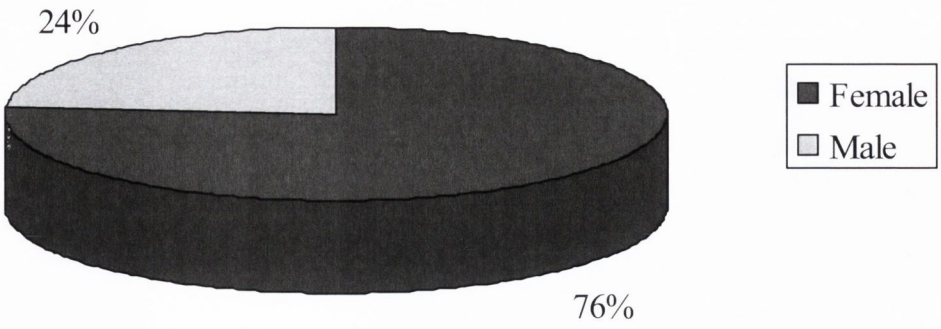


Figure 4.2 Histogram of Age Distribution in Faller Cohort

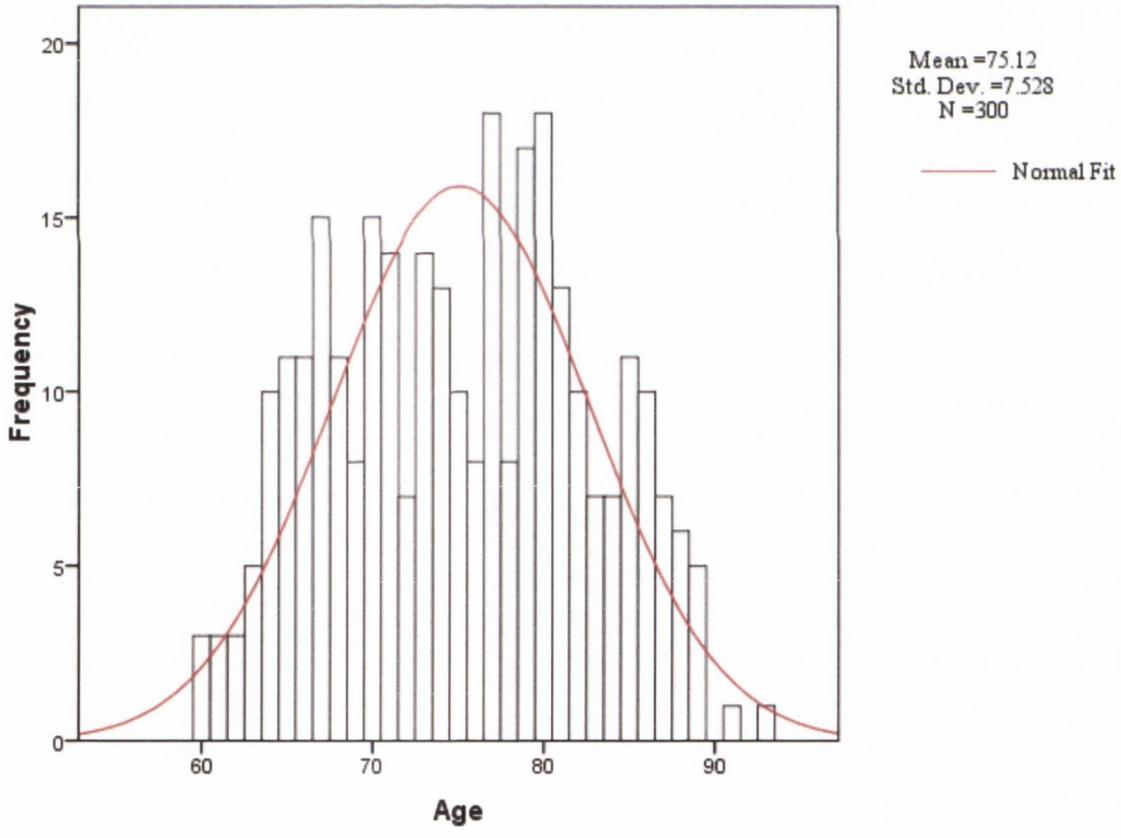


Table 4.1 Characteristics of Faller Population (n = 301)

Parameter	**n (%)**	
Gender (females)	76.3%	
Social class 1 & 2 [a]	29.5%	
Lives alone	43.5%	
Parameter	**Mean+/- S.D**	**Range**
Age	75 (7.5)	
MMSE [b]	26.7 (3)	0-30
Timed Up and Go Test [c]	11.8 secs. (5.7)	
Balance Score [d]	49.1 (8.1)	0-56
Depression Score [e]	2.12 (2.1)	0-8
Anxiety Score [f]	6 (4.1)	0-21
Independent Activities of Daily Living Score [g]	24.5 (3.4)	0-40
Age-Adjusted Charleson Comorbidity Score	5.5 (3.3)	

[a] Higher social class.

[b] Folstein Mini-mental State Examination

[c] The Timed Up & Go: A test of basic functional mobility for frail elderly persons (Podsiadlo and Richardson, 1991).

[d] Berg Balance Score (Berg *et al.*, 1989)

[e] Center for the Epidemiological Studies-Depression- Shortened Version (8 items)

[f] Hospital Anxiety and Depression Scale (7-item Anxiety Subscale)

[g] Lawton Instrumental Activities of Daily Living Scale

standard deviation also (49.1 +/- 8.1). Mean anxiety and depression scores for the total group were below cut-offs for potential anxiety and depression. The mean number of co-morbid illnesses within this group of fallers was high at 5.5 (+/- 3.3).

4.3.2 Characterization of the Frailty Syndrome

Frailty was characterized using the Biological Syndrome Model by Fried et al as described previously in both Chapter 2 & 3 of this thesis. On application of the Fried frailty criteria to the faller group, 98 (32.6%) could be classified as robust or non-frail, 163 (54.2%) could be classified as being at an intermediate stage of frailty (pre-frail) and 40 (13.3%) were defined as completely frail (Figure 4.3). There was no significant difference in frailty dependent on gender. (χ^2, p = 0.232) There was a significant difference in mean age between groups of fallers with the frailer groups being older (Figure 4.4: One-way ANOVA, p = 0.003). There was also a higher burden of co-morbid illnesses within both pre-frail [5.5 ± 3.1] and frail fallers [8 ± 3.2] when compared to robust fallers [3.7 ± 2.9] (Figure 4.5: One-way ANOVA, p < 0.0001).

4.3.3 The Relationship between Frailty and Fear of Falling

The unadjusted mean fear of falling scores by groups is displayed in Table 4.2. The *F* and *P* values were derived from a three-way ANOVA. There was a significant difference in fear of falling according to frailty groups showing lower MFES scores with increasing frailty representative of higher levels of fear of falling (p <0.0001). This difference was not apparent between groups defined according to age however there was a significant difference in fear of falling according to gender, with more fearful male fallers compared to female fallers (p = 0.011). A polynomial contrast

Figure 4.3 Pie Chart of Frailty Distribution in Older Faller Cohort

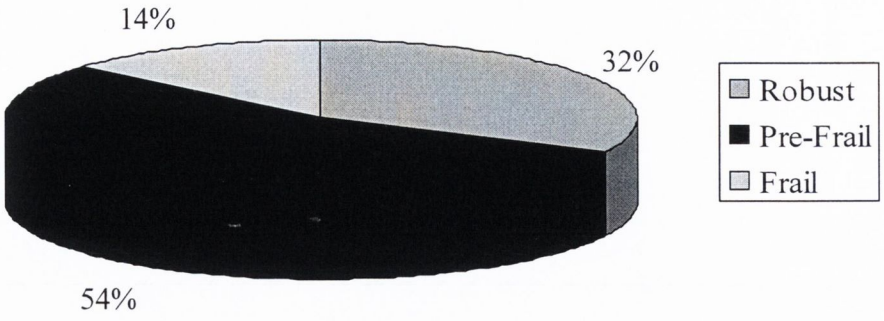


Figure 4.4 Means Plot showing Age between Frailty Groups in Older Fallers

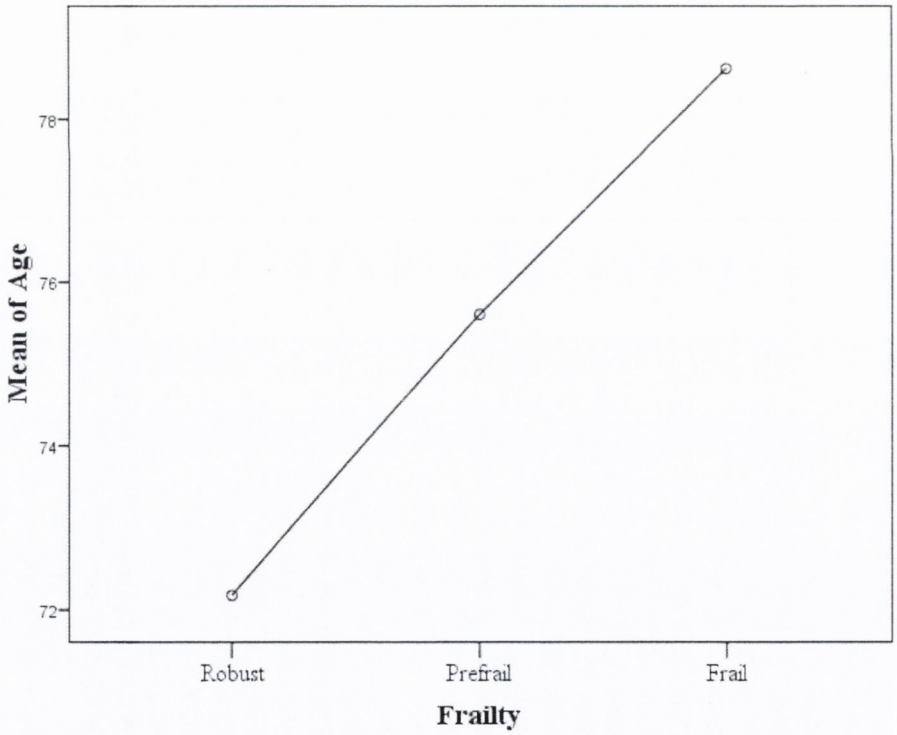


Figure 4.5 Means Plot showing Comorbidity Scores between Frailty Groups

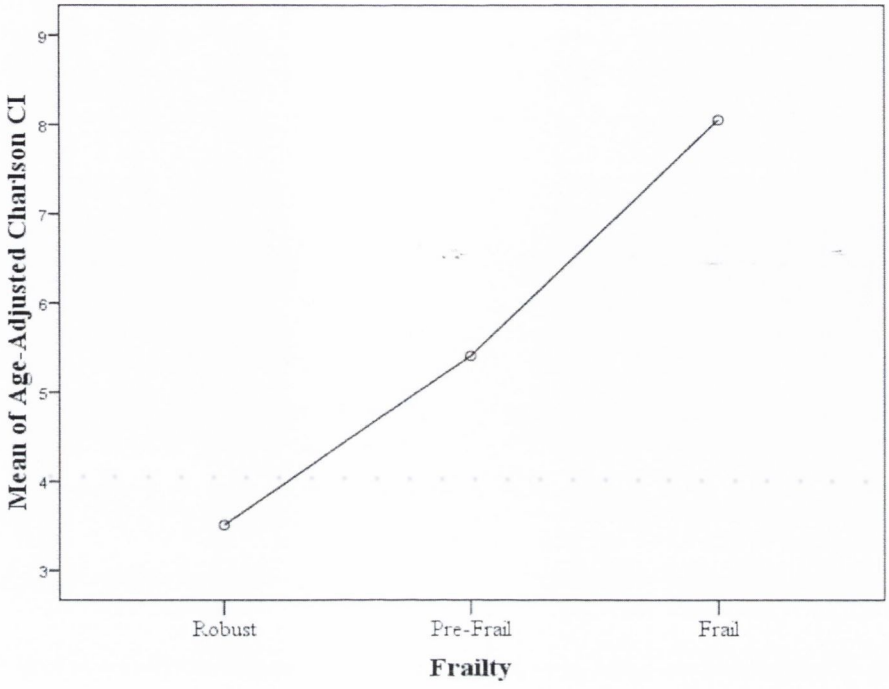


Table 4.2 MFES Scores according to Age, Gender and Frailty

	N	MFES Score Mean (SD)[a]	*F*(df)[b]	*P* value	*P* value trend
Gender					
Males	61	8.04 (2.38)	6.612 (1,276)	0.011	—
Females	221	8.71 (1.62)			
Age					
60-69 years	78	8.92 (1.64)	1.858 (2,276)	0.158	0.292
70-79 years	117	8.75 (1.65)			
80+ years	87	8.01 (2.10)			
Frailty					
Robust	95	9.23 (1.41)	40.993 (2, 276)	<0.0001	<0.0001**
Pre-Frail	153	8.66 (1.54)			
Frail	35	6.24 (2.30)			

** Statistically significant $p < 0.001$

[a] One-way ANOVA, [b] Three-way factorial ANOVA model

indicated that the linear trend for MFES scores to decrease with frailty was significant at $p < 0.0001$. Pairwise contrasts showed that the difference in marginal means between robust and pre-frail groups was statistically significant at 0.46 points (95% CI 0.049, 0.879, $p = 0.029$). The difference in marginal means was also significant between robust and frail groups at 2.9 points (95% CI 2.23, 3.51, $p < 0.0001$) as well as between pre-frail and frail groups at 2.4 points (95% CI 1.81, 3.0, $p < 0.0001$).Profile plots indicated there was no interaction between frailty and age or gender in the analysis of fear of falling scores (Figure 4.6 and Figure 4.7)

4.3.4 A Comparison of the Psychological Correlates of Fear of Falling in Fallers Transitioning to Frailty compared to Fallers classified as Robust

For the purposes of our regression analysis we categorized the participants into two groups, fallers who were completely robust (non-frail) with 0 criterion present and a frailer group consisting of fallers with 1 or 2 frailty criteria who were intermediately or pre-frail and those with 3 or more criteria considered to be fully frail. We pooled intermediate level of frailty with full frailty within our regression analysis as this best represented a group transitioning to frailty. Being at a pre-frail or intermediate stage of frailty has consistantly been shown to infer risk of developing full-blown frailty and also a high risk of poorer outcomes when compared to non-frail individuals (Fried et al., 2004). To ascertain which psychological correlates were independently associated with fear of falling in both the robust and frailer faller groups, we conducted sequential multiple regression analysis to include measures of depression, anxiety, cognition, neuroticism and loneliness, also accounting for factors such as age and gender (Table 4.3). Using nonparametric correlation analysis (Spearman rho),

Figure 4.6 Means Plot of Fear of Falling Scores Dependent on Age and Frailty

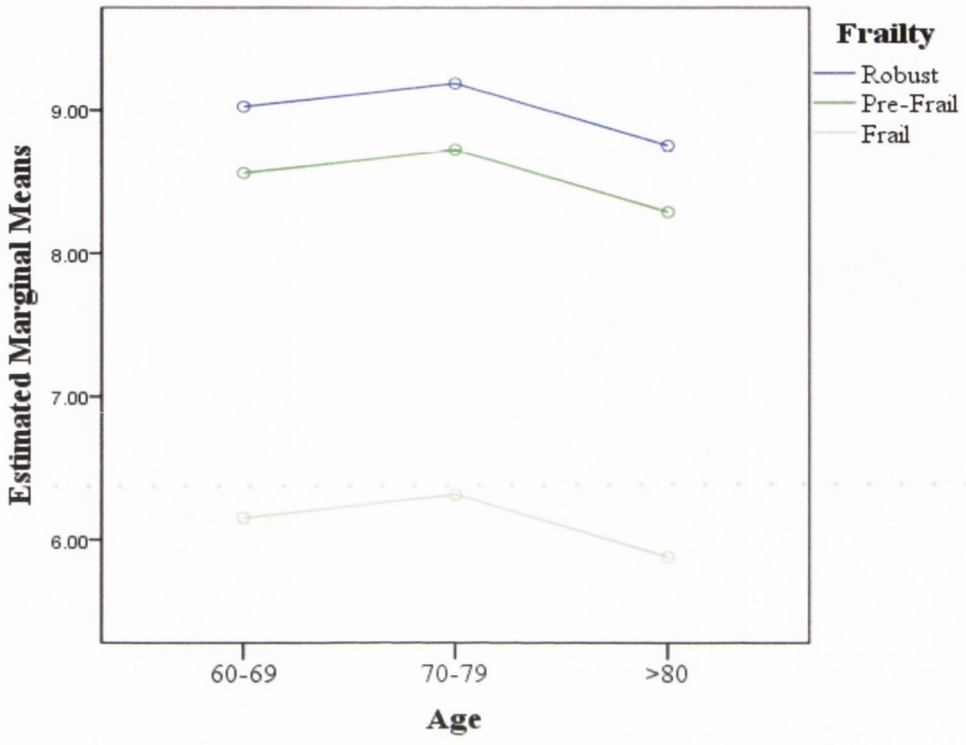


Figure 4.7 Means Plot of Fear of Falling Dependent on Gender and Frailty

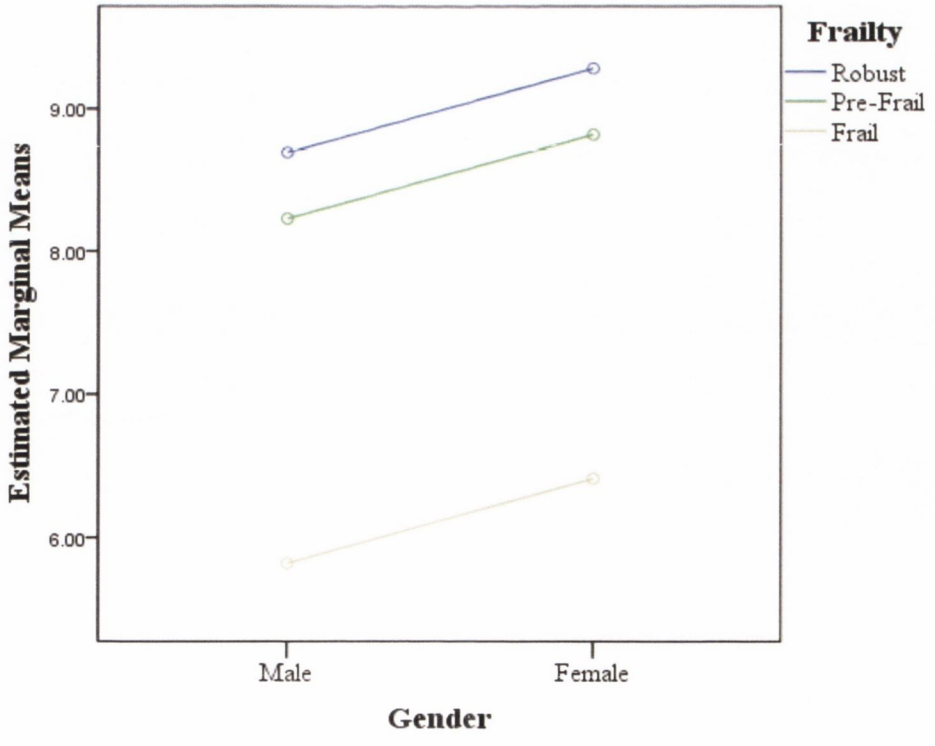


Table 4.3 Sequential Multiple Regression Models of Psychological Correlates and Fear of Falling (MFES) Scores in Robust and Frailer Fallers.

	Beta	Significance	R^2
Model 1: Robust Fallers (n = 98)			
Age	**- 0.319**	**p = 0.011***	0.309
Gender	**0.451**	**p < 0.0001****	
Cognition (MMSE) [a]	**- 0.270**	**p = 0.035***	
Depression (CESD) [b]	- 0.002	p = 0.987	
Anxiety [c]	- 0.172	p = 0.221	
Neuroticism [d]	0.044	p = 0.768	
Loneliness [e]	0.008	p =0.942	
Model 2: Pre-Frail/Frail Fallers (n = 203)			
Age	0.004	p = 0.965	0.122
Gender	0.054	p = 0.567	
Cognition (MMSE) [a]	0.110	p = 0.235	
Depression (CESD) [b]	**- 0.286**	**p = 0.026***	
Anxiety [c]	- 0.033	p = 0.783	
Neuroticism [d]	- 0.011	p = 0.927	
Loneliness [e]	- 0.033	p = 0.753	

* Statistically significant p = < 0.05, ** p < 0.001

[a] Cognition as measured using the Mini Mental State Examination

[b] Center for the Epidemiological Studies-Depression (CESD-8) Scale

[c] Anxiety Subscale of the Hospital Anxiety and Depression Scale

[d] Neuroticism Scale of the Eysenck Personality Inventory (EPI)

[e] Loneliness measured using the de Jong Loneliness Scale

variables were entered into the multivariate regression models determined by the strength of their association.

Age, female gender and lower cognitive scores were associated with lower MFES scores reflective of greater fear of falling in the group of fallers considered robust. However for those fallers who fulfilled either pre-frail or frail criteria, higher depression score was the only factor associated with lower MFES scores and greater fear of falling on multivariate analysis. Furthermore, a separate subanalysis identifed that the odds ratio of having case level depressive disorder (CESD-8 $\geq$ 4) if you were a frailer faller fulfilling any of the frailty criteria was significantly higher than if you were classified as a robust faller. (Figure 4.8: OR = 3.1, CI 1.5, 6.2, p = 0.001)

4.3.5 Supplementary Sensitivity Analysis

As subjective exhaustion is measured as a frailty criterion using the same CES-D scale utilized to assess depression it may reflect a potential confounder in our analysis of the relationship between depressive symptoms and fear of falling in frailer older fallers. We therefore performed a sensitivity analysis using a 4 point frail score which omitted the "exhaustion" criterion for frailty and consisted solely of the four other frailty criteria and explored whether the associations remain. We were able to maintain the cut-off of one or more of the four criterion remaining for determining pre-frailty and frailty as it is merely the cumulative presence of any of the frailty criteria that determines the pre-frail or frail syndrome. On multivariate regression analysis the association between depression scores and the MFES as a measure of fear of falling remained even when adjusting for age, gender and cognition in the analysis (Table 4.4).

Figure 4.8 Case-level Depression according to Robust and Frailer Faller Groups

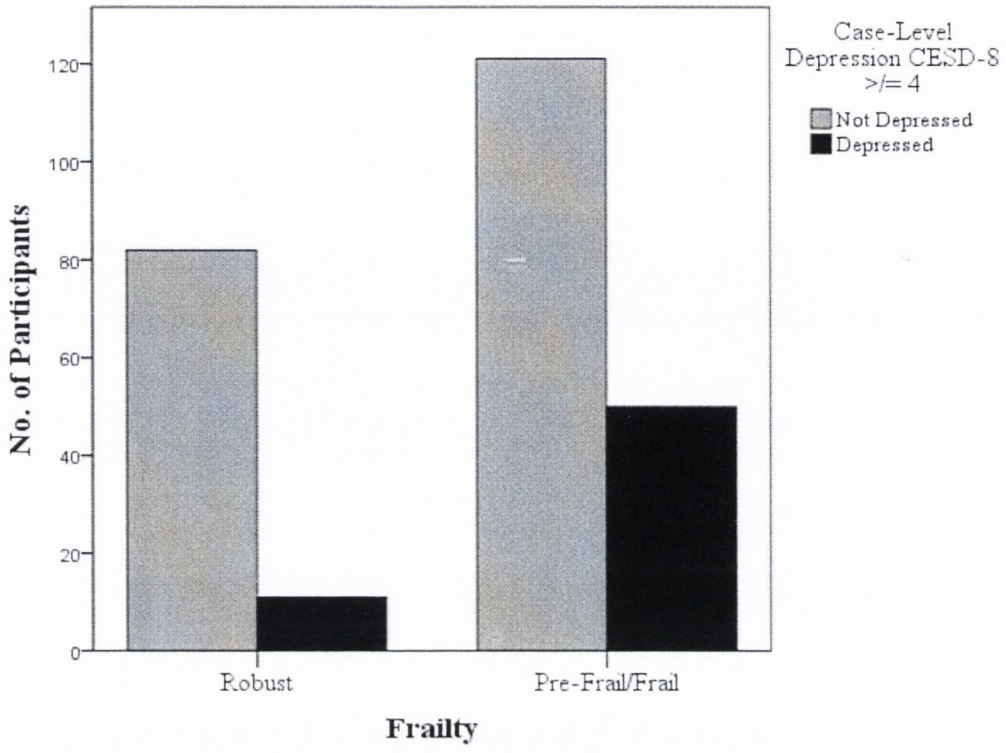


Table 4.4 Multiple Regression Model of Psychological Correlates and Fear of Falling (MFES) Scores in Frailer Fallers classified using a 4-criterion Frail score.

	Beta	**Significance**	**R^2**
Pre-Frail/Frail Fallers [a] (n = 134)			
Age	**- 0.225**	**p = 0.019***	0.207
Gender	0.064	p = 0.460	
Cognition (MMSE) [b]	0.160	p = 0.076	
Depression (CESD) [c]	**- 0.286**	**p = 0.010***	

* Statistically significant p = < 0.05

[a] Modified Frailty Index excluding exhaustion criteria

[b] Center for the Epidemiological Studies-Depression (CESD-8) Scale

[c] Cognition as measured using the Mini Mental State Examination

4.3.6 Power Calculation

Given our sample was split into those categorised as either robust or frailer fallers a post-hoc statistical power calculation for multiple regression analysis was completed for each subset. Given an R^2 of 0.309 for Model 1 (Robust Fallers), the observed power with seven predictors, an alpha of 0.05 and a sample size of 98 was 0.99. For Model 2 (Pre-Frail/Frail Fallers) with an R^2 of 0.122, seven predictors, an alpha of 0.05 and a sample size of 203 the observed power was calculated to be 0.98. When our sensitivity analysis was completed with a modified frailty index omitting the exhaustion criteria we observed a power of 0.99, given an R^2 of 0.207, with four predictors, an alpha of 0.05 and a sample size of 134.

4.4 Summary of Findings

We have found that, when compared to robust fallers, pre-frail and frail individuals displayed a greater fear of falling as indicated by a significantly lower mean MFES score. On multivariate analysis accounting for a number of psychological factors only age, female gender and poorer cognition were retained as the factors significantly associated with fear of falling in robust fallers in an optimal model accounting for around 30% of variance. This is consistent with current literature where older females and those with poor cognition have been found to have higher rates of fear of falling (Arfken et al., 1994). In our group of pre-frail and frail fallers however, increasing depression score was the only significant psychological factor associated with increasing fear of falling in an optimal model accounting for 12.2% of the observed variance. This association between depression and fear of falling scores was retained in a sensitivity analysis where a four-point frailty score was used to define frailer fallers omitting the criteria of exhaustion. Finally we confirmed that the odds ratio of

having case-level depression was increased 3-fold if you were a frailer faller when compared to those fallers considered robust or non-frail.

Of the limited evidence available to us in the current literature on fear of falling and frailty, our findings are consistent with one other study, which evaluated activity related fear of falling in a cohort of older individuals defined as transitioning to frailty according to criteria established by Speechley and Tinetti in 1991 (Kressig *et al.*, 2001). They report that individuals fearful of falling and transitioning to frailty were more likely to be depressed than non-fearful individuals. A confounding factor in this study was the fact that a diagnosis of depression is one of the criteria used by the Speechley & Tinneti index to define frailty (Speechley and Tinneti, 1991). Within our study we have utilised a more recent and well-validated measure of the biological syndrome of frailty identified by Fried et al. The identification of those at an intermediate level of frailty using this measure has been robustly shown to infer risk of developing full-blown frailty and the multiple adverse outcomes associated with frailty also. Theoretically this transitional stage is the last opportunity to affect frailty as it is at this point that it may be reversed (Fried *et al.*, 2004).

In view of the growing importance of fear of falling as an area of increasing public health concern, our study makes an important contribution. Depressive symptoms are associated with fear of falling in frailer older fallers and these fallers transitioning to frailty have an increased likelihood of depressive disorder compared to their more robust counterparts. Our study provides preliminary evidence that addressing depressive symptoms in fallers at a transitional level of frailty may be important to reduce fear of falling in this group.

Chapter 5

The Impact of Frailty on Cognitive Performance

5.1 Introduction

The loss of cognitive abilities is one of the most feared outcomes of aging. Unfortunately, up to half of the 85 years and older population suffers from some form of cognitive impairment, making the fear a reality for all too many. Maintaining cognitive health in late life has important implications for overall well-being and independence, health services utilization and costs, long-term institutional care, and caregiver burden, as well as personal and societal resources (Andel *et al.*, 2005).

Three types of cognitive changes are recognized in late life: normative cognitive aging, cognitive impairment, and dementia (Fillit *et al.*, 2002).

5.1.1 Cognitive Impairment

While declines in cognitive functioning are not an inevitable part of aging, the majority of older adults experience some slowed speed of processing (Salthouse, 1996). Other abilities such as memory, spatial ability, and reasoning are also more likely to decline with normal aging, whereas verbal abilities, information, and comprehension tend to show stability (Kramer et al., 2004). Several terms have been used to describe cognitive decline in normal aging including age-associated memory impairment (AAMI) (Crook *et al.*, 1986), age-related cognitive decline (Crook *et al.*, 1986), and aging-associated cognitive decline (Levy, 1994). Mild cognitive impairment (MCI) (Petersen and Negash, 2008) and cognitive impairment no dementia (CIND) (Elby *et al.*, 1995) are considered intermediate states between normal cognitive aging and dementia where individuals experience cognitive deficits greater than expected for their age, but do not fulfill diagnostic criteria for dementia.

Both MCI and CIND may be associated with a heightened risk of progression to dementia (Hsiung *et al.*, 2006; Petersen *et al.*, 2001); although there is ongoing debate in the literature whether these entities merely represent early or incipient dementia rather than true risk states or factors (Morris *et al.*, 2001). Finally, dementia is a chronic syndrome characterized by acquired cognitive deficits in more than one cognitive domain, currently including memory, that are severe enough to affect daily (social and occupational) functioning, do not occur solely in the context of delirium, and cannot be fully accounted for by another mental disorder (APA, 2000).

The focus of research in the area of cognition has shifted somewhat to the search for effective preventative strategies to reduce the prevalence of cognitive impairment and dementia in older age groups. By definition, primary prevention of disease requires risk factors to be modified before the onset of disease. Neurodegenerative and cerebrovascular diseases are generally chronic, progressive conditions with pathology developing over years before symptoms and deficits are experienced. There is a heightened awareness of the importance of identifying early at risk states for cognitive decline to facilitate targeting of vulnerable groups with preventive strategies and early treatment to minimize the effects of cognitive impairment.

5.1.2 Cognitive Decline and Frailty

Cognitive decline has been previously reported in frail persons (Campbell and Buchner, 1997; Ory *et al.*, 1993; Rockwood *et al.*, 1994; Strawbridge *et al.*, 1998). The combination of cognitive impairment and isolated components of frailty, such as slow walking speed, have also been associated with progression to dementia (Waite *et al.*, 2005). Recent research has begun to explore whether the frailty syndrome may

constitute a risk factor for dementia. The longitudinal association between frailty and incident cognitive decline and AD has been reported in community dwelling older persons who did not present with dementia at baseline (Buchman *et al.*, 2007).This study found that baseline level and rate of change of the frailty score (Fried's criteria) were associated with rate of change in cognition (composite measure of 19 neuropsychological tests) over a 3-year follow-up period, suggesting that frailty occurs before the onset of dementia of the Alzheimer's type and is associated with rate of cognitive decline in elderly people.

Further studies have shown that whilst frailty at baseline is associated with more cognitive complaints with incident dementia even after adjustment for many potential confounders; the risk of developing future dementia in frail older persons is only significantly greater in those with cognitive impairment at baseline (Avila-Funes *et al.*, 2009). This study showed that the risk of developing dementia in cognitively impaired individuals is about five times as high as in participants with no sign of cognitive impairment, irrespective of their frailty status. Therefore, although the association between physical frailty and cognitive impairment is widely accepted, a temporal relationship between frailty and dementia, if it exists, seems to depend perhaps on not only the frailty status of the older person but also on those exhibiting a specific cognitive profile. Frailty therefore may not necessarily be a predictor of dementia, but rather a separate pathophysiological process, independent of cognitive decline. It could be hypothesised then, that it is the coincidence of frailty and cognitive impairment that exacerbates the vulnerability of a subject, increasing the risk of developing dementia.

Despite the fact previous work has associated increasing frailty with incident Alzheimer's disease and mild cognitive impairment (Boyle *et al.*, 2010; Buchman *et al.*, 2007), there is a paucity of research investigating the specific domains of cognitive performance frailty relates to nor whether it is an early indicator of poorer cognitive performance in those who have not yet developed established cognitive impairment. Understanding how frailty relates to specific areas of cognitive performance may be important in order for us to identify the specific cognitive profiles that may coincide with emerging physical frailty to infer increasing risk for poorer outcomes and established cognitive impairment.

5.2 Summary of Aims

Primary aims of this study were to (i) examine the relationship between cognitive performance and frailty within a cohort of independent non-demented community dwelling elderly, (ii) to identify which markers of frailty are associated with poorer cognitive performance, (iii) To clarify the specific areas of cognitive performance that pre-frail and frail elders perform poorly on when compared to their robust or non-frail counterparts.

5.3 Results

5.3.1 Population Demographics and Characteristics

Within the convienient sample of 624 community dwelling older people recruited and through the TRIL (Technology Research for Independent Living) Clinic, 500 participants underwent an extended battery of neuropsychological tests to evaluate cognition as well as an assessment of frailty within the context of their comprehensive geriatric assessment. Cognitive status was assessed in a variety of domains using

standardised instruments as described in Chapter 2 of this thesis. These domains included language, executive function, spatial ability, verbal and non-verbal memory. Only 31% of this group were male Figure 5.1. The mean age within the group was 72 (+/- 7) years Figure 5.2. The population characteristics of the 500 independent community-dwelling adults are displayed in Table 5.1. Mean MMSE score was high within the group at 28. Educational attainment was variable in the sample with 28.5% reporting to have completed primary level only, 52.6% secondary level, and 18.9% third level. Mean number or co-morbid illnesses within the group was 4 (+/- 3).

5.3.2 Characterization of Frailty and Cognitive Performance

Frailty was characterized using the Biological Syndrome Model by Fried et al as described previously in both Chapter 2 & 3 of this thesis. On application of the Fried frailty criteria, 257 (51.4%) could be classified as robust or non-frail, 214 (42.8%) could be classified as being at an intermediate stage of frailty (pre-frail) and 29 (5.8%) were defined as completely frail (Figure 5.3). There was no significant difference in frailty dependent on gender (χ^2, $p = 0.991$). There was a significant difference in mean age between groups of fallers with the frailer groups being older (Figure 5.4: One-way ANOVA, $p = 0.001$). There was also a higher burden of co-morbid illnesses within both pre-frail [4 ± 3] and frail fallers [6 ± 4] when compared to robust fallers [3 ± 3] (Figure 5.5: One-way ANOVA, $p < 0.0001$). No significant difference was found in educational level across frailty groups (χ^2, $p = 0.991$). Neuropsychological test characteristics for the total group are summarised in Table 5.2.

Figure 5.1 Pie Chart of Sex Distribution in Older Cohort

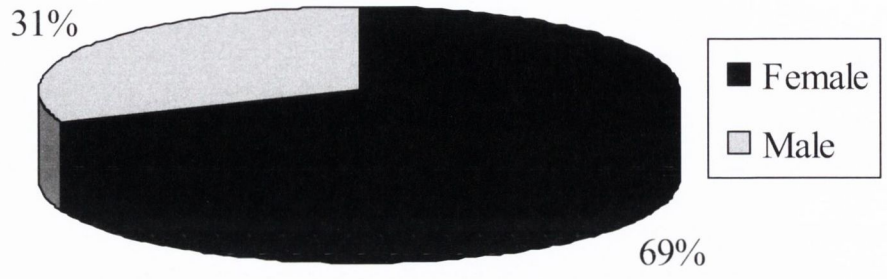


Figure 5.2 Histogram of Age Distribution in Older Cohort

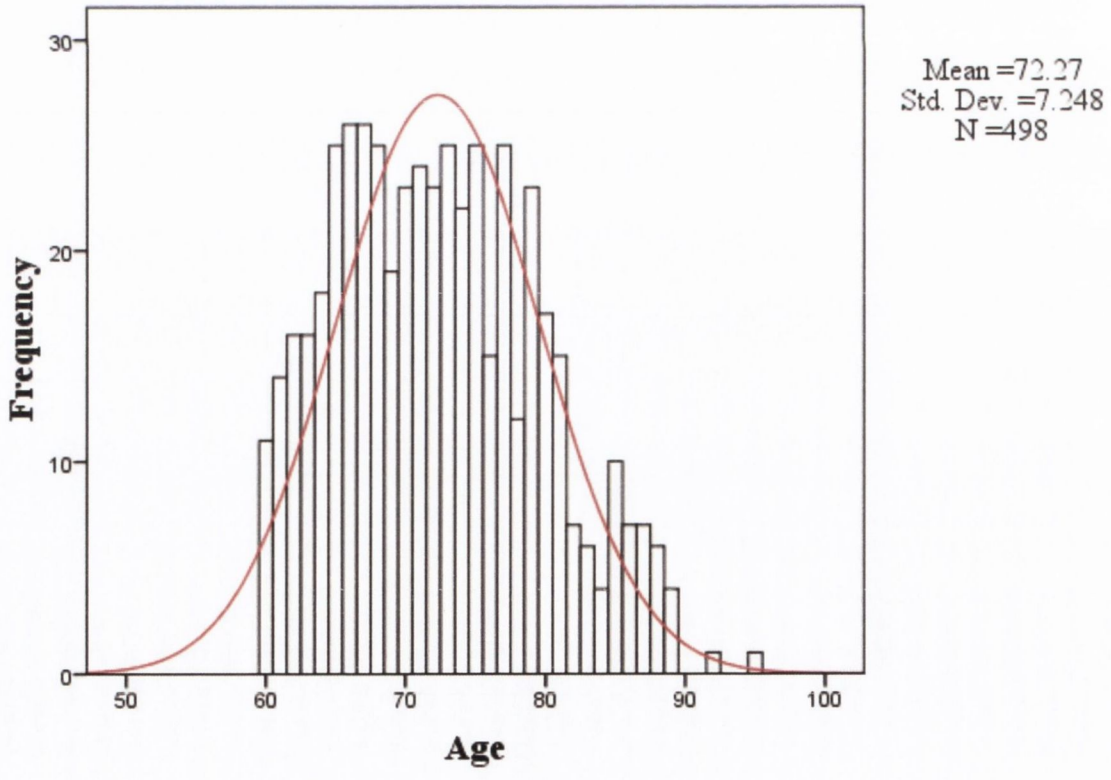


Table 5.1 Summary Data regarding Participant Characteristics

Parameter		**n (%)**
Gender (Females)		69 %
Social Class 1 & 2 [a]		34.2 %
Smoker	Never Smoked	45.7%
	Ex-Smoker	45.5%
	Current Smoker	8.9%
Education	Primary Level	28.5%
	Secondary Level	52.6%
	Third Level	18.9%
Parameter	**Mean+/- S.D**	**Range**
Age	72 (7)	
MMSE [b]	28 (3)	0-30
Co-Morbidities [c]	4 (3)	

[a] Higher social class.

[b] Folstein Mini-mental State Examination

[c] Age-Adjusted Charleson Comorbidity Score

Figure 5.3 Pie Chart of Frailty Distribution in Older Cohort

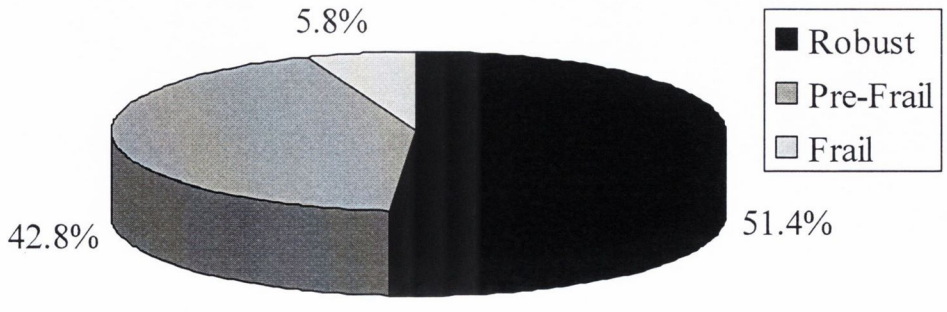


Figure 5.4 Means Plot showing Age Difference between Frailty Groups

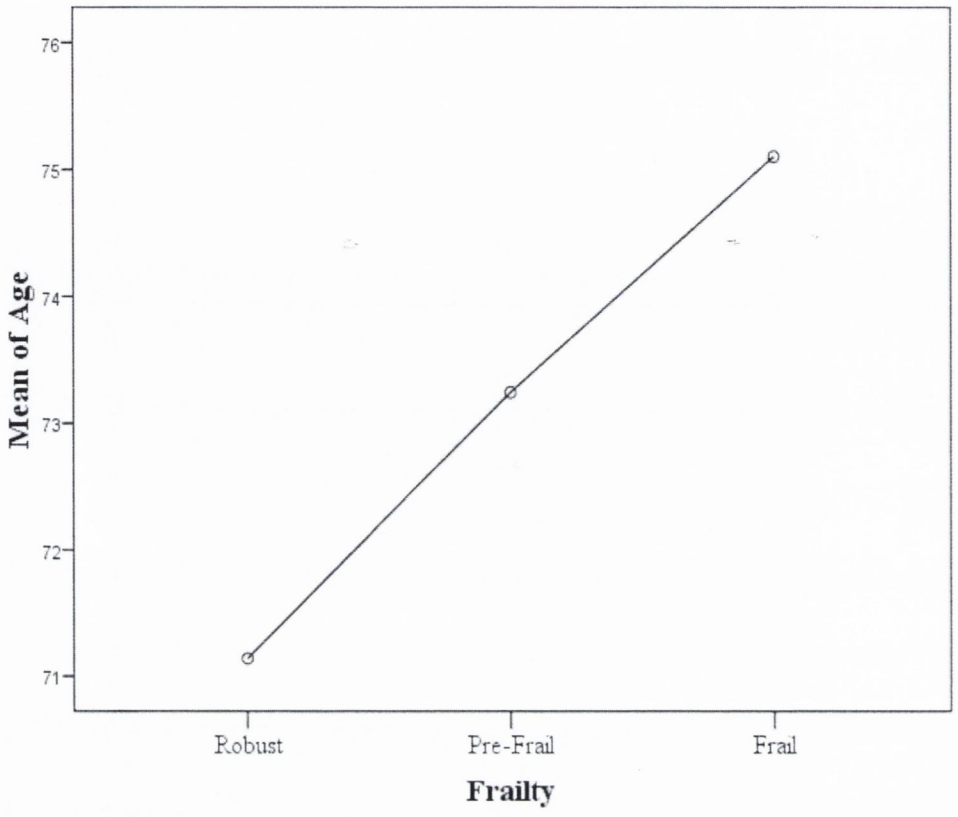


Figure 5.5 Means Plot showing Co-morbidity Scores between Frailty Groups

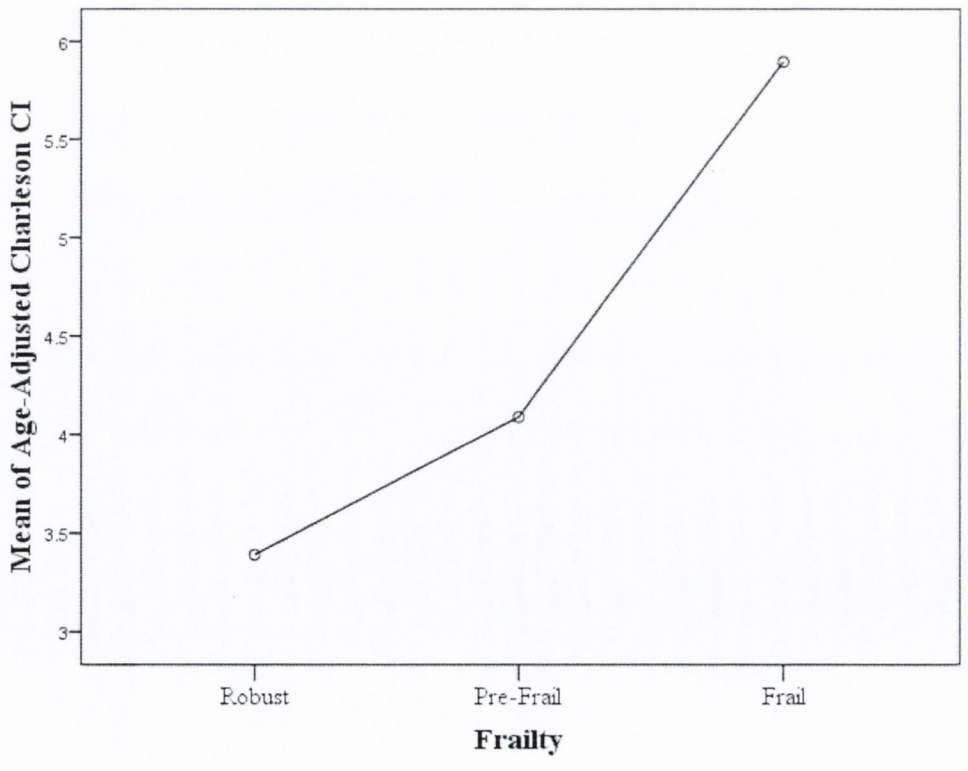


Table 5.2 Summary Data regarding Neuropsychological Test Scores

Neuropsychological Tests	**Mean (S.D)**
Mini-mental state examination	28 (3)
Verbal Memory	
- Immediate word recall	5.81 (1.7)
- Delayed word recall	3.76 (2.0)
(subtests from WMS-III [a])	
Prospective Memory	
- Hidden belongings	6.52 (2.4)
- Remembering Appointment Task	3.11 (1.4)
(subtests from RBMT-E [b])	
Executive Function	
- Language: Category Fluency (Animals)	17 (5.3)
- Forward & Backward Digit Span	6.94 (2.6)
- Similarities	6.36 (1.6)
(subtests from the WAIS- III [c])	
- Trails A	55.41 (28)
- Trails B	130.44 (70)
(TMT Parts A & B [d])	
CAMCOG Subtests [e]	
Visual Memory	
- Recognition	3.4 (1.2)
- Recall	5.7 (0.6)
Naming (Visual Task)	5.6 (0.6)
Drawing (Praxis Task)	5.2 (1.2)
Praxis (Abstract & Motor Task)	10.82 (1.6)

[a] Wechsler Memory Scale Third Edition

[b] The Extended Rivermead Behavioural Memory Test

[c] Wechsler Adult Intelligence Scale-Third Edition

[d] Trail Making Test Parts A & B

[e] Cambridge Examination for Mental Disorders of the Elderly

5.3.3 The Relationship between Frailty and Cognitive Performance

To enable the comparison of neuropsychological tests with different ranges, Test scores were standardised using a z-transformation (subject score minus sample mean divided by sample standard deviation). A composite score consisting of the average of the sum of the standardised test scores was then used as a global measure of cognitive performance (global composite: GC). This method has been used in a number of other studies to establish a score representative of global cognitive performance from a standard battery of neuropsychlogical tests (Buchman *et al.*, 2007; Chin *et al.*, 2008; Dufouil *et al.*, 1997). The Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) was performed as a second general index of cognitive functioning. Participants with scores in the lowest quintile within both global composite score and MMSE were classified as having poorer cognitive performance. This method is similar to that utilized in a large longitudinal study of over one thousand participants where subdimensions of frailty were investigated to include poor cognitive performance (Sarkisian *et al.*, 2008).

On evaluation of cognitive performance the proportion of poor cognitive performers on both MMSE scores and global cognitive scores was significantly higher in pre-frail and frail groups when compared to the robust group (Figure 5.6 & 5.7: (χ^2, $p = 0.005$, $p < 0.0001$ respectively). Using linear regression analysis to further investigate this association between frailty and cognitive performance, frailty maintained a negative correlation with higher cognitive scores, both the global composite score and the MMSE even when age, gender and educational level were added to the regression model, suggesting that higher frailty is significantly associated with poorer cognitive performance (Table 5.3). Logistic regression models were then constructed to

Figure 5.6 Lowest MMSE Scores according to Frailty Group

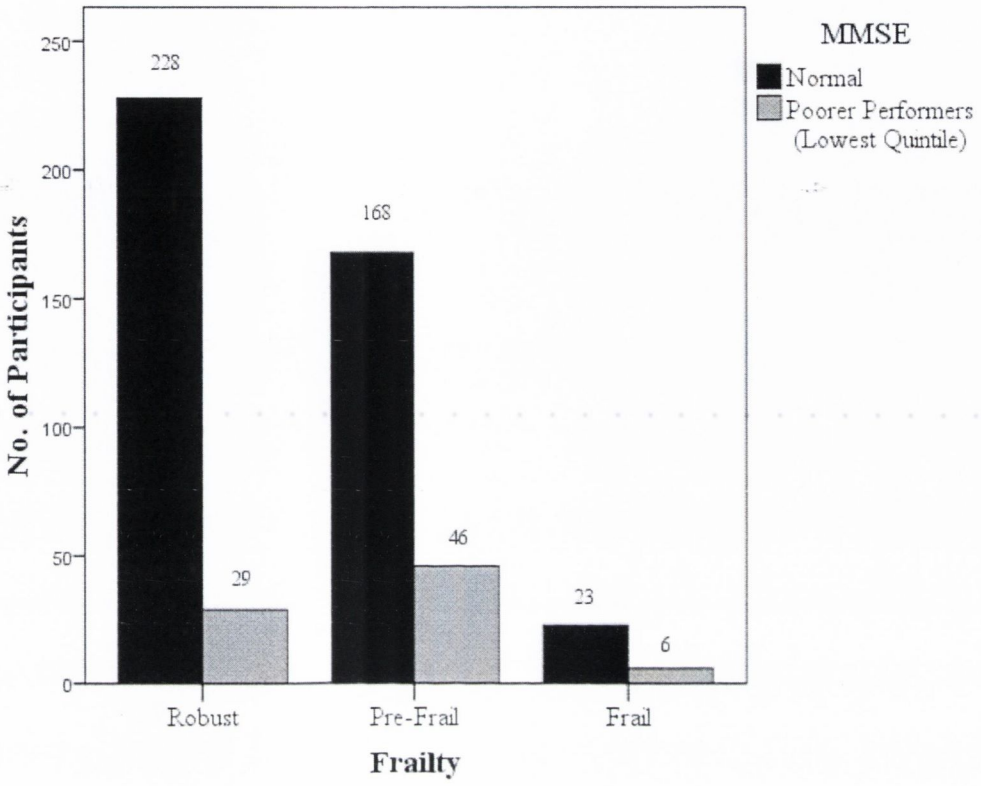


Figure 5.6 Lowest Global Cognitive Scores according to Frailty Group

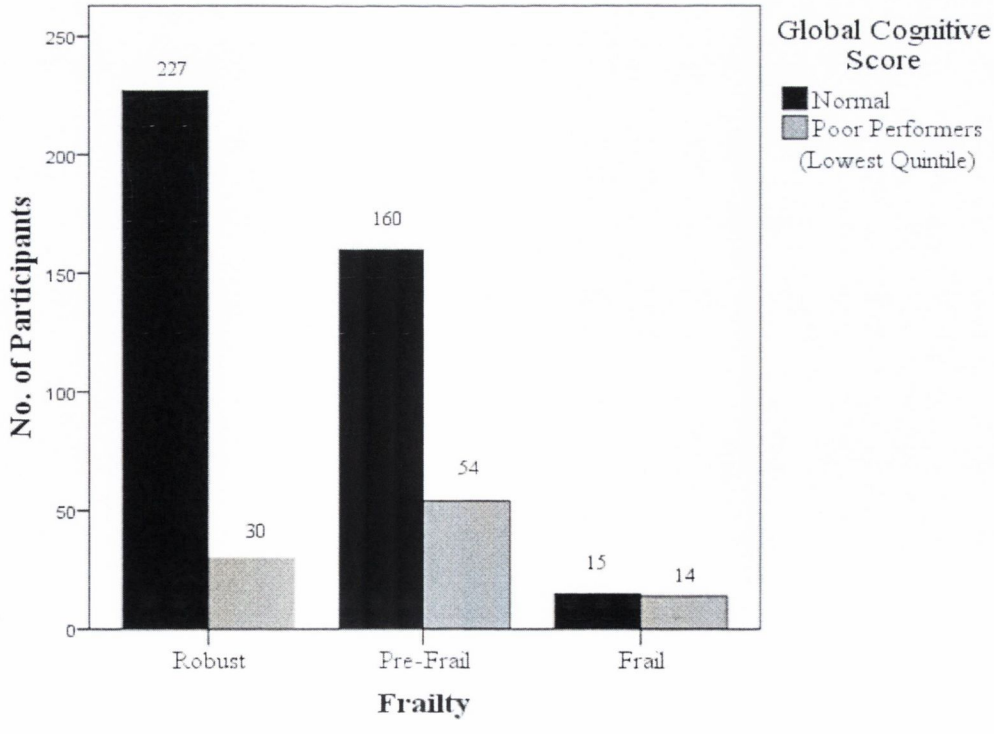


Table 5.3 Regression Models of Frailty and Cognitive Performance

	Beta	Significance	R^2
Model 1: Global Cognitive Score			
Frailty	**- 0.276**	**p < 0.0001****	**0.129**
Age	**- 0.149**	**p = 0.001***	
Gender	- 0.052	p = 0.220	
Educational Level	0.077	p = 0.072	
Model 2: MMSE Score			
Frailty	**- 0.315**	**p = 0.003***	**0.180**
Age	**- 0.073**	**p <0.0001***	
Gender	0.026	p = .528	
Educational Level	**0.276**	**p < 0.0001***	

* = Statistically significant: P < 0.05, ** p < 0.001

evaluate which specific frailty criteria had increased odds of poorer global cognitive performance adjusting for age, gender and educational level. We found that weakness as measured by grip strength, reduced physical activity and age were the three criteria that retained a significant association with poor cognitive performance with increased odds of reduced global performance of 2.15 for weakness and 2.71 for reduced physical activity (Table 5.4: OR = 2.15 CI 1.29, 3.58 p = 0.003, OR = 2.71 CI 1.42, 5.18 p = 0.003 respectively).

The mean neuropsychological test scores according to frailty group are displayed in Table 5.5. The *F* and *P* values were derived from a three-way ANOVA adjusting for age, gender and educational level. There was a significant difference in neuropsychological test scores across the many of the tests according to frailty groups showing poorer scores with increasing frailty, representative of reduced cognitive performance in both pre-frail and frail groups. Significant differences indicative of reduced performance were apparent for both pre-frail and frail groups in the areas of verbal memory, prospective memory, executive functioning and praxis. Reduced cognitive performance was not apparent in the memory subtests of the CAMCOG, however a significant difference was found with poorer performance for pre-frail and frail groups within the CAMCOG naming test. Polynomial contrasts indicated that the linear trend for neuropsychological test scores to disimprove with frailty was significant across the same areas of verbal memory, prospective memory, naming, executive functioning, and praxis. Whilst there were also significant differences in neuropsychological test scores dependent on age and educational level as would be expected, individual profile plots for each set of neuropsychological tests indicated

Table 5.4: Logistic Regression Model showing Odds Ratio of Frailty Criteria determining Poorer Cognitive Performance as Measured using a Global Composite Score to include Age, Gender and Education.

Variable	B	S.E	Sig.	OR	95% CI	
					Lower	Upper
Slowed Gait	0.033	0.397	0.948	1.03	0.47	2.23
Weight Loss	0.238	0.904	0.793	1.27	0.22	7.45
Weakness (Grip)	**0.748**	**0.260**	**0.003***	**2.15**	**1.29**	**3.58**
Exhaustion	0.346	0.288	0.230	1.41	0.80	2.50
Reduced Activity	**0.997**	**0.331**	**0.003***	**2.71**	**1.42**	**5.18**
Age	**0.038**	**0.017**	**0.027***	**1.04**	**1.01**	**1.07**
Gender	0.524	0.281	0.063	1.69	0.97	2.93
Educational Level	-0.116	0.108	0.283	0.90	0.72	1.10

* = Statistically significant: $P < 0.05$, ** $p < 0.001$

SE=Standard Error, OR = Odds Ratio

Table 5.5 Neuropsychological Test Scores according to Frailty Groups (Adjusted for Age, Gender and Educational Level)

	Test Score Mean (SD)[a]			F^b	*P* value	*P* value trend
	Robust	Pre-Frail	Frail			
Verbal Memory[c]						
Immediate Word Recall	6.14(1.5)	5.58(1.8)	4.55(1.5)	11.6	0.001*	<0.0001**
Delayed Word Recall	4.05(2.0)	3.59(2.0)	2.50(1.8)	6.5	0.002*	0.001*
Prospective Memory[d]						
Hidden Belongings	6.94(2.0)	6.07(2.7)	6.29(1.8)	3.4	0.033*	0.469
Appointment Task	3.21(1.3)	3.06 (1.6)	1.83(1.5)	3.2	0.044*	0.016*
Executive Functioning						
Category Fluency	17.8(5.02)	16.09(5.2)	15.1(5.3)	7.0	0.001*	0.012*
Digit Span[e]	7.3(2.5)	6.7(2.6)	5.50(2.0)	7.1	0.001*	0.001*
Similarities[e]	6.9(1.15)	5.81(1.9)	6.14(1.7)	12.0	<0.0001**	0.22
Trails A[f]	48.8(23.4)	61.8(31.3)	72(25.7)	13.9	<0.0001**	0.001*
Trails B[f]	110.5(53)	151.7(78.3)	183.9(7.3)	4.8	0.009*	0.003*
CAMCOG Subtests[g]						
Memory:						
Recognition	3.41(1.1)	3.36(1.2)	3.0(1.4)	1.3	0.281	0.114
Recall	5.74(0.5)	5.58(0.7)	5.62(0.5)	1.9	0.142	0.454
Naming	5.71(.54)	5.54(.68)	5.38(.52)	3.2	0.042*	0.07*
Praxis:						
Drawing	5.51(0.8)	4.92(1.3)	3.67(2.2)	31	<0.0001**	<0.0001**
Abstract & Motor Task	11.21(1.2)	10.51(1.7)	9.44(2.6)	25	<0.0001**	<0.0001**

* = Statistically significant: P < 0.05, ** p < 0.001

[a] One-way ANOVA, [b] Three-way factorial ANOVA model to include Age and Gender

[c] Wechsler Memory Scale Third Edition

[d] The Extended Rivermead Behavioural Memory Test

[e] Wechsler Adult Intelligence Scale-Third Edition

[f] Trail Making Test Parts A & B

[g] Cambridge Examination for Mental Disorders of the Elderly

that there was no interaction between frailty and age, gender or educational level in the analysis of test scores.

5.3.4 The Relationship between Frailty and Impaired Executive Functioning

Executive function was assessed using the Trail Making Test (TMT), a well-established psychomotor test originally developed as part of the Army Individual Test Battery. The TMT has been widely used in clinical evaluations for the assessment of deficits in executive cognitive functions (Bell-McGinty *et al.*, 2002; Carlson *et al.*, 1999; Lezak, 1995) and is administered in two parts. TMT Part A is a visual-scanning task; the participant is required to draw lines sequentially connecting consecutively numbered circles (1–25) randomly arranged on a page as quickly as possible. Part B adds a measure of cognitive flexibility (Bechtold-Kortte *et al.*, 2002), by asking the participant to connect the same number of circles in an alternating sequence of numbers and letters (1, A, 2, B etc.). Both parts of the tests are timed. For this analysis, we used a difference score defined as ΔTMT calculated as the difference between times (Part B–Part A). The ΔTMT score is used to control for the effect of motor speed on TMT performance and is considered a more accurate measure of executive function than the performance on Part B alone (Corrigan and Hinkeldey, 1987; Lezak, 1995). Participants in this analysis were grouped according to tertiles of ΔTMT performance with the lowest tertile (ΔTMT<70 s) representing good executive function, the middle tertile (ΔTMT = 70–156 s) representing intermediate executive function and the highest tertile (ΔTMT>156 s) representing impaired executive function. These methods were based on similar methods used by other research groups to identify impaired executive functioning (Coppin *et al.*, 2006).

A logistic regression model was then constructed to evaluate whether frailty was associated with increased odds of impaired executive functioning adjusting for age, gender and educational level. For the purposes of our regression analysis we categorized the participants into two groups, participants who were completely robust (non-frail) with 0 frailty criteria present and a frailer group consisting of participants with 1 or 2 frailty criteria who were intermediately or pre-frail and those with 3 or more criteria considered to be fully frail. The likelihood of having impaired executive functioning was increased fourfold if you were a pre-frail or frail elder even when adjusting for age, gender, educational level, and global cognition as measured by the MMSE (Table 5.6 : OR = 4.31 CI 2.24, 8.72 p = <.001).

5.4 Summary of Findings

Cognitive function was assessed using reliable tests of language, executive function, spatial ability, and verbal and nonverbal memory. A previously tested well-distributed summary score was used for the purposes of analysis. Global cognitive performance was found to be significantly poorer within both pre-frail and frail elderly. On linear regression analysis frailty retained a significant association with poorer cognitive scores even when age, gender and education were controlled for. Weakness as defined by impaired grip strength and reduced physical activity were the specific frailty criteria that inferred higher odds of reduced global cognitive performance. Pre-frail and frail elders displayed significantly poorer performance on neuropsychological tests of verbal and prospective memory, executive functioning and praxis when compared to their more robust counterparts. The likelihood of having impaired executive functioning was increased fourfold if you were a pre-frail or frail elder.

Table 5.6 Logistic Regression Model showing Odds Ratio of Frailty Determining Impaired Executive Functioning as measured using ΔTMT >/= 156secs.

Variable	B	S.E	Sig	OR	95% CI	
					Lower	Upper
Age	- 0.005	0.024	0.846	1.00	0.95	1.04
Gender	0.679	0.386	0.079	1.97	0.99	4.46
Education	**- 0.541**	**0.166**	**0.001***	**0.60**	**0.21**	**0.79**
MMSE	- 0.045	0.071	0.401	0.96	0.80	1.05
Pre-Frail & Frail	**1.433**	**0.362**	**<0.0001****	**4.20**	**2.24**	**8.72**

* = Statistically significant: P < 0.05, ** p < 0.001

SE=Standard Error, OR = Odds Ratio

The biological syndrome model of frailty even at the pre-frail stage appears to be closely associated with poorer global cognitive performance in a healthy non-demented elderly cohort. There is a close correlation with frailty and impaired executive functioning in those without established cognitive decline. Any intervention targeting frail patients should also consider the need for cognitive evaluation. Likewise, case management for a person targeting cognitive performance should perhaps contemplate the possible co-existence of the biological syndrome of frailty with an attempt to coordinate interventions to address both conditions. It is important to deepen our understanding of the relationship between frailty and health outcomes such as cognition, both of which contribute to the loss of functional independence, increased health costs and decreased quality of life for our older population.

Chapter 6

Frailty and Dementia

6.1 Introduction

Dementia refers to a group of diseases characterised by a gradual and irreversible impairment of the intellect, memory, and personality, without any alteration of conscious level. Dementia can result in a previously able-bodied and independent person becoming completely dependent. Alzheimer's disease (AD) is the most prevalent dementing disease, accounting for more than half of all cases of dementia and is currently the focus of a great deal of scientific endeavour. AD is characterised at a pathological level by the accumulation of neurofibrillary tangles and senile plaques with resultant neuronal dysfunction, cell death and cerebral atrophy. It is characterised clinically by progressive decline across a broad range of cognitive functions with resultant impairment of activities of daily living, increasing dependency and premature death. The diagnosis has traditionally been made as part of a two step diagnostic process where there is firstly identification of the dementia syndrome (a history of decline in function confirmed by clinical examination and neuropsychological tests) combined with clinical features of the AD phenotype (progressive worsening of memory and other cognitive functions with an absence of systemic disorders or other brain diseases that could account for these deficits).

6.1.1 Alzheimer's Disease and Mild Cognitive Impairment

A definite diagnosis of AD is only made when there is histo-pathological confirmation of the clinical diagnosis and the diagnoses of probable and possible AD are made on the basis of the cumulative clinical and neuroimaging characteristics as outlined in the NINDS-ADRDA criteria (McKhann *et al.*, 1984). These criteria have

recently been revised to reflect to reflect the increasing knowledge regarding the clinical and radiological features of AD (86-94% of patients present with a progressive impairment of episodic memory early in the course of the disease which correlates with pathologic change and MRI volumetric loss of medial temporal lobe structures such as the entorhinal cortex, hippocampal formation and parahippocampal gyrus) (Dubois *et al.*, 2007). Other parts of the brain become involved as the Alzheimer's pathology advances with resultant deficits in additional cognitive domains such as executive function, language, praxis, visuospatial processing and gnosis. The emergence of neuropsychiatric symptoms also constitutes a clinical characteristic of disease progression.

The stages of progression of AD may be defined according to functional categories or according to cognitive scores such as performance on mini-mental state examination (MMSE) (Folstein *et al.*, 1975), whereby ≥24 is normal or mild cognitive impairment, < 24 but > 16 is mild AD, moderate AD is < 16 but > 6 and severe AD is < 6. The prodromal (symptomatic predementia phase of AD) is generally included in the mild cognitive impairment (MCI) category, a group of patients with cognitive impairment of heterogeneous aetiology and generally unaffected activities of daily living from which 10% - 15% per year may be expected to progress to dementia. Current treatments for AD are largely symptomatic in nature and have limited effects on disease pathophysiology and progression. Current trends are towards increasing numbers of patients in the moderate to severe stages of dementia who require the greatest input in terms of community and residential based resources. The development of therapies which delay disease onset or progression are some years away and in the interim the burden of disease is set to rise markedly.

A number of important demographic and health system trends over the next few decades will lead to a rapid expansion of our global older population and with that increase the number of community dwelling elderly with significant disabilities due to dementia (Anderson and Hussey, 2000; Brookmeyer *et al.*, 1998; Hoffman *et al.*, 1996). Currently, there are about 24.3 million people with dementia in the world, with 4.6 million new cases of dementia every year. The number of people affected will double every 20 years to 81.1 million by 2040 (Ferri *et al.*, 2005). In line with population ageing, over the next three decades the number of Irish people diagnosed with dementia will also increase, from current estimates of around 38 000 to future estimates of 50 000 by 2016, 70 000 by 2026 and to over 100 000 by the year 2036 (O'Shea, 2007). It is clear that the projected explosion in the prevalence of dementia over the next 50 years will place a significant burden on the provision of care for this vulnerable older population and this underscores the importance of evaluating future clinical and policy interventions aimed at reducing dementia's impact on individuals, families and society.

6.1.2 Frailty and Alzheimer's Disease

Frailty as a distinct physiologic syndrome can be delineated from co morbidity and is known to contribute to significant health decline disability and mortality. In the Alzhemier patient it may significantly influence the burden of illness associated with this disease. The frailty syndrome has not yet been investigated in full within an AD patient cohort.Although the clinical hallmark of AD is progressive loss of memory and other cognitive abilities, several studies have shown that persons with AD also exhibit changes in mobility and body composition suggesting that many older persons with AD may be frail (Cronin-Stubbs *et al.*, 1997; Scarmeas *et al.*, 2005). Recent

work indicates that core components of frailty, including impaired grip strength, slowed gait, and low body mass index (BMI), predict subsequent development of dementia (Rosano *et al.*, 2005; Stewart *et al.*, 2005; Wang *et al.*, 2006). Similarly physical frailty has been associated with incident mild cognitive impairment and Alzheimer disease in community dwelling elders (Boyle *et al.*, 2010). To date there remains a paucity of literature available on frailty in the context of dementia and MCI. Given the belief that early intervention in the frailty pathway may lead to reversal of the syndrome, frailty may represent an important target in our attempts to minimize poorer outcomes for Alzheimer patients. It would seem appropriate to invest expertise and effort to identify the association if any between frailty and cognitive and functional impairment in AD.

6.1.3 Frailty and Quality of Life in Alzheimer's Disease

A diagnosis of AD or MCI can mean considerable heterogeneity in terms of age, comorbidity, course of illness, cognitive impairment, functional limitations, and abnormalities of behaviour. Cognitive impairment at any stage is known to profoundly affect the lives of patients and their families. Without a cure, the main question in care is how to promote wellbeing and maintain an optimal quality of life. Addressing life quality is increasingly included as part of clinical guidelines for treating cognitively impaired patients (Lucas-Carrasco, 2007). Given the complexity of dementia, there has been discussion about how best to measure the impact of cognitive impairment on individuals and their families in terms of life quality. An emerging consensus has identified a need to evaluate broad patient-rated outcomes as measured by health-related quality of life (HR-QOL).

Quality of life (QOL) and HR-QOL are often used interchangeably, with little distinction between the two concepts. HR-QOL represents health related wellbeing and so can be measured as a disease specific entity. Key dimensions of HR-QOL are physical functions, sensations, self-care/dexterity, cognition, pain/discomfort and emotional/psychological wellbeing. Understanding what contributes to HR-QOL has repeatedly shown to work for improvement in patient management. HR-QOL is recognized as an end point, perhaps equal in importance to survival and only treatments which improve HR-QOL are regarded as effective intervention even without survival benefit (Pasetto *et al.*, 2007). Knowledge of key factors that may be associated with HR-QOL in cognitively impaired patients improves our ability to intervene with preventative or supportive strategies to minimize the burden of illness. Frailty may also be a factor that influences HR-QOL in elderly who are cognitively impaired and therefore may represent a key target for intervention given its potential reversibility.

6.1.4 The Cost of Dementia Care

In the majority of Western countries the provision of dementia care is provided first and foremost by the informal care network, and for a prolonged period of time (Antonucci *et al.*, 2001; Orgogozo, 1997; Zarit *et al.*, 1999). This is mainly and most often made up of the family alone, which constitutes an essential resource in keeping the patient at home.(Brodaty and Luscombe, 1998; Murray *et al.*, 1999) When the informal care network fails, this leads to the intervention of the formal care network, with home help provided in parts of the country where an effective set-up exists, and then subsequently to institutionalisation (Schneider *et al.*, 1999) From an economic perspective, the total worldwide societal costs of dementia care were estimated to be

USD 315.4 billion in 2005 (Wimo *et al.*, 2007).Dementia is a costly condition, drawing on a variety of public and private resources, and there is increasing pressure to define the cost components with a view to improving resource allocation and accountability in this area in the long term. The annual cost of dementia in Ireland based on the best available data from 1998 was £248 million and the impact of both health inflation and changing demographics means that current figures are well in excess of this amount (O'Shea, 2000). The cumulative message from Europe wide studies is that dementia is a leading disease in terms of economic burden falling on families and on residential care facilities.

The large increase in the prevalence of dementia will generate substantial additional burdens on the formal health care system and the on the network of informal caregivers that typically provides most of the daily care required by individuals with dementia (Langa *et al.*, 2001). Due to the global burden, and especially, due to the burden on informal caregivers, dementia is the main cause for institutionalisation in the elderly (Aguero-Torres *et al.*, 2001). However, most elderly people prefer to live as long as possible in their familiar surroundings (Goldsmith, 1996). On the one hand, it may be preferable for these patients to remain in their homes, not only for economic reasons, but also because they remain able to maintain the integrity of their social network, preserve environmental landmarks, and enjoy a better quality of life. On the other hand, institutionalisation can be expedient for subjects who suffer from more severe dementia, because caring for these patients at home is a stressful and demanding process that affects caregivers' psychological and physical well-being and jeopardizes the feasibility of continued home care (Sorensen *et al.*, 2006).

In the absence of a cure for dementia it is important for future research to focus on better understanding modifiable factors driving health-care costs in dementia and cognitive impairment to continue to inform public policy responses to affect the already significant effort expended by informal caregivers(Arno *et al.*, 1999). There is evidence that relevant interventions can postpone institutionalization, be cost effective and improve quality of life for patients and caregivers (Andren and Elmstahl, 2008; Ballard *et al.*, 2002; Mittelman *et al.*, 2004; Wimo *et al.*, 1993) The identification of factors associated with drivers of both informal and more formal health-care costs, facilitates the application of health and social strategies to permit those patients with dementia to stay in their homes as long as possible.

6.2 Summary of Aims

Primary aims of this study were (i) to characterize frailty in a group of cognitively impaired community-dwelling elders and to enable a consideration of the relation, if any, between frailty and the domains of clinical heterogeneity in a group of patients with AD and MCI, (ii) to enable a consideration of the relation between HR-QOL in AD, frailty and other domains of clinical importance such as: cognition, activity limitation, behavioural disorder, carer burden and depression, (iii) to determine the role of frailty as a driver of increasing economic cost and resource utilization in the context of cognitive impairment.

6.3 Results

6.3.1 Population Demographics and Characteristics

A convienient sample of 115 cognitively impaired patients and their primary caregivers were recruited and assessed through the ECAD (Enhancing Care in

Alzheimer Disease Study), 44 men (38%) and 71 women (62%). 95 participants had a diagnosis of Alzheimer's Dementia (AD) and 20 a diagnosis of Amnestic Mild Cognitive Impairment (MCI). Summary data regarding patient clinical characteristics are shown in Table 6.1. Mean age was 74.13 (+/-9.14) years and mean MMSE score was 20.5 (6.5). Educational attainment was variable in the sample with 43.7% reporting to have completed primary level only, 32% secondary level, and 24.3% third level. Within the cognitively impaired patients 78.3% were medical card holders entitling them to access free primary care services, and 53.3% held private health insurance.

6.3.2 Characterization of the Frailty Syndrome

Frailty was characterized using the Biological Syndrome Model by Fried et al as described previously in both Chapter 2 & 3 of this thesis. Primary caregivers of the cognitively impaired participant confirmed all self-report criteria. Similar to our previous studies frailty score represented an ordinal variable of 6 criteria ranging from 0 indicating completely robust with no frailty criteria present to 5 representing complete frailty. Based on the same categorizations used in the limited current literature available investigating associations between frailty and cognitive impairment, patients with 0 criterion were classified as non-frail, those with 1- 2 frailty criteria to be intermediately frail and those with 3 or more criteria to be fully frail (Buchman *et al.*, 2007). Using our definition 51.3 % of patients could be classified as robust or not-frail, whilst 48.7% were at an intermediate or complete stage of frailty (29.6% intermediately frail, 19.1% fully frail) Figure 6.1. The only significant difference in frail criteria between either AD or MCI patients was in the category of

Table 6.1 Summary Data regarding Patient Clinical Characteristics (n = 115).

Parameter (n%)			
Gender	**Male**	**Female**	
	44(38%)	71(62%)	
Parameter		**Mean+/- S.D**	**Range**
Age (years)		74.13 (9.14)	
Cognitive Function (MMSE) [a]		20.5 (6.5)	(1-30)
Illness severity (CDR SOB) [b]		6.17 (3.78)	(0.5-18)
Neuropsychiatric Symptoms (NPI) [c]		24.38 (26.12)	(0-132)
Activities of daily living (DAD) [d]		12.52 (11.86)	(0-40)
Dependence Scale [e]		6 (3)	(0-14)
DEMQOL-Proxy [f]		93 (16)	(31-124)

[a] Mini Mental State Examination.

[b] Washington University Clinical Dementia Rating Scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.

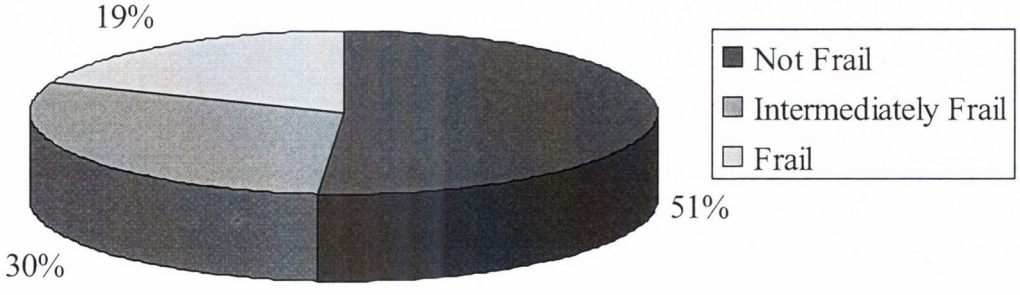
[c] Neuropsychiatric Inventory (NPI).

[d] Disability Assessment for Dementia scale.

[e] A measure of patient dependency was assessed using the Dependence Scale.

[f] Health-related Quality of Life as measured using the Dementia Specific DEMQOL-Proxy Report.

Figure 6.1 Pie Chart of Frailty Distribution in Cognitively Impaired Cohort



weight loss which occurred more frequently in the AD group (Fisher's exact test, p= 0.04). There was no significant difference in presence of frailty dependent on gender.(Fisher's exact test, p= .443) Given the pathology was a binary variable (patients either had MCI or AD) it was tested as an additional predictor variable for frailty using a proportional odds ratio model with frailty the outcome measure included as an ordinal variable. Frailty was not significantly different in either group. (OR = 2.15, CI 0.88, 5.23, p = 0.092) Therefore it was deemed both groups could be pooled for analysis.

6.3.3 The Correlates of Frailty in Cognitive Impairment

Frailty was included in all analysis as an ordinal variable with 6 categories from 0-5. Bivariate analysis using the Spearman correlation coefficient was performed to assess the strength of association between frailty and our explanatory factors which represented markers of clinical heterogeneity in our sample, to include; age, number of co-morbid illnesses, cognitive impairment, a measure of global illness severity, functional limitations and neuropsychiatric symptoms. A proportional odds ratio model was then constructed to evaluate the relationship between frailty and the explanatory factors. Variables that on bivariate analyses were associated with frailty were entered into the model determined by the strength of their association. We set the critical value for significance in all analysis at $p< 0.05$. Test of parallel lines was completed to test the proportional odds assumption and the validity of our logistic regression model. The explanatory variables that were significantly associated with frailty on bivariate analysis are shown in Table 6.2. Deteriorating functional ability, increasing neuropsychiatric symptoms, a higher number of medical comorbidities, increasing

Table 6.2 Correlates of Frailty on Bivariate Analysis

Variable	Spearman's Rho Correlation Coefficient	Significance
Fuctional limitations (DAD) [a]	0.427	p< 0.001**
Neuropsychiatric symptoms (NPI) [b]	0.333	p= 0.001**
No. of Comorbidities	0.285	p= 0.002**
Illness severity (CDR-SOB) [c]	0.270	p= 0.004**
Cognition (MMSE) [d]	- 0.223	p= 0.019*
Age	0.199	p= 0.045*

* Statistically significant p = < 0.05, ** p < 0.001

Table 6.3 Proportional Odds Model depicting Key Correlates of Frailty.

Variable	Estimate	S.E	Sig	OR	95% CI	
					Lower	Upper
Co-morbidities	**0.526**	**0.159**	**0.001****	**1.69**	**1.24**	**2.31**
Age	**0.063**	**0.023**	**0.007***	**1.07**	**1.02**	**1.12**
Fuctional limitations (DAD) [a]	0.013	0.028	0.648	1.01	0.96	1.07
Neuropsychiatric symptoms [b]	0.010	0.009	0.233	1.01	0.99	1.03
Illness severity (CDR-SOB) [c]	0.049	0.122	0.690	1.05	0.83	1.33
Cognition (MMSE) [d]	0.041	0.061	0.503	0.96	0.85	1.08

** Statistically significant p < 0.001

[a] Disability Assessment for Dementia scale

[b] Neuropsychiatric Inventory (NPI)

[c] Washington University Clinical Dementia Rating Scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.

[d] Cognition was measured using the Mini Mental State Examination

illness severity, declining cognitive scores and advancing age all correlated with escalating frailty. Having identified these significant associations we conducted ordinal logistic regression. A proportional odds model was constructed to include the variables described in Table 6.2 to determine the key correlates of frailty in our cognitively impaired older cohort (Table 6.3). Increasing number of medical comorbidities and advancing age were retained as the factors positively associated with escalating frailty. For each additional co-morbid illness, the expected odds of increasing frailty were 1.69 greater. (CI 1.24, 2.31, p = 0.001) With each advancing year, the odds of increasing frailty were 1.07 times greater. (CI 1.02, 1.12, p = 0.007). Test of parallel lines was completed to verify the proportional odds assumption in our logistic regression model. No difference was identified in the coefficients between models and so the validity of our model was confirmed. (p = 0.999)

6.3.4 The Relationship between Frailty and Quality of Life in AD.

The unadjusted mean quality of life scores by groups are displayed in Table 6.4. The *F* and *P* values were derived from a three-way ANOVA. There was a significant difference in quality of life according to frailty groups showing lower DEMQOL-Proxy scores with increasing frailty representative of poorer health-related life quality (p = 0.007). This difference was not apparent between groups defined according to either gender or age. A polynomial contrast indicated that the linear trend for DEMQOL-Proxy scores to decrease with frailty was significant at p < 0.014. Pairwise contrasts showed that the difference in marginal means between non-frail and intermediately frail groups was statistically significant at 10.54 points (95% CI 3.19, 17.88, p = 0.005). The difference in marginal means was also significant between non-frail and frail groups at 10.14 points (95% CI 2.08, 18.19, p < 0.014), however

Table 6.4 DEMQOL Scores according to Age, Gender and Frailty

	N	DEMQOL Score Mean (SD)[a]	*F*(df)[b]	*P* value	*P* value trend
Gender					
Males	39	94.90 (15.92)	0.624 (1,87)	0.432	—
Females	62	91.81 (15.34)			
Age					
50-59 years	7	98.43 (10.28)	0.630 (3,87)	0.598	0.268
60-69 years	20	92.90 (14.03)			
70-79 years	37	93.03 (11.55)			
80+ years	30	90.07 (20.70)			
Frailty					
Robust	50	98.04 (13.30)	5.314 (2, 87)	0.007	0.014*
Pre-Frail	30	87.77 (17.93)			
Frail	21	88.48 (13.62)			

* Statistically significant p = < 0.05

[a] One-way ANOVA, [b] Three-way factorial ANOVA model

there was no significant difference in means between intermediately frail and frail groups at 0.4 points (95% CI -9.12, 8.33 p = 0.928).Profile plots indicated there was no interaction between frailty and age or gender in the analysis of quality of life scores (Figure 6.2 and Figure 6.4)

6.3.5 The Correlates of Quality of Life in those with Cognitive Impairment

A priori sample size calculation for multiple regression analysis of the DEMQOL-Proxy showed that to detect a medium effect size (power = 0.8 and alpha = 0.05) with 7 predictor variables required a minimum sample size of 103. Given our sample size was in excess of this at 115 participants it is presumed we had more than sufficient power to evaluate the variables of largest effect under investigation. Bivariate analysis using the Spearman correlation coefficient was carried out to assess the strength of association between a number of independent variables and HR-QOL as measured by the DEMQOL-Proxy. Independent variables included in our analysis were a measure of cognitive impairment MMSE, a measure of functional limitations (DAD Score), A measure of global severity of illness using the CDR-Sum of Boxes Score, a measure of neuropsychiatric symptoms (NPI Inventory) as well as our measure of frailty. Caregiver factors that have been shown to influence quality of life proxy reports in cognitive impairment include carer depression and burden. We therefore included a measure of both in our analysis to evaluate their influence on quality of life scores.

Bivariate analysis revealed that neither age nor gender had a significant correlation with HR-QOL scores (Spearman's rho, p = 0.512, p = 0.147, respectively). Similarly neither caregiver depression scores nor burden scores correlated significantly with HR-QOL. (Spearman's rho, p = 0.399, p = 0.103, respectively) The explanatory

Figure 6.2 Means Plot of DEMQOL Scores Dependent on Age and Frailty

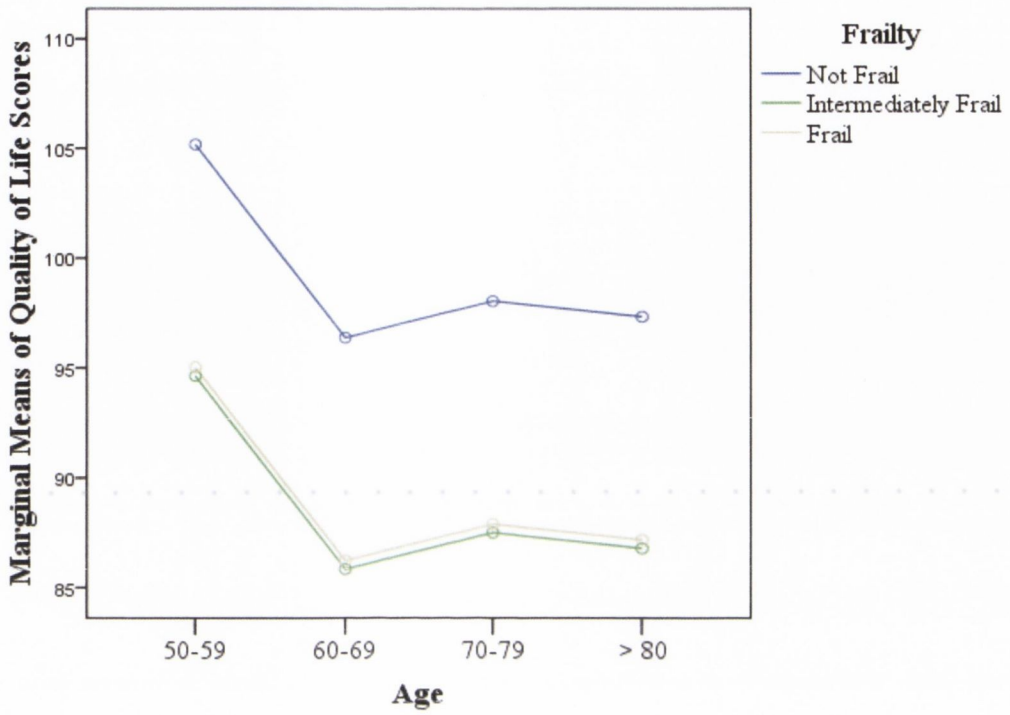
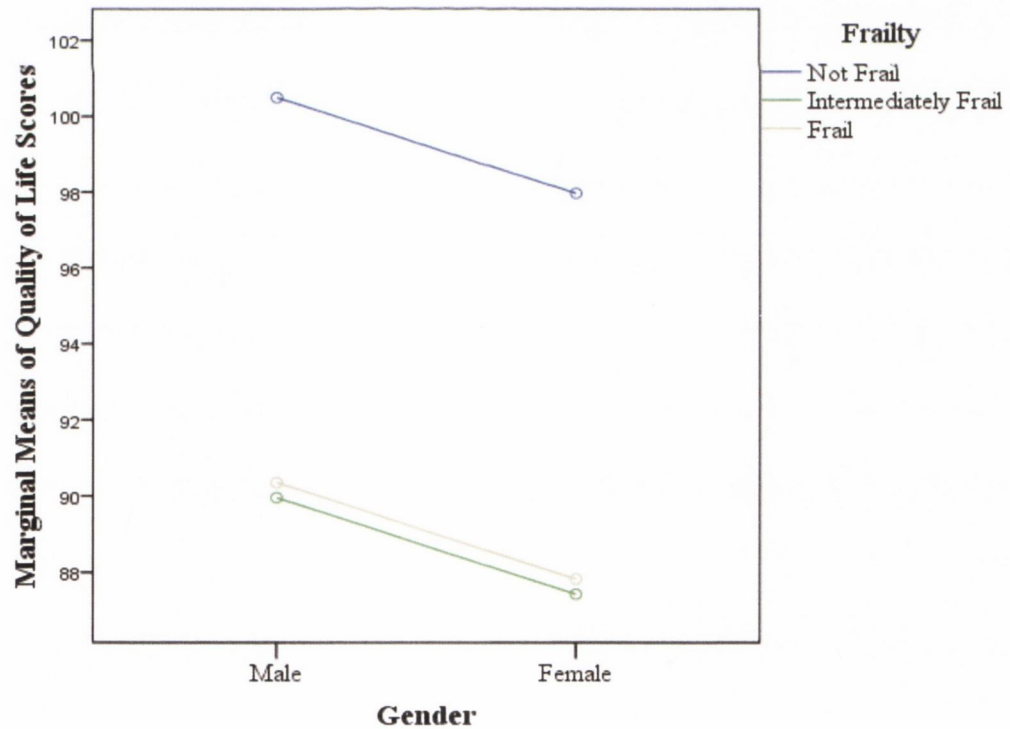


Figure 6.3 Means Plot of DEMQOL Scores Dependent on Gender and Frailty



variables that were significantly associated with the DEMQOL-proxy on bivariate analysis are shown in Table 6.5, they include neuropsychiatric symptoms ($p < 0.0001$), functional limitations ($p < 0.0001$), illness severity ($p = 0.001$) and frailty ($p = 0.001$). Cognition determined by the MMSE showed a trend towards correlation but did not quite reach statistical significance ($p= 0.058$).

To evaluate which patient variables best predicted HR-QOL, neuropsychiatric symptoms (NPI), functional status (DAD), dementia severity (CDR-SOB) and frailty were entered into a sequential multivariate regression model dependent on their association with the outcome variable, the DEMQOL-proxy. Neuropsychiatric symptoms and frailty were retained in the optimal model which explained 26.4% of the variance in observed HR-QOL (Table 6.6). The sample was then split into patients with milder impairment (MMSE $\geq$ 20, n = 71) and moderate to severe disease (MMSE < 20, n = 42) to determine if the relationships changed according to severity of cognitive impairment. The same stepwise linear regression analyses were conducted in both groups. In patients with mild impairment, frailty and neuropsychiatric symptoms were retained as the optimal predictors ($p = 0.037$, $p \leq .001$, respectively) which explained 36.2% of the variance in HR-QOL. In patients with moderate to severe impairment, functional limitations remained the sole predictor ($p = 0.017$) explaining 37.7% variance in HR-QOL.

Given our sample was split into patients with milder impairment and moderate-to-severe disease a post-hoc statistical power calculation for multiple regression analysis was completed for each subset. Given an R2 (0.362) for Model 2 (MMSE $\geq$ 20), the observed power with four predictors, an alpha of 0.05 and a sample size of 40 was

Table 6.5 Bivariate Correlates of HR-QOL in Cognitively Impaired Patients

Variables	Spearman's rho	Significance
Age	-0.068	p = 0.512
Gender	-0.146	p = 0.147
Cognition (MMSE)	-0.192	p = 0.058
Caregiver Depression (CESD-10)	-0.090	p = 0.399
Caregiver Burden (Zarit)	-0.173	p = 0.103
Fuctional limitations (DAD score)	**-0.497**	**p < 0.0001****
Illness severity (CDR SOB)	**-0.333**	**p = 0.001***
Neuropsychiatric symptoms	**-0.601**	**p < 0.0001****
Frailty	**-0.328**	**p = 0.001***

* = Statistically significant: P < 0.05, ** p < 0.001

[a] Mini Mental State Examination

[b] Center for the Epidemiological Studies-Depression (CESD-10) Scale

[c] Zarit Burden inventory Disability Assessment for Dementia scale

[d] Washington University Clinical Dementia Rating Scale Sum of Boxes (SOB) Score

[e] Disability Assessment for Dementia Scale

[f] Neuropsychiatric Inventory (NPI)

Table 6.6

Sequential Multiple Regression Models of Quality of Life in the Total Sample and in Patients with Mild and Moderate to Severe Cognitive Impairment.

	Beta	Significance	R^2
Model 1: Total Sample (n = 115)			
Neuropsychiatric symptoms	**-0.377**	**p = 0.001***	0.264
Functional limitations (DAD)	-0.118	p = 0.446	
Illness severity (CDR SOB)	0.051	p = 0.707	
Frailty	**-0.192**	**p =0.047***	
Model 2: MMSE ≥ 20 (n = 71)			
Neuropsychiatric symptoms [a]	**-0.505**	**p < 0.0001****	0.362
Functional limitations (DAD)[b]	0.030	p = 0.845	
Illness severity (CDR SOB)[c]	-0.070	p = 0.595	
Frailty	**-0.240**	**p = 0.037***	
Model 3: MMSE < 20 (n = 42)			
Neuropsychiatric symptoms	-0.121	p = 0.567	0.377
Functional limitations (DAD)	**-0.798**	**p = 0.017***	
Illness severity (CDR SOB)	0.472	p = 0.113	
Frailty	-0.212	p = 0.250	

* = Statistically significant: P < 0.05, ** p < 0.001

[a] Neuropsychiatric Inventory (NPI)

[b] Disability Assessment for Dementia Scale

[c] Washington University Clinical Dementia Rating Scale Sum of Boxes (SOB) Score

0.97. For Model 3 (MMSE <20) with an R2 of 0.377, four predictors, an alpha of 0.05 and a sample size of 71 the observed power was calculated to be 0.99.

6.3.6 The Effect of Frailty on Costs of Care

Two cost outcomes were identified, estimated and used as dependent variables in the statistical analysis. These included: (i) formal health and social care costs; (ii) daily informal caregiving costs. Formal health and social care costs were estimated for a set of resource activities including general practice visits, hospitalizations, outpatient clinic consultations, accident and emergency visits, respite care, meals on wheels services, and additional health and social care professional consultations (registered nurse, physiotherapist, psychologist, chiropodist, occupational therapist, social worker, and home help aides). Data on utilisation over a six month period was collected and the total costs of care estimated by applying the appropriate unit cost estimate for each resource activity. Unit cost data were obtained from a variety of national Irish data sources and were adjusted to constant Euros in 2008 prices using an appropriate inflation index (CSO, 2010) (Table 6.7).

Daily informal care costs were calculated from estimates of caregiving hours for each patient as measured by the Resource Utilisation in Dementia instrument (RUD-Lite) (Wimo and Winblad, 2003). This includes the total number of hours dedicated to basic activities of daily living (ADL), instrumental activities of daily living (IADL) and supervising the patient over the previous month. Hours of care per task per carer were summed to obtain an estimate of total daily caregiving hours per patient. Informal care was valued using the opportunity cost method as data were available on the labour force participation status for each carer. To this end, carers were

Table 6.7 Unit Cost Estimates: Health, Social and Informal Care

Resource Activity	Activity	Unit Cost (€)	Source
Formal Health and Social Care			
Hospital Admissions	1 Admission	5030	Casemix Unit, DOHC
A&E Visit	Per Visit	273	Casemix Unit, DOHC
Geriatrician Visit (OPD)	Per Visit	160	Casemix Unit, DOHC
Neurologist Visit (OPD)	Per Visit	160	Casemix Unit, DOHC
Psychiatrist Visit (OPD)	Per Visit	160	Casemix Unit, DOHC
Physiotherapist Visit	Per Visit	29	Salary Scales, DOHC
Occupational Therapist Visit	Per Visit	29	Salary Scales, DOHC
Social Worker Visit	Per Visit	29	Salary Scales, DOHC
Other (Specialist) Visit	Per Visit	29	Salary Scales, DOHC
GP Visit	Per Visit	50	Smith et al 2010
Respite Day Care	Per Visit	100.32	O'Shea E. & Kennelly B 2008
Home Help Visit	Per Visit	19	Salary Scales, DOHC
Meals on Wheels	Per Visit	6.90	O'Dwyer et al 2008
Registered Nurse Visit	Per Visit	33	Salary Scales, DOHC
Informal Care			
Carers in Employment	Per Hour	22.36	Central Statistics Office
Carers not in Employment	Per Hour	5.59	Central Statistics Office

categorised as 'employed' and 'unemployed'. For the 'employed' category, the opportunity cost of time was valued at the average industrial wage of €22.36 per hour (McDaid, 2001). For the 'unemployed' category, the opportunity cost of time was valued as a percentage (25%) of the average industrial wage; that is, the value adopted for the analysis was €5.59 per hour (McDaid, 2001). The daily informal care cost per patient was calculated by multiplying total care hours by the relevant hourly wage rate.

When all individual resource activities were costed and summed, the mean cost per patient of health and social care was €2141 (SD: 3845) over 6 months. In respect of daily informal care, individuals received an average of 1.23 (SD: 2.3) hours for basic ADLs, 2.65 (SD: 2.62) hours for IADLs, and 0.60 (SD: 1.1) hours for supervision. This translated into a mean cost per patient of €43 (SD: 64) per day. The unadjusted mean daily informal care costs by groups are displayed in Table 6.8. The *F* and *P* values were derived from a three-way ANOVA. There was a significant difference in informal care costs according to frailty groups showing higher mean costs with increasing frailty representative of greater daily informal care costs ($p < 0.0001$). This difference was not apparent between groups defined according to either gender or age. A polynomial contrast indicated that the linear trend for informal care costs to increase with frailty was significant at $p < 0.0001$. Pairwise contrasts showed that there was no significant difference in marginal mean costs between non-frail and intermediately frail groups (95% CI -45.7, 10.6 $p = 0.219$). However there was a significant difference in marginal mean daily informal costs between non-frail and frail groups at 79.26 euros (95% CI -110.61, -47.90, $p < 0.0001$), as well as a significant difference in mean daily costs between intermediately frail and frail groups

Table 6.8 Informal Care Costs according to Age, Gender and Frailty

	N	Informal Care Costs Mean (SD)[a]	*F*(df)[b]	*P* value	*P* value trend
Gender					
Males	44	38.68 (60.01)	0.000 (1,94)	0.985	—
Females	71	45.09 (66.46)			
Age					
50-59 years	7	47.67 (72.64)	0.343 (3,94)	0.598	0.613
60-69 years	20	44.02 (60.65)			
70-79 years	41	38.85 (56.15)			
80+ years	33	53.52 (76.96)			
Frailty					
Robust	59	22.88 (38.92)	12.814 (2, 94)	$< 0.0001^{**}$	$< 0.0001^{**}$
Pre-Frail	34	40.23 (55.75)			
Frail	22	99.34 (92.77)			

** Statistically significant $p < 0.001$

[a] One-way ANOVA, [b] Three-way factorial ANOVA model

at 61.70 euros (95% CI -95.22, -28.19 $p < 0.0001$). Profile plots indicated there was no interaction between frailty and age or gender in the analysis of daily informal care costs (Figure 6.4 and Figure 6.5). The unadjusted mean formal health and social care costs by groups are displayed in Table 6.9. There was no significant difference in formal health and social care costs across age, gender or frailty groups.

To further evaluate the effect of frailty multiple regression models were built to include frailty and other factors previously established to act as drivers of increasing care costs. The independent variables included in the models were frailty, a measure of patient dependence, a measure of neuropsychiatric symptoms, cognitive scores, number of medical co-morbidities and age. Daily informal care costs and formal health and social care costs acted as the dependent variables in the regression models. As medical card status and private health insurance status have both been shown to influence the utilisation of health care services in Ireland (MacGregor and O'Neill, 2007) these variables were also included in the model evaluating the predictors of formal and social care costs. Variables were entered into a sequential multivariate regression model dependent on their association with the outcome variable

The results from the multivariate regression analysis are presented in Table 6.10. Patient dependence, frailty and number of co-morbid illnesses were retained in the optimal model which explained 43.3% of the variance in observed daily informal care costs in dementia and cognitively impaired patients. Dependence was the sole factor retained in an optimal model explaining 19% of the variance in formal health and social care costs.

Figure 6.4 Means Plot of Informal Care Costs Dependent on Age and Frailty

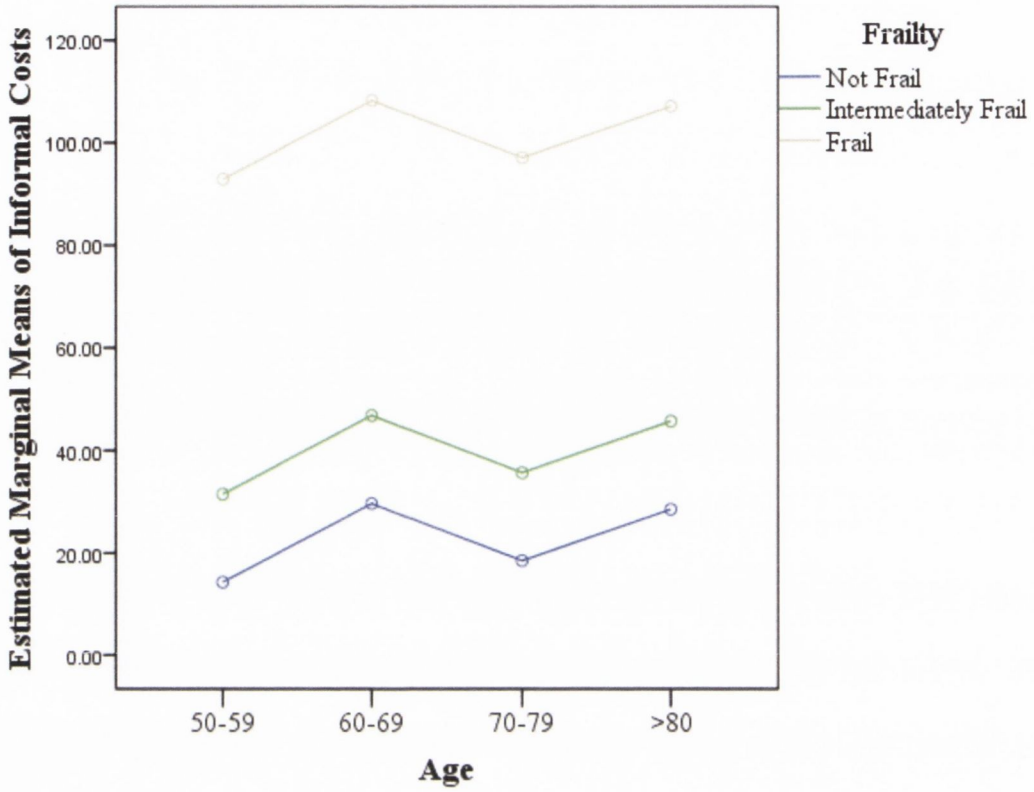


Figure 6.5 Means Plot of Informal Care Costs Dependent on Gender and Frailty

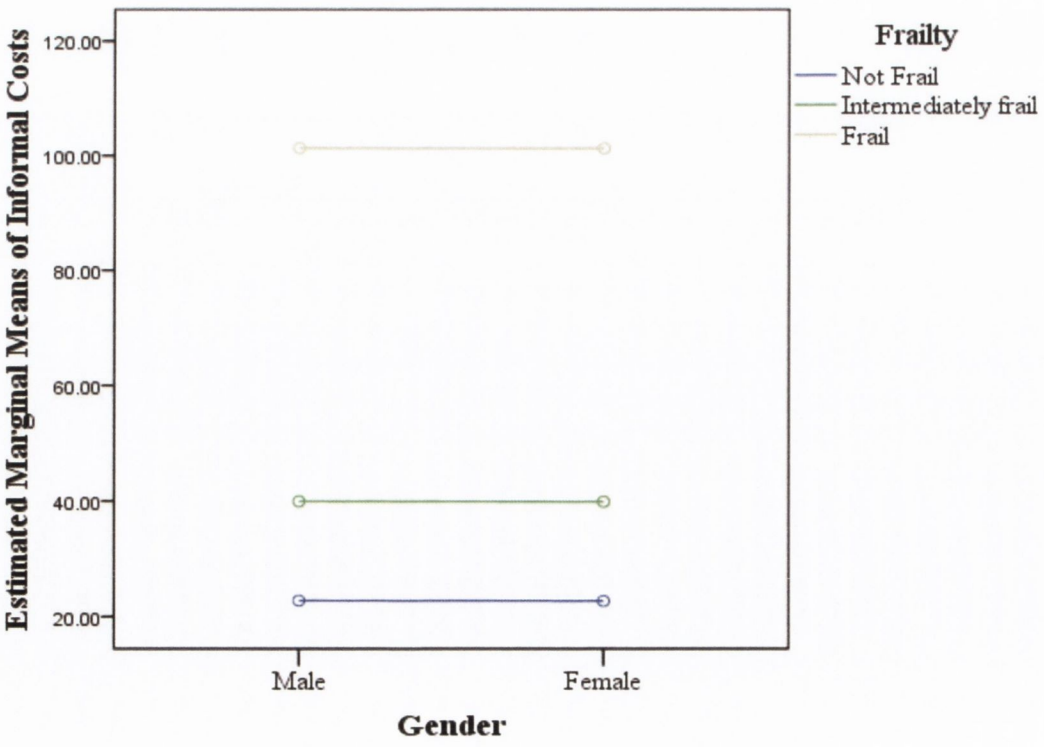


Table 6.9 Formal Health and Social Care Costs according to Age, Gender and Frailty

	N	Informal Care Costs Mean (SD)[a]	*F*(df)[b]	*P* value	*P* value trend
Gender					
Males	44	1535 (2360)	0.965 (1,94)	0.328	—
Females	71	2517 (4503)			
Age					
50-59 years	7	246 (370)	1.348 (3,94)	0.264	0.071
60-69 years	20	1949 (2863)			
70-79 years	41	1785 (3411)			
80+ years	33	2971 (3594)			
Frailty					
Robust	59	1572 (3336)	1.495 (2, 94)	0.230	0.100
Pre-Frail	34	2469 (4032)			
Frail	22	3161 (4669)			

[a] One-way ANOVA, [b] Three-way factorial ANOVA model

Table 6.10 Sequential Multiple Regression Models of Drivers of Informal Care Costs and Formal Health and Social Care Costs.

	Beta	Significance	R^2
Model 1: Informal Care Costs			
Age	0.005	p = 0.957	0.433
Gender	0.002	p = 0.976	
Patient Dependence [a]	**0.401**	**p = 0.001***	
Frailty	**0.361**	**p < 0.0001****	
Neuropsychiatric Symptoms [b]	0.060	p = 0.540	
Cognition (MMSE) [c]	- 0.063	p = 0.528	
No. of Co-Morbidities	**- 0.233**	**p = 0.011***	
Model 2: Formal Health and Social Care Costs			
Age	0.049	p = 0.689	0.190
Gender	0.142	p = 0.172	
Patient Dependence [a]	**0.459**	**p = 0.002***	
Frailty	0.001	p = 0.992	
Neuropsychiatric Symptoms [b]	- 0.092	p = 0.443	
Cognition (MMSE) [c]	0.114	p = 0.361	
No. of Co-Morbidities	- 0.042	p = 0.702	
Medical Card	0.106	p = 0.350	
Private Insurance	- 0.047	p = 0.665	

* = Statistically significant: P < 0.05, ** p < 0.001

[a] A measure of patient dependency was assessed using the Dependence Scale.

[b] Neuropsychiatric Inventory (NPI)

[c] Mini Mental State Examination

6.4 Summary of Findings

We present preliminary data that suggest frailty is a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity. An association between frailty and ageing has already been shown in older cohorts (Lipsitz, 2008). Our findings suggest that in the cognitively impaired it continues to be an important correlation, other factors notwithstanding. Increasing burden of co-morbid illness inferring a higher likelihood of frailty is also consistent with current theory, where the cumulative effect of multiple age and disease related impairments leads to a degradation of physiologic systems. Frailty emerges from this vulnerable health state and may contribute to further decline in functional performance and an increased risk of poorer outcomes (Boyd *et al.*, 2005; Rockwood, 2004). Optimized management of co-morbid illness in dementia patients and adoption of stringent preventative health strategies in those at the stage of MCI may play a role in minimizing the health impact of frailty in this group.

Over half of our cognitively impaired participants could be classified as robust or not-frail and a large proportion, almost 30% were at a level of intermediate frailty a stage considered to be potentially reversible.We have identified an important correlation between advancing frailty and health related quality of life in cognitively impaired patients. When linear regression models were constructed, increasing neuropsychiatric symptoms and frailty were the key predictors of HR-QOL in the total sample. However when we evaluated the sample according to cognitive status we found that increasing frailty and neuropsychiatric symptoms were more significant determinants of HR-QOL in the earlier stages of disease whilst deteriorating functional ability was

the most important determinant of HR-QOL as disease progressed. The importance of identifying frailty as a key factor associated with HR-QOL in the earlier stages of cognitive impairment and dementia lies in the reversibility of frailty at an early stage and its potential role as a novel target for intervention (Fried *et al.*, 2004).

Further findings from this study suggest that frailty is also associated with increased costs of care for dementia and cognitively impaired patients. Frailty retained a strong association with daily informal care costs even in the context of other known risk factors for increasing care costs such as dependence and co-morbid illnesses (Taylor *et al.*, 2001; Zhu *et al.*, 2008). Thus, interventions that reduce frailty as well as patient dependence on others may be associated with cost savings. Such information is of particular importance for clinicians and policymakers who are charged with planning for future care needs for patients with dementia in Ireland and elsewhere.

Chapter 7

Frailty in Dementia Caregivers

7.1 Introduction

The global prevalence of dementia is rising and it represents an increasing challenge for older adults, caregivers, families and healthcare systems worldwide (Ferri et al., 2005). In the Irish context recent figures from the Central Statistics Office predict a proportional increase in the population aged over 65 from 11.03% in 2006 to a possible high of 18.5% in 2026 (Walsh, 2008). Given that dementia is largely an age-related disease it has been estimated that the number of patients with dementia may rise from an estimated 38,000 people in 2006 to exceed 70,000 by 2026 (O'Shea, 2007). It is clear that the family bears the greatest burden associated with dementia care. Approximately three-quarters of people with dementia live at home and traditionally the state only intervenes when family care is absent or breaks down (O'Shea and O'Reilly, 1999). Indeed family care is used as a substitute for community care and previous data from an opportunistic sample of 98 informal carers of patients with dementia in Ireland indicated that two thirds felt completely overwhelmed by the experience (O'Shea, 2003). Informal caregivers represent a valuable and frequently neglected resource.

7.1.1 The Effect of the Caregiving Role

Caregivers bear more than the simple financial burden of caring for patients with dementia. Providing care for a relative with any disability is accompanied by a considerable emotional, psychological and physical cost. Informal caregivers report higher levels of depression and anxiety, use psychotropic medication more frequently, engage in fewer protective health behaviours, and are at increased risk of illness and

mortality (Clipp and George, 1990; Schulz and Beach, 1999a; Vitaliano, 1990, 1996, 2003). Nearly half of caregivers in some studies meet diagnostic criteria for depression, many with no history of depression prior to assumption of the caregiving role (Clyburn *et al.*, 2000). Adverse caregiver outcomes have been robustly associated with poorer patient outcomes highlighting the need to identify factors relating to caregiver well being and attempt to address them (Kramer, 1993). Late intervention to address caregiver needs is likely to lead to increased caregiver distress and caregivers who experience a more abrupt entry into the caregiving role are more likely to institutionalise their relatives (Gaughler, 2005). A smooth transition to the caregiving role may be critical to continued success of caregiving at home.

For this reason identifying factors that may influence caregiver outcomes positively is becoming increasingly important due to our knowledge that poor caregiver outcomes are associated with poor patient outcomes also.(Ostir, 2004) The concept of positive health is more than the mere absence of disease or disability, it implies full functioning or efficacy of mind and body as well as social adjustment.The changing demographics of Irish society mean an increasing number of patients will be diagnosed with dementia in the years to come. There is currently little information regarding the psychosocial consequences of dementia in the Irish context. There is particularly little information regarding the informal carers of patients with dementia who provide the majority of all care provision in the home with little professional input or support from formal services. An increased understanding of the health factors associated with the demands placed on caregivers will facilitate effective planning of potential interventional strategies to achieve improved outcomes for patients and carers alike.

Many new families each year set upon a long trajectory of caring for a person with dementia, a trajectory referred to by certain authors as the 'caregiver career' (Aneshensel *et al.*, 1995; Keady and Nolan, 2003). Of the estimated 4.5 million individuals with AD, more than 70% live at home, where family and friends provide nearly 75% of their care, the amount of time that primary caregivers spend providing informal care to their loved ones with dementia ranges from 69 to 117 hours per week (Acton, 2002; Willette-Murphy *et al.*, 2006). The stress and burden that accompanies caring for individuals experiencing the slow progressive deterioration of AD can have both negative physical and emotional health effects. In addition to physical assistance with activities of daily living, many of these caregivers help with instrumental activities of daily living, face challenging behavioural problems, provide financial assistance, and navigate the complex health care system in an effort to meet the health care needs of the care recipient. The very nature of the caregiving role therefore often leaves little time or resources for caregivers to attend to their own health needs and health promoting practices.

The dominant conceptual model for caregiving assumes that the onset and progression of chronic illness and physical disability are stressful for both the patient and the caregiver. Caregiving has all the features of a chronic stress experience: It creates physical and psychological strain over extended periods of time, is accompanied by high levels of unpredictability and uncontrollability, has the capacity to create secondary stress in multiple life domains such as work and family relationships, and frequently requires high levels of vigilance (Schulz and Sherwood, 2008). As a result of these stressors, the caregiver may experience effects such as psychological distress,

impaired health habits, physiologic responses, psychiatric illness, physical illness, and even death (Christakis and Allison, 2006; Langa *et al.*, 2001; Pinquart and Sorensen, 2003, 2007; Pinquart and Sorenson, 2003; Schulz and Beach, 1999b; Schulz *et al.*, 1995; Vitaliano *et al.*, 2003). The detrimental psychological effects of caregiving are generally more intensive than the physical effects. Caregiver's deterioration in health is often moderated by individual differences in resources and vulnerabilities, such as socioeconomic status, prior health status, and level of social support. Older caregivers, people of low socioeconomic status, and those with limited support networks report poorer psychological and physical health than caregivers who are younger and have more economic and interpersonal resources (Pinquart, 2001; Schulz *et al.*, 1995; Vitaliano *et al.*, 2003).

7.1.2 Frailty and the Caregiving Role

Given that caregiving can be detrimental to health, it is appropriate to investigate what aspects of the caregiving experience account for these effects. It is thought that the multisystem dysregulations associated with frailty become clinically apparent when unmasked by stressors (Clyburn LD, 2000). Recent studies have found elevated plasma levels of the biological markers associated with frailty such as IL-6 and CRP to be linked with the effects of Alzheimer caregiving stress and age (Clyburn LD, 2000). Despite this, to date no study has looked at the clinical frailty phenotype as a whole within dementia caregivers. Previously identified primary stressors in caregiving such as severity of care recipient cognitive impairment, level of help required for daily living and patient neuropsychiatric symptoms may be associated with emerging frailty in caregivers. Secondary stressors associated with dementia

caregiving such as perceived stress, caregiver burden, relationship quality, loneliness and isolation may also have an association.

Research examining the role of psychological factors within the continuum of frailty in dementia caregivers would be beneficial. The benefit of this work will be apparent both to primary caregivers and those they are caring for. Knowledge of contributing factors that may be associated with poorer caregiver outcomes improves our ability to intervene with preventative or supportive strategies to minimize the burden of illness on both patients and their caregivers. In general, caregiver interventions have been found to have meaningful effects and reviews have called for futher research to guide effective targeting of symptoms and ensure maximal therapeutic benefit from future interventional strategies (Brodaty et al., 2003).

7.2 Summary of Aims

Primary aims of this study are to; (i) investigate the presence of clinical frailty markers in a sample of primary caregivers whose care recipients have a diagnosis of possible/probable Alzheimer's disease, (ii) to establishing a detailed clinical picture of both patient and caregiver related drivers of carer frailty. A key focus will be on the dynamics of the carer-patient relationship carer stress and burden, mutuality and preparedness for the caregiving role, carer isolation and loneliness and how these psychological aspects of the caregiving role contribute to emerging frailty. We expect our findings may prove beneficial in identifying areas for future intervention studies and rehabilitation programmes in which the aim is to improve health outcomes for caregivers.

7.3 Results

7.3.1 Population Demographics and Characteristics

108 primary caregivers of Alzheimer dementia (AD) and mild cognitive impairment patients were assessed. Caregivers were classified according to their age as either younger caregivers (Age < 65, n = 47) or older caregivers (Age ≥ 65, n = 61). Summary data regarding dementia patients is displayed in Table 7.1. Almost 62% of dementia patients were female with a mean age of 74 ± 9. There was an acceptable spread of educational level across the group of cognitively impaired participants. Mean MMSE score was 20 ± 6, with a mean CDR Sum of Boxes score of 6.17 ± 3.78. Both the MMSE and Clinical Dementia Rating Sum of Boxes score represent the severity of cognition and global performance in dementia patients. These mean scores would reflect a 'moderate' level of disease severity. As our analysis involved looking at the two groups of caregivers both younger and older we compared dementia severity scores within both groups to ensure there was no difference in severity of illness for care recipients of either group. The mean MMSE score and CDR Sum of Boxes score of care recipients within the two groups of older and younger caregivers was not found to be significantly different (Student-t test p = 0.489, p = .137 respectively). Figure 7.1 shows the breakdown of the relationship between caregiver and care recipient with a large proportion almost 67% representing spousal caregivers.

Summary data regarding younger and older caregivers is displayed in Table 7.2 and Table 7.3. The gender split across the two groups was almost equivalent, mean age for older caregivers was 76 ± 6, for younger caregivers it was 51 ± 10. There were a higher proportion of single caregivers within the younger category with 23.4% being

Table 7.1 Population Characteristics Alzheimer's Dementia Patients (n = 108)

Gender (females) 61.7%	
Age (mean [SD]) 74 (9)	
Education:	Primary schooling only 39.1%
	Post primary education 28.6%
	Third-level 21.6%
Mini-mental state examination (mean [SD]) 20 (6)	
CDR Sum of Boxes[a] (mean [SD]) 6.173 (3.78)	
Disability in Dementia Score (mean [SD]) 12.52 (11.86)	
Neuropsychiatric Inventory 24.38 (26.12)	

[a] Washington University Clinical Dementia Rating Scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.

Figure 7.1 Relationship of Caregiver to Care Recipient

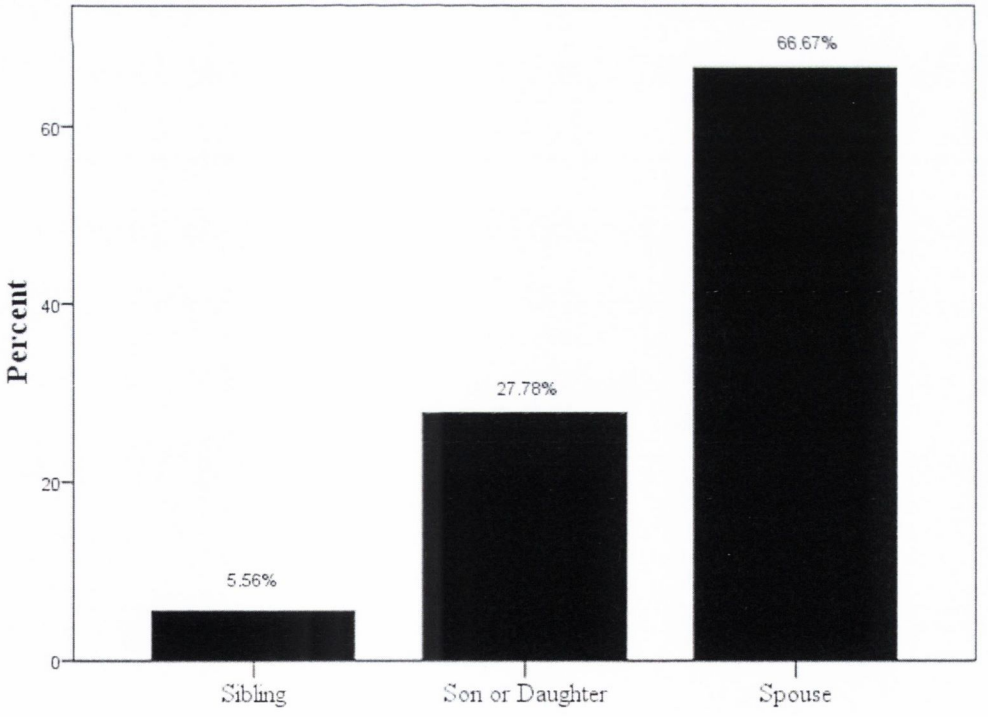


Table 7.2 Population Characteristics Older Caregivers ≥ 65 years (n = 61)

Gender (females) 51.7%
Age (mean [SD]) 76 (6)
Care Recipient MMSE Score (mean [SD]) 21.05 (6.36)
Married 96.7%
Widowed 3.3%
Living with care recipient 96.7%
Aware of Support Groups 20.0%
Member of Support Group 5.0%
Receiving Home Help 20.0%
Care recipient attending day care at least once a week 13.3%
Received respite care 10%

Table 7.3 Population Characteristics Younger Caregivers < 65 years (n =47)

Gender (females) 57.4%
Age (mean [SD]) 51 (10)
Care Recipient MMSE Score (mean [SD]) 20.18 (6.37)
Married 72.3%
Single 23.4%
Separated/Divorced 4.3%
Living with care recipient 42.6%
Aware of Support Groups 40.4%
Member of Support Group 12.8%
Receiving Home Help 38.3%
Care recipient attending day care at least once a week 21.3%
Received respite care 17.1%

single and 4.3% divorced compared to just 3.3% of older caregivers being widowed. There was a higher proportion of older caregivers who lived with their care recipient at 96.7% compared to younger caregivers at 42.6% (Fisher's exact test, $p < .001$) A higher proportion of younger caregivers were more aware of dementia support groups, were members of dementia support groups, were receiving home help and had engaged their care recipient in day or respite care. Figures 7.2 & 7.3 show the employment status of both groups of caregivers with the majority of older caregivers being retired whilst more of the younger caregivers continued in some form of employment.

7.3.2 Characterization of the Frailty Syndrome

Frailty was characterized using the Biological Syndrome Model by Fried et al as described previously in both Chapter 2 & 3 of this thesis. On application of the Fried frailty criteria 57(53%) of the total group of caregivers could be considered robust, 49 (45%) were categorised as pre-frail and only 2 (1.9%) caregivers were completely frail (Figure 7.4). Within younger caregivers (< 65), 30 (63.8%) were robust with no frailty criteria present and 17 (36.2%) were pre-frail, none of the younger caregivers fulfilled sufficient criteria to be considered fully frail (Figure 7.5).Whereas within older caregivers (≥ 65) only 27 (44.3%) were considered robust, 31 (46.3%) were categorised as pre-frail and 2 (3.4%) as fully frail. Given the minimal number of caregivers who could be defined fully frail and for the purposes of our analysis we categorized frailty into two groups, caregivers who were completely robust (non-frail) with 0 criterion present and a frailer group consisting of caregivers with 1 or 2 frailty criteria who were intermediately or pre-frail and those with 3 or more criteria considered to be fully frail. Being at a pre-frail or intermediate stage of frailty has

Figure 7.2 Employment Status of Caregivers < 65 years

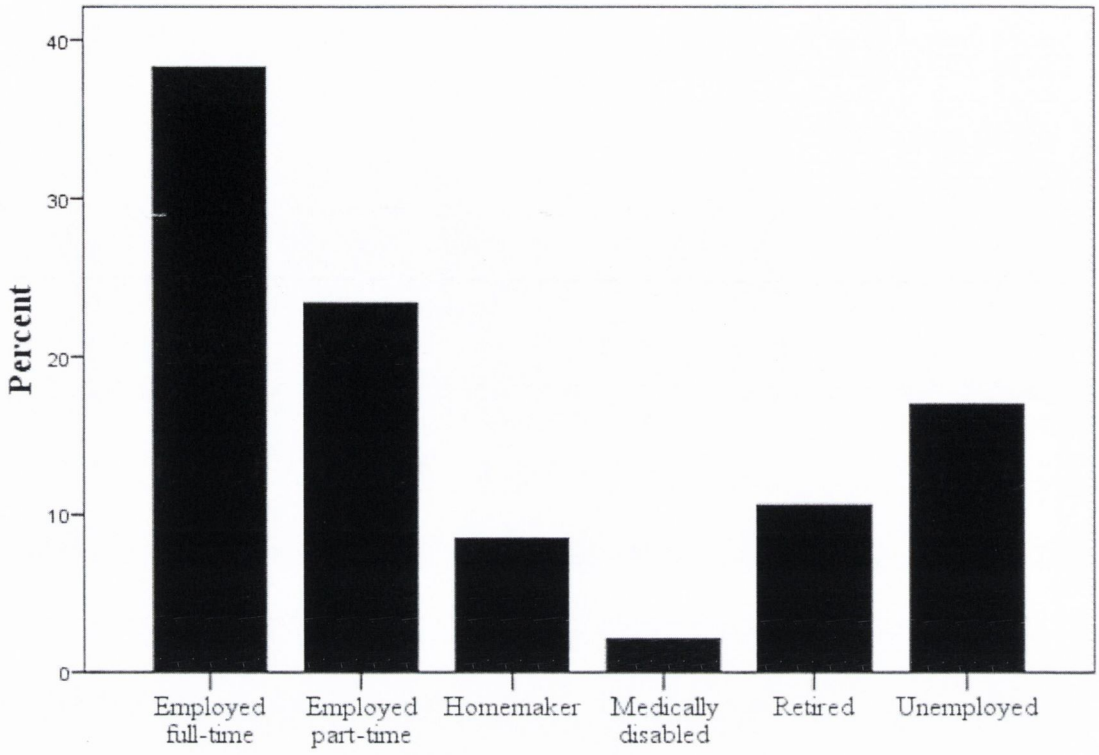


Figure 7.3 Employment Status of Caregivers ≥ 65 years

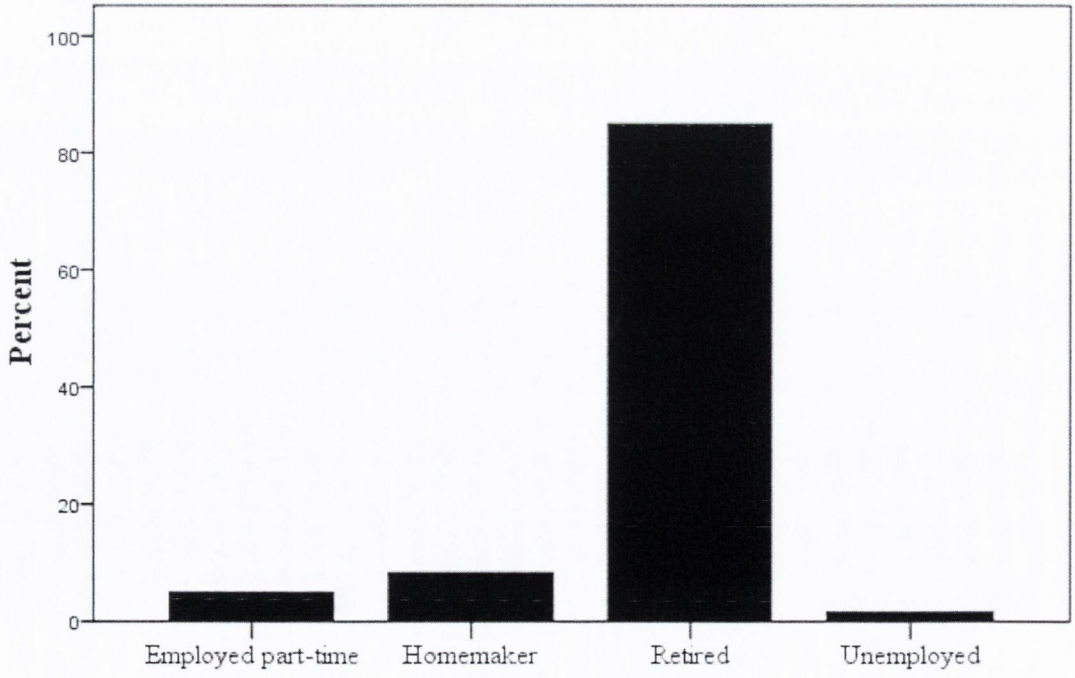


Figure 7.4 Pie Chart of Frailty Distribution in Alzheimer Caregivers

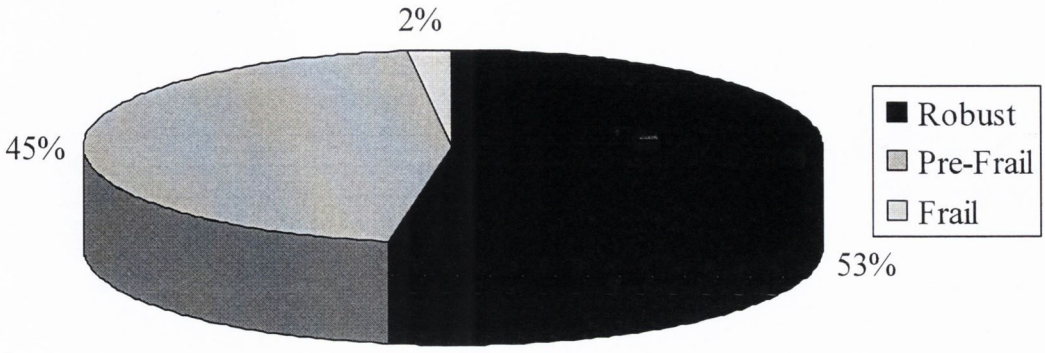


Figure 7.5 Pie Chart of Frailty Distribution in Younger Caregivers (<65)



consistantly been shown to infer risk of developing full-blown frailty and also a high risk of poorer outcomes when compared to non-frail individuals (Fried *et al.*, 2004).The difference in frailty as defined above between younger and older caregiving groups did not reach statistical significance (Figure 7.6: Fisher's exact test, $p = 0.078$). The only significant difference in frail criteria between either younger or older caregivers was in the category of grip strength which occurred more frequently in the older group (Table 7.4 Fisher's exact test, $p= 0.023$).

7.3.3 Frailty and Psychological Health in Caregivers

A number of measures were used to determine the psychological health status of caregivers. These included an assessment of perceived stress, caregiver burden, depression, loneliness and social isolation as well as a measure of the positive aspects of caregiving. We also included measures capturing the strength of the relationship between caregiver and care recipient as measured by a mutuality scale, a measure of readiness or preparedness for the caregiving role as assessed by a caregiving preparedness scale, and an assessment of recent life events. These measures were evaluated in both younger and older caregivers dependent on whether they could be considered robust with no frailty criteria present or they fulfilled > 1 frailty criteria which represented those caregivers potentially transitioning to full-blown frailty. Student-t tests were used to compare the mean psychological health scores across the frailty groups in both younger and older caregiver categories.

Within older caregivers, the frailer group had higher mean life events scores reflective of an increased incidence of recent significant lifetime events (Table 7.5). Frailer older caregivers also had higher mean perceived stress scores when compared to

Figure 7.6 Pie Chart of Frailty Distribution in Older Caregivers (≥ 65)

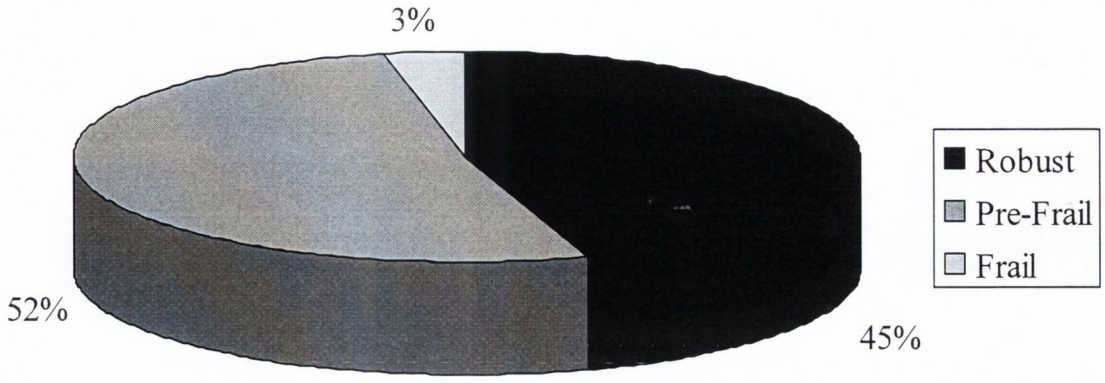


Table 7.4 Difference in Frailty Criteria across Young and Old Caregiver groups

Criteria	Caregiver < 65 (n = 47)	Caregiver ≥ 65 (n = 61)	p
BMI < 18.5 kg/m^2	6	12	0.436
Slowed Gait	0	3	0.254
Impaired Grip Strength	**4**	**16**	
0.023*			
Exhaustion	4	6	0.533
Physical Activity	8	10	0.581

Fisher's exact test, * $p < 0.05$

Table 7.5 Psychological Health Scores in Robust and Frailer Older Caregivers

Parameter (Mean +/- SD)	Robust	Pre-Frail/Frail	p
Positive Aspects [a]	29.04(10.4)	32.3(10.2)	0.144
Perceived Stress [b]	**12.9(7.6)**	**17.5(6.9)**	**0.025***
Self-Efficacy [c]	47.9(18.7)	47.3(16.8)	0.894
Preparedness [d]	16.9(6.2)	17(6.4)	0.966
Life Events [e]	**0.5(0.8)**	**1(0.9)**	**0.034***
Lubben Total Score [f]	18.8(4)	16.4(4.7)	0.054
• Family Subscale	8.6(2.8)	7.9(3.6)	0.468
• **Friends Subscale**	**10.2(2)**	**8.5(2.7)**	**0.012***
Loneliness [g]	22.1(2.7)	22.1(3.3)	0.997
Depression [h]	8.5(5.6)	7(5.5)	0.328
Burden [i]	30.6(15.8)	25.3(18.3)	0.247
Mutuality [j]	41.1(13.3)	45.2(13.6)	0.261

Student-t test, * $p < 0.05$

[a] Positive Aspects of Caregiving Scale

[b] Perceived Stress Scale – 10 item

[c] Caregiver Self-Efficacy Scale

[d] Preparedness Subscale of the Family Care Inventory

[e] Geriatric Adverse Life Event Scale

[f] Lubben Social Network Scale – 6 item

[g] De Jong Loneliness Scale

[h] Center for Epidemiological Studies Depression Scale

[i] Zarit 22-item Burden Inventory

[j] Mutulity Subscale of the Family Care Inventory

robust older caregivers. Frailer older caregivers also showed a trend toward lower mean Lubben scores representative of social isolation although this did not quite reach statistical significance. However these frailer older caregivers did have significantly lower mean scores specifically on the 'Friends' subscale of the Lubben measure of social isolation, suggesting that these frailer caregivers were more likely to feel isolated from a friendship network compared to robust caregivers.

Within younger caregivers the frailer group also had higher mean perceived stress scores when compared with those caregivers who were considered robust (Table 7.6). Frailer younger caregivers also had lower preparedness scores suggesting that they felt less ready for the caregiving role when compared to their more robust counterparts. Statistically higher mean burden scores in the frailer group also indicated they reported more subjective burden with the caregiving role than the non-frail younger caregivers. Interestingly the frailer group of younger carers also showed significantly lower mutuality scores endorsing a poorer relationship between carer and care recipient for this group.

On logistic regression analysis using a frailty score of ≥ 1 as our outcome measure the association between perceived stress and increased likelihood of fulfilling any frail criteria was retained in both older and younger caregivers even controlling for the addition of factors such as age, gender and number of co-morbid illnesses (Table 7.7 & 7.8). In older caregivers having higher perceived stress scores inferred a significantly greater likelihood of fulfilling one or more frailty criteria by a factor of 1.91 (OR 1.91, $p = 0.04$ CI 1.09, 1.20). Similarly in younger caregivers having higher perceived stress inferred a significantly greater likelihood of fulfilling one or more

Table 7.6 Psychological Health Scores in Robust and Frailer Younger Caregivers

Parameter (Mean +/- SD)	Robust	Pre-Frail	p
Positive Aspects [a]	31.7(7.2)	28.2(10.5)	0.205
Perceived Stress [b]	**13.1(7.2)**	**18.3(7.4)**	**0.031***
Self-Efficacy [c]	50.1(19.9)	43.1(17.8)	0.242
Preparedness [d]	**18.7(6.6)**	**14.6(4.1)**	**0.025***
Life Events [e]	0.5(0.7)	0.7(1.1)	0.466
Lubben Total Score [f]	17.4(4.8)	16.2(4.8)	0.388
• Family Subscale	8.3(2.8)	7.9(2.8)	0.645
• Friends Subscale	9.1(2.3)	8.7(2.8)	0.607
Loneliness [g]	21.4(2.7)	21.7(3.1)	0.721
Depression [h]	7.1(5.6)	10.6(7.1)	0.076
Burden [i]	**32.3(14.4)**	**42.9(15.3)**	**0.025***
Mutuality [j]	**42.7(12.7)**	**31.5(11.4)**	**0.005***

Student-t test, * $p < 0.05$

[a] Positive Aspects of Caregiving Scale

[b] Perceived Stress Scale – 10 item

[c] Caregiver Self-Efficacy Scale

[d] Preparedness Subscale of the Family Care Inventory

[e] Geriatric Adverse Life Event Scale

[f] Lubben Social Network Scale – 6 item

[g] De Jong Loneliness Scale

[h] Center for Epidemiological Studies Depression Scale

[i] Zarit 22-item Burden Inventory

[j] Mutulity Subscale of the Family Care Inventory

Table 7.7 Logistic Regression Model of Frailty (≥ 1 Frail Criteria) and Psychological Health Factors in Older Caregivers adjusted for Age, Gender and Co-morbid Illnesses.

Variable	B	S.E	Sig	OR	95% CI	
					Lower	Upper
Positive Aspects [a]	0.02	0.03	0.57	1.02	0.96	1.08
Perceived Stress [b]	**0.09**	**0.05**	**0.04**	**1.91***	**1.09**	**1.2**
Self-Efficacy [c]	-0.01	0.02	0.55	0.99	0.95	1.02
Preparedness [d]	0.01	0.05	0.79	1.01	0.91	1.11
Life Events [e]	-0.88	0.47	0.06	0.41	0.16	1.04
Lubben Total Score [f]	-0.11	0.08	0.15	0.89	0.76	1.05
• Family Subscale	-0.07	0.11	0.55	0.93	0.75	1.15
• Friends Subscale	-0.26	0.15	0.07	0.77*	0.57	1.03
Loneliness [g]	-0.01	0.12	0.91	0.99	0.78	1.25
Depression [h]	-0.03	0.06	0.64	0.97	0.86	1.09
Burden [i]	-0.01	0.02	0.48	0.99	0.95	1.03
Mutuality [j]	0.01	0.02	0.55	1.01	0.97	1.05

Significance $p < 0.05$

[a] Positive Aspects of Caregiving Scale

[b] Perceived Stress Scale – 10 item

[c] Caregiver Self-Efficacy Scale

[d] Preparedness Subscale of the Family Care Inventory

[e] Geriatric Adverse Life Event Scale

[f] Lubben Social Network Scale – 6 item

[g] De Jong Loneliness Scale

[h] Center for Epidemiological Studies Depression Scale

[i] Zarit 22-item Burden Inventory

[j] Mutulity Subscale of the Family Care Inventory

Table 7.8 Logistic Regression Model of Frailty (≥ 1 Frail Criteria) and Psychological Health Factors in Younger Caregivers adjusted for Age, Gender and Co-morbid Illnesses.

Variable	B	S.E	Sig	OR	95% CI	
					Lower	Upper
Positive Aspects [a]	-0.19	0.11	0.09	0.83	0.66	1.02
Perceived Stress [b]	**0.15**	**0.06**	**0.01**	**1.17**	**1.03**	**1.30**
Self-Efficacy [c]	-0.03	0.02	0.13	0.97	0.93	1.0
Preparedness [d]	**-0.15**	**0.07**	**0.03**	**0.86**	**0.75**	**0.98**
Life Events [e]	0.58	0.46	0.21	1.78	0.72	4.39
Lubben Total Score [f]	-0.06	0.07	0.39	0.94	0.82	1.08
• Family Subscale	-0.06	0.12	0.61	0.94	0.74	1.19
• Friends Subscale	-0.07	0.13	0.61	0.94	0.72	1.20
Loneliness [g]	0.06	0.14	0.64	1.07	0.81	1.39
Depression [h]	0.11	0.06	0.05	1.12	0.99	1.25
Burden [i]	**0.07**	**0.03**	**0.009**	**1.08**	**1.01**	**1.14**
Mutuality [j]	**-0.09**	**0.03**	**0.01**	**0.91**	**0.86**	**0.97**

Significance $p < 0.05$

[a] Positive Aspects of Caregiving Scale

[b] Perceived Stress Scale – 10 item

[c] Caregiver Self-Efficacy Scale

[d] Preparedness Subscale of the Family Care Inventory

[e] Geriatric Adverse Life Event Scale

[f] Lubben Social Network Scale – 6 item

[g] De Jong Loneliness Scale

[h] Center for Epidemiological Studies Depression Scale

[i] Zarit 22-item Burden Inventory

[j] Mutulity Subscale of the Family Care Inventory

frailty criteria by a factor of 1.17 (OR 1.17, p = 0.01, CI 1.03, 1.30). Perceived stress was the only factor that retained its significant association with frailty in older caregivers once age, gender and co-morbid illness was controlled for.

In younger caregiver however, preparedness, caregiver burden and mutuality also retained a significant association with the fulfilment of one or more frailty criteria. Preparedness scores had a negative correlation with those who fulfilled any frailty criteria, so that higher scores (i.e. more prepared caregivers) had a reduced likelihood of fulfilling any frailty criteria. The likelihood of those with lower preparedness scores fulfilling ≥ 1 frailty criteria was increased by a factor of 1.16 (OR 0.86, p = 0.03 CI 0.75, 0.98). Mutuality scores also had a negative correlation with those younger caregivers who fulfilled any frailty criteria, so that those with higher mutuality scores reflective of a more stable relationship with their care recipient had a reduced likelihood of fulfilling any frailty criteria. The likelihood of those with lower mutuality scores reflective of a poorer relationship with their care recipient was increased by a factor of 1.1 (OR 0.91, p = 0.01 CI 0.86, 0.97). Finally the likelihood of fulfilling ≥ 1 frailty criteria in younger caregivers was significantly increased by a factor of 1.08 in those who reported higher caregiver burden scores (OR 1.08, p = 0.01 CI 0.86 0.97).

7.3.4 Care Recipient Drivers of Caregiver Frailty

Odds ratio was used to describe the likelihood of care recipient factors contributing to the risk of caregivers fulfilling one or more frail criteria and being in a state of transition to frailty. Care recipient factors consisted of clinical markers of disease to include measures of cognition (MMSE), functioning (Disability Assessment for

Dementia Scale), global severity of dementia as rated using the Clinical Dementia Rating Sum of Boxes Score, patient dependence using the cargiver rated dependence scale and neuropsychiatric symptoms (Neuropsychiatric Inventory). Binary logistic regression determined which care recipient explanatory variables predicted frailty in caregivers controlling for other known risk factors for caregiver frailty such as age, gender and other comorbid illness (Table 7.9 & 7.10). Interestingly the only care recipient factors which retained a significant association with frailty was in younger caregivers where poorer functional ability in care recipients as rated by the DAD scale and higher scores for presence of neuropsychiatric symptoms increased the likelihood of caregivers being in a stage of pre-frailty by a factor of 1.08 and 1.04 respecitively (OR 1.04 p = 0.03 CI 1.01 1.16; OR 1.08 p = 0.02 CI 1.01 1.07)

7.4 Summary of Findings

On investigating the presence of clinical frailty markers in a sample of both older ($\geq$ 65) and younger ($<$ 65) primary caregivers of patients with established cognitive impairment we identified a higher than anticipated level of pre-frailty in the younger caregiver group. This was despite the fact there was a relatively low level of full blown frailty within the caregivers, with none of the younger caregivers fulfilling criteria for full-blown frailty and only two of our older caregivers fulfilling criteria. Within our analysis of the data we interpreted those caregivers who fulfilled one or more frail criteria as being at an intermediate stage of frailty and so representative of those caregivers at a stage of transition to full blown frailty. Being at a pre-frail or intermediate stage of frailty has consistantly been shown to infer risk of developing full-blown frailty and also a high risk of poorer outcomes when compared to non-frail individuals (Fried et al., 2004).

Table 7.9 Logistic Regression Model of Frailty (≥ 1 Frail Criteria) and Care Recipient Factors in Older Caregivers adjusted for Age, Gender and Co-morbid Illnesses.

Variable	B	S.E	Sig	OR	95% CI	
					Lower	Upper
MMSE [a]	-0.06	0.05	0.24	0.94	0.85	1.04
DAD [b]	0.01	0.03	0.75	1.01	0.95	1.07
Dependence [c]	0.01	0.10	0.89	1.01	0.83	1.23
CDR SoB [d]	0.05	0.09	0.59	1.05	0.88	1.25
NPI [e]	- 0.01	0.01	0.38	0.99	0.97	1.01

Significance $p < 0.05$

[a] Mini-mental state examination
[b] Disability Assessment in Dementia Scale
[c] Dependence Scale
[d] Washington University Clinical Dementia Rating Scale (CDR)
[e] Neuropsychiatric Inventory

Table 7.10 Logistic Regression Model of Frailty (≥ 1 Frail Criteria) and Care Recipient Factors in Younger Caregivers adjusted for Age, Gender and Co-morbid Illnesses.

Variable	B	S.E	Sig	OR	95% CI	
					Lower	Upper
MMSE [a]	-0.03	0.05	0.50	0.96	0.87	1.07
DAD [b]	0.08	0.04	0.03	1.08*	1.01	1.16
Dependence [c]	0.18	0.13	0.16	1.20	0.93	1.54
CDR SoB [d]	0.10	0.09	0.27	1.11	0.93	1.31
NPI [e]	0.03	0.02	0.02	1.04*	1.01	1.07

Significance $p < 0.05$

[a] Mini-mental state examination
[b] Disability Assessment in Dementia Scale
[c] Dependence Scale
[d] Washington University Clinical Dementia Rating Scale (CDR)
[e] Neuropsychiatric Inventory

Within older caregivers those at a transitionary stage of frailty ($\geq$ 1 frailty criteria) had significantly increased incidence of recent life events, had higher perceived stress and were more likely to feel isolated from a friendship network when compared to robust older caregivers. Controlling for factors such as age, gender and number of co-morbid illnesses, perceived stress was the only factor that retained a significant association with frailty, increasing the likelihood of older caregivers being at a stage of transitionary frailty. We did not identify any specific care recipient factors that increased the likelihood of a transitioning to frailty in older caregivers.

Within our group of younger caregivers the frailer carers also had higher perceived stress when compared to their robust counterparts. In addition to this they appeared to report lower levels of preparedness for the caregiving role, endorsed a higher level of carer burden and also endorsed lower mutuality or a poorer relationship with their care recipients when compared to younger caregivers who were robust or not frail. Controlling for known risk factors for frailty such as age, female gender and number of co-morbid illnesses in younger caregivers, these associations showed consistancy. Higher levels of perceived stress, less preparedness for the caregiving role, higher subjective burden and poor mutuality with their care recipient all increased the likelihood of younger caregivers being in a stage of pre-frailty. We also identified that a poorer functioning in the area of activities of daily living as measured using a disability score, as well as a higher level of neuropsychiatric symptoms were two care recipient factors that also increased the likelihood of being at a transitionary state of frailty for younger caregivers.

Chapter 8

Discussion

8.1 The Psychological Consequences of Frailty

We have found that frail elders experience more symptoms of anxiety and depression than those who are robust. Both pre-frail and frail older persons were an at-risk population more likely to have borderline and case-level anxiety and probable case-level depression. When multiple logistic regression models were constructed our findings were consistent, frailty indicated a significantly higher likelihood of both case-level anxiety and depression even when other risk factors were accounted for. Our findings suggest that older persons who are becoming increasingly frail according to the frailty phenotype could also be considered psychologically frail with an increased likelihood of emotional disturbance.

8.1.1 Frailty and Depression

Little previous research has systematically examined anxiety and depression and their association with the biological syndrome model of frailty using well validated psychological measures. One previous study looked at self-reported psychiatric illness in older people and found that for each additional deficit defining frailty, odds of psychiatric illness increased (Andrew and Rockwood, 2007). A further large epidemiological study also identified a relationship between depressive symptoms and incident frailty (Woods *et al.*, 2005). This study utilized a measure for depression however that includes exhaustion as a symptom, which was also a key feature within their frailty measurement and may represent a confounding factor. To avoid this we ensured the exhaustion criteria for frailty was not included in any analysis involving the CESD-8. Whilst this may have underestimated the level of frailty associated with

depressive symptoms it ensured exhaustion was not a confounding factor in our results.

The current consensus to include a measure of exhaustion as a criteria for the frailty phenotype may in fact reflect the likelihood that there is a psychobiological component to the fraity syndrome as suggested by our findings. Mental fatigue could be described as a symptom of depressive illness. It may in part explain the strength of association with depression at both a pre-frail and frail stage. Those who are depressed may be more likely to become frail secondary to disengagement from daily activities, psychomotor retardation and poor nutritional intake. Or indeed those who are frail may be more likely to develop depressive symptoms due to impairment of their functional abilities and social withdrawal. Drawing the conclusion as to which comes first frailty or depression is not possible given the cross-sectional nature of our work however given our findings certainly warrants further investigation within the context of a longitudinal study.

8.1.2 Frailty and Anxiety

There is an even greater paucity of literature evaluating the relationship between frailty and quantified levels of anxiety in older persons. One recent study did examine health anxiety specifically and its correlation with varying degrees of frailty in a small sample of community-dwelling elders (Bourgault-Fagnou and Hadjistavropoulos, 2009). They identified that seniors with high levels of frailty experienced greater levels of health anxiety. The authors of this paper called for further studies investigating the association between frailty and generalized anxiety in older adults. The importance of learning more about factors associated with anxiety in old age

cannot be overestimated. People with anxiety disorders make heavy use of medical services (Kennedy and Schwab, 1997). Despite this, most cases of anxiety disorder in late life remain undiagnosed and untreated. Inadequately treated anxiety leads to distress, functional impairment, and increased medical morbidity and mortality (Jones *et al.*, 2004). In combination with increasing frailty it is an additional risk for poorer outcomes.

Within our study frailty remained significant as a determinant for anxiety in a model where other known risk factors were included, and we identified a strong association between increasing levels of frailty and borderline and case-level anxiety disorder as measured by the HADS-A. The use of this scale may in part explain the strength of association found between frailty and symptoms of anxiety. The HADS is designed to be adept at picking up symptoms of anxiety in those with underlying physical comorbidities as it has been purposely designed with the omission of somatic indicators of anxiety and depression. In this way it may be particularly attuned to identifying anxious symptoms in those with a higher burden of comorbid illness such as our frailer participants. There is a complex interplay between anxiety and physical health decline such as that seen in increasing frail states. First, realistic worry and pathologic anxiety could be consequences of co-morbid physical illness. Second, chronic anxiety might itself contribute to deteriorating health and increasing medical morbidity or mortality and act as a driver for frailty. Unfortunately it is beyond the scope of this paper to determine cause and effect; however we generate important directions for research. Future work in the form of a prospective study should attempt to disentangle why frailty is related to anxiety, what mediates this relationship and to determine causality.

8.1.3 Frailty, Loneliness and Social Isolation

Our work has also identified an association between frailty, loneliness and increasing social isolation. An absence of loneliness and social engagement have already been identified as important factors in successful aging for older adults (Depp and Jeste, 2006). Robust evidence of the health-promoting affects of social relationships is available, socially isolated older adults are known to be at increased risk of all cause mortality (Fratiglioni *et al.*, 2004). Deficits in social support have been associated with a wide variety of adverse health outcomes in older age (Reblin and Uchino, 2008; Uchino, 2006), ranging from physical health to depression and self-harm (Dennis *et al.*, 2005). We further contribute to the current literature showing an important association between loneliness and adverse physical health consequences (O'Luanaigh and Lawlor, 2008) by identifying an association between increasing frailty, loneliness and social isolation.

Loneliness is the subjective experience of social isolation. It has been defined as an unpleasant subjective state of sensing a discrepancy between the desired amount of companionship or emotional support and that which is available in the person's environment (Blazer, 2002). There are two types of loneliness that can co-exist or occur independently; social and emotional loneliness (Weiss, 1973). Social loneliness occurs through isolation and is caused by a lack of social integration and embeddedness. This type of loneliness may, for instance be experienced following relocation and could be best resolved by acquiring new contacts. Emotional loneliness on the other hand develops because of an absence of a reliable attachment figure, such as a partner (O'Luanaigh and Lawlor, 2008). We have identified in a cohort of community dwelling older adults that whilst loneliness is associated with increasing

frailty this association appears to relate to emotional loneliness specifically rather than social loneliness despite the co-existing association we identified between increasing social isolation scores and increasing frailty.

This finding may relate to the age of our cohort, the incidence and prevalence of emotional loneliness in particular amongst an older population is known to be raised (O'Luanaigh and Lawlor, 2008). This is thought to be due to the death of aging relatives and friends with the probability of having or finding new intimate attachments decreasing particularly in the face of diminishing social networks and increasing isolation. This may explain our finding of an association between frailty and emotional loneliness in older adults rather than social loneliness even in the context of the association between frailty and increasing social isolation. Frailty may contribute to functional limitations in older adults and restrict their social activities, in this way contributing to increasing isolation and loneliness. Conversely it may be a constricted and isolated environment and the psychological consequences of loneliness that contribute to reduced activities and a pathway to frail health. Identifying the direction of these relationships is not possible given the cross-sectional nature of our work, however certainly warrants evaluation in a longitudinal context.

8.1.4 Frailty, Anxiety and Loneliness

In an attempt to further tease apart these associations we completed, a supplementary mediation analysis. The relationship between depression, loneliness and social isolation has already been well-established in the literature. We were interested in investigating whether anxiety which we had established as a novel psychological factor associated with frailty had any influence on our identified relationship between

frailty and both loneliness and social isolation. Examination of the mediation effects revealed that anxiety fully mediated the relationship between frailty and both loneliness and social isolation. The association between frailty, loneliness and social isolation was no longer significant when anxiety was controlled for.

In terms of the current literature an association between anxiety and aspects of loneliness and social isolation certainly have been identified. Evidence linking social and psychological factors and anxiety disorders has been reported in several studies. It has for example been found that not having a partner (Alonso *et al.*, 2004; Plaisier *et al.*, 2008b) living alone (Rimehaug and Wallander, 2010), low quality of social network (Plaisier *et al.*, 2008a), loneliness in adolescence (Chang *et al.*, 2008) all are factors that are associated with anxiety disorders. Small social networks have also been found to be significantly more common among individuals with a high level of anxiety symptoms (Falk and Dahl, 2010).In a recent large prospective population based study, loneliness and not feeling part of a whole was found to be associated with increased risk of anxiety disorders (Flensborg-Madsen *et al.*, 2011).Lack of social support and bereavement have also previously been associated with anxiety specific to an elderly cohort (Vink, 2008).Similarly we know that chronic health issues, poor self-perceived health and functional limitations in older adults are linked to an increased risk of anxiety (Vink, 2008). Given these known associations between physical health and anxiety as well as between anxiety and loneliness, our finding of anxiety as a mediator in the relationship between physical frailty, loneliness and social isolation is not so surprising.

8.1.5 Limitations

Limitations of the work discussed here include its cross-sectional design and the use of a convenience sample, which may have introduced a selection bias making the external validity of our findings questionable. Our sample included those who self-referred to the study; these participants may have certain characteristics that were over-represented. For example many participants were independently mobile, healthy, and fell within a "younger old" age group. Therefore we may have failed to capture a higher level of frailty and so lack the ability to generalize. This is reflected in the lower level of full-blown frailty evident in our population at 6.7%. However this figure remains consistent with current literature where the prevalance of frailty has been shown to lie between 7 and 32% (Mitnitski *et al.*, 2005). A significant proportion of participants were defined pre-frail rather than frail again representing a somewhat 'healthier' study population. Despite this the proportion of pre-frail individuals we identified is consistent with findings from the large Cardiovascular Health Study where up to 46% of the total cohort at baseline, were considered to be intermediately frail (Fried *et al.*, 2001). Further limitation is our use of a modified version of the frailty index with the exclusion of the 'exhaustion' criteria in order to facilitate the analysis of frailty and depression using the CESD-8. This led to an underestimation of frailty as reflected in our results and may have influenced our findings relating frailty and depression.

8.1.6 Conclusion

Despite these limitations our work provides preliminary cross-sectional results that suggest an association between frailty and the mental health of older people. Frailty is associated with a higher likelihood of anxiety and depression along with loneliness,

history of depression requiring pharmacotherapy and adverse life events. Our findings suggest that even at the earliest stage of pre-frailty there is an association with increased symptoms of emotional distress and a higher likelihood of case-level depression and anxiety. Frailty may be relevant in identifying older people at risk of deteriorating mental health.

Our data heightens awareness of the links between frailty and emotional disturbance. It suggests that health care professionals who work with frail seniors should consider the possible co-existence of depression and anxiety. Our results also emphasize the importance for professionals to be especially aware of potential anxiety disorders in individuals who are generally appearing to be lonely or have poor social relations with increasing social isolation. We add further evidence in support of a possible psychosocial or psychobiological component of the frailty syndrome. In scenarios that predict future health service delivery in the Western world, the rapid increase in frail elderly is seen as one of the major challenges of health care (Bergman *et al.*, 2007). Our study encourages further prospective research to clarify causality and to determine if frailty may be a potential interventional target for those with symptoms of depression and/or anxiety who are at risk of the development of case-level disorders or if timely identification and appropriate intervention for anxiety and depression in frailer individuals translates to improved outcomes for this vulnerable group of older people.

Researchers, policy makers, administrators and health care providers generally agree that frailty can have an important impact on affected individuals, their families, the health care system and society as a whole. We have further contributed to this

consensus by highlighting the associations between frailty, depression and anxiety. In the context of a comprehensive geriatric assessment the psychological correlates of frailty should be considered and screened for. Both frailty and symptoms of depression and anxiety are easily measured and if identified at an early stage represent potentially modifiable factors to improve outcomes for our older population.

8.2 Frailty and Fear of Falling

In our evaluation of a cohort of older fallers we identified that, when compared to robust fallers, pre-frail and frail fallers displayed a greater fear of falling as indicated by a significantly lower mean MFES. On multivariate analysis accounting for a number of psychological factors only age, female gender and poorer cognition were retained as the factors significantly associated with fear of falling in robust fallers in an optimal model accounting for around 30% of variance. This is consistent with current literature where older females and those with poor cognition have been found to have higher rates of fear of falling (Arfken *et al.*, 1994). In our group of pre-frail and frail fallers however, depression score was the only significant psychological factor associated with fear of falling in an optimal model accounting for 12.2% of the observed variance. The odds ratio of having depression consistent with probable case-level disorder was increased 2.6-fold if you were a frailer faller when compared to those fallers considered robust.

Of the limited evidence available to us in the current literature on fear of falling and frailty, our findings are consistent with one other study, which evaluated activity related fear of falling in a cohort of older individuals defined as transitioning to frailty according to criteria established by Speechley and Tinetti in 1991 (Kressig *et al.*, 2001). They report that individuals fearful of falling and transitioning to frailty were

more likely to be depressed than non-fearful individuals. A confounding factor in this study was the fact that depression is one of the criteria used by the Speechley & Tinneti index to define frailty (Speechley and Tinneti, 1991). Within our study we have utilised a more recent and well-validated measure of the biological syndrome of frailty identified by Fried et al. The identification of those at an intermediate level of frailty using this measure has been robustly shown to infer risk of developing full-blown frailty and the multiple adverse outcomes associated with frailty also. Theoretically this transitional stage is the last opportunity to affect frailty as it is at this point that it may be reversed (Fried *et al.*, 2004).

8.2.1 Frailty, Depression and Fear of Falling

Previous studies have identified that fear of falling is independently associated with depression and that older persons who report being very afraid of falling have the highest levels of depression (Chou and Chi, 2008a). In those who are depressed, fear of falling has also been shown to be the only factor strongly associated with activity restriction, other factors only showing marginal associations (Deshpande *et al.*, 2008). A more recent study has also confirmed that high levels of perceived fall risk as measured by fear of falling are likely to result in future falls, independent of physiological risk, and the disparity between physiological and perceived fall risk contributes to risk mainly through psychological pathways with a propensity towards neuroticism, a higher prevalence of irrational fears and increasing depressive symptoms (Delbaere *et al.*, 2010) The importance of psychological factors such as depression associated with fear of falling is therefore supported by current literature.

Mixed findings in relation to the causal direction between fear of falling and depression have been reported however. Two recent prospective studies suggest that fear of falling most likely contributes detrimentally to depressive symptoms through the mediating effect of social withdrawal but that this effect is not reciprocal (Chou and Chi, 2008b; Murphy *et al.*, 2003). Emerging frailty may contribute to activity restriction and social withdrawal leading to adverse psychological consequences such as fear of falling and subsequently depression, or vice versa, depression may lead to social withdrawal, activity limitations and the development of frailty and subsequent fear of falling. Determining this level of causality is beyond the scope of this study due to its cross-sectional design. However our findings suggest the association between depression and fear of falling may be specific to those older fallers that can be placed on the frailty trajectory according to the biological syndrome model. This has implications for the development of future fall prevention strategies that also wish to target fear of falling.

Addressing co-morbid depression and fear of falling in frailer older fallers may reduce the morbidity associated with falls in this vulnerable group. The use of antidepressants however may increase the risk of further falls, although the evidence remains conflicted as to whether this risk is the same across all classes of antidepressants and whether this effect is independent of concurrent mental health morbidity (Arfken *et al.*, 2001). Dependent on the severity of the depressive episode, pharmacotherapy should be considered however additional methods to address both depressive symptoms and physical frailty may be worth considering.

Progressive resistance training has shown to be an effective approach to treat both depression in older adults and frailty (Binder *et al.*, 2005; Singh *et al.*, 2005). Similar programmes targeting the combined effect of increasing physical frailty and depressive symptoms may impact upon fear of falling and fall prevention. Similarly psychotherapeutic approaches may play a role. Multicomponent cognitive behavioural intervention (CBT) has already been shown to have positive and durable effects on fear of falling and associated activity avoidance and recurrent falls in older people (Zijlstra *et al.*, 2009). It also has been shown to be as efficacious as pharmacotherapy in the treatment of mild to moderate depressive disorder and depressive symptoms in older adults (Hollon and Ponniah, 2010). As mentioned previously however few randomized controlled intervention trials evaluating fear of falling as an outcome measure have included specific cognitive restructuring techniques known to be efficacious in the treatment of depression and anxiety (Zijlstra *et al.*, 2007).

Our findings suggest minimization of fear of falling within groups of fallers transitioning to frailty may be achieved through interventions which address depression specifically. We suggest that fallers at a transitional level of frailty may represent a particularly vulnerable group psychologically who would benefit most from interventional stratagies that have specific intervention components based on a CBT approach as well as targeted exercise and physiotherapy interventions to address frailty.Our recommendations then would be that health care professionals who work with frail seniors who have fallen or are at risk of a fall should consider the possible co-existence of depressive symptomatology. The multidisciplinary team approach to falls assessment particularly in older persons considered either frail or even pre-frail should include an assessment of emotional health and multifactor interventions may

require specialist intervention to address any underlying affective disorders to ensure adequate rehabilitation.

8.2.2 Limitations

The major limitation of this study is that discussion is based on a cross-sectional design. A longitudinal study is warranted to substantiate causal relationships. We have also focused our analysis solely on a group of fallers categorized according to their level of physical frailty. Our specific focus on fallers is due to the fact that fear of falling is a known phenomenon that occurs subsequent to even one fall. Fall interventions also most often are directed at those individuals who have previously experienced a fall. Our objective in this study was to contribute to the current knowledge on targeted falls intervention by evaluating whether there was any difference in the psychological factors underlying fear of falling in fallers when they differed in terms of their physical frailty. Thereby improving our ability to target fear of falling in frail fallers specifically, who are already known to be increasingly vulnerable. Nonetheless, fear of falling does occur in older persons who have never experienced a fall and we acknowledge that our work could be expanded by also examining the psychological factors underlying fear of falling in frail and robust non-fallers. Breaking the vicious cycle between fear of falling and recurrent falls is crucial, despite any limitations in this study we contribute important information that may assist in the provision of more targeted falls intervention programs that address physical and psychological health improvements. We have identified an increased likelihood of depressive symptoms and associated fear of falling in older fallers transitioning to frailty that may facilitate the focus of falls interventions in this group.

8.3 The Impact of Frailty on Cognitive Performance

We examined the relationship between cognitive performance and frailty within a cohort of independent non-demented community dwelling elderly. Our aims were to identify which markers of frailty were associated with poorer cognitive performance and to clarify the specific areas of cognitive performance that pre-frail and frail elders perform poorly on when compared to their robust or non-frail counterparts. Cognitive function was assessed using reliable tests of language, executive function, spatial ability, verbal and nonverbal memory. A previously tested well-distributed summary score was used for the purposes of analysis. Global cognitive performance was found to be significantly poorer within both pre-frail and frail elderly. On linear regression analysis frailty retained a significant association with poorer cognitive scores even when age, gender and education were controlled for. Weakness as defined by impaired grip strength and reduced physical activity were the specific frailty criteria that inferred higher odds of reduced global cognitive performance. Pre-frail and frail elders displayed significantly poorer performance on neuropsychological tests of verbal and prospective memory, executive functioning and praxis when compared to their more robust counterparts. The likelihood of having impaired executive functioning was increased fourfold if you were a pre-frail or frail elder.

8.3.1 Frailty and Cognition

Our finding that frailty is associated with poorer cognitive performance is consistent with the current literature. Cognition has already been considered as a potential component of frailty, and it has been demonstrated that it is associated with adverse health outcomes (Rockwood, 2004; Rockwood et al., 2005) . Several studies have reported that physical frailty is associated with low cognitive performance (Gill et al.,

1996; Strawbridge et al., 1998) and incidence of Alzheimer's disease (Buchman et al., 2007). In fact a study, conducted in a large sample of French community-dwelling elderly persons, showed that frail individuals with cognitive impairment have a higher risk of IADL and ADL disability and of incident hospitalization and dementia than subjects with none of these conditions, even after adjusting for potentially confounding variables (Avila-Funes et al., 2009). The authors of this study concluded that adding the criterion of cognitive impairment results in better identification of elderly persons with intrinsic vulnerability than when only the domains of physical function were considered, therefore suggesting that cognitive function be one of the criteria used to define frailty (Avila-Funes et al., 2009).

We have further identified that the frailty criteria of impaired grip strength and reduced physical activity inferred higher odds of reduced global cognitive performance within our cohort. Several longitudinal studies have shown that poor physical function and changes in the motor system are associated with cognitive impairment and incident dementia. For example, slow gait speed and poor standing balance have been associated with greater risk of dementia in older persons with apparent cognitive impairment at baseline than in those with no cognitive impairment (Verghese et al., 2002; Wang et al., 2006). Although in our study slowed gait speed did not retain a significant association with poorer cognitive performance on adjustment for age, gender and years of education, both impaired grip strength and reduced physical activity did retain a significant association. Similar findings have been identified in other recent studies, in particular a prospective study of changes in MMSE scores in over two thousand seven hundred cognitively normal older adults (Shin *et al.*, 2011). On follow up after four years only weaker grip strength persisted

to be significant for a decline in MMSE scores after adjustment for age, years of education and baseline MMSE score. Other studies have also found an association between poor hand grip strength and the risk of dementia and Alzheimer's disease (Raji *et al.*, 2005; Wang *et al.*, 2006).

8.3.2 Frailty, Cognition and Physical Activity

Our finding that the frailty criteria of reduced or inadequate physical activity is closely associated with poorer cognitive performance is also in keeping with current literature. There is evidence to suggest that aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults without known cognitive impairment (Angevaren et al., 2008). The temporal association found between improvements in cardiovascular fitness and in cognitive functions is suggestive of a causal link, however larger studies are still required to confirm whether the aerobic training component is necessary, or whether the same can be achieved with any type of physical exercise (Angevaren et al., 2008). Our findings suggest that in our cohort of relatively healthy non-demented community dwelling elders the odds of performing poorly cognitively are increased almost three-fold if you are not engaging in sufficient physical activity. Whilst we certainly cannot suggest a causal link given the cross-sectional nature of our work, our findings contribute to the growing body of evidence that points to the importance of regular physical activity in later life.

8.3.3 Frailty and Specific Areas of Cognitive Performance

In the context of this work we also attempted to identify the specific cognitive areas where pre-frail and frail elders displayed significantly poorer performance when

compared to their more robust counterparts. We identified a range of neuropsychological tests where performance was poorer including verbal and prospective memory, executive functioning and praxis. Our finding that performance within the area of executive functioning appeared to be worse in pre-frail and frail elders seemed to be the most consistent within the battery of neuropsychological tests completed. We found poorer performance for pre-frail and frail elders in the tests of category fluency, CAMCOG naming subtests, digit span testing, trail-making tests and in tests of praxis, both the drawing and abstract and motor task which all require some element of executive function in their completion. Using previously established cut-off points for the Trail-Making Test, a well-established psychomotor test for the assessment of deficits in executive cognitive functions we then investigated the likelihood of having impaired executive functioning if you were a pre-frail or frail elder and found it to be increased fourfold.

8.3.4 Frailty and Executive Functioning

Executive function (EF) refers to a variety of higher cognitive processes that use and modify information from many cortical sensory systems in the anterior and posterior brain regions to modulate and produce behaviour (Fuster, 1999; Goethals et al., 2004). These integrative functions include both cognitive and behavioural components that are necessary for effective, goal-directed actions and for the control of attentional resources which are at the basis of the ability to manage independent activities of daily living (Stuss and Levine, 2002). Impaired executive function has been associated with Alzheimer's disease, dementia patients are often impaired in a variety of tasks that are commonly considered a measure of executive function (Collette et al., 2001; Lambon Ralph et al., 2003; Logie et al., 2004) A number of studies have

found executive dysfunction to occur in the earliest stages of AD and it has also been identified at the stages of mild cognitive impairment (Baudic et al., 2006; Grambaite et al., 2011; Havet, 2006)

Vascular risk factors and systemic inflammation have been linked to executive dysfunction in later-life. Midlife hypertension, diabetes, smoking, and obesity have been associated with an increased rate of progression of vascular brain injury, global and hippocampal atrophy, and decline in executive function a decade later (Debette et al., 2011). Markers of systemic inflammation such as interleukins-12 and 6 have also been linked with impaired processing speed and executive function, even after controlling for relevant confounding factors (Trollor et al., 2011). So too have elevated plasma viscosity, increased circulating levels of CRP, and increased fibrinogen, been found to predict poorer subsequent cognitive ability in the areas of executive functioning (Marioni et al., 2009). Interestingly risk factors for cardiovascular disease (e.g., diabetes) and common vascular diseases (e.g., congestive heart failure, brain infarcts) have also both been related to both frailty (Newman et al., 2001)and AD (Arvanitakis et al., 2004) . As well as increased markers of inflammation such as C-reactive protein or proinflammatory interleukins which have all commonly been implicated in frailty (Puts et al., 2005),cognitive impairment (Weaver et al., 2002), and AD (Ehl et al., 2003; Ma et al., 2005). Our finding of an association between frailty and impaired executive functioning in healthy elderly community dwellers is perhaps understandable then, given the evidence of their common biological associations such as chronic inflammation and vascular co-morbidity.

However, a single common biological pathway is unlikely to completely explain the relationship between frailty, executive dysfunction and global cognitive decline. Although as described previously the association between physical frailty and cognitive impairment has been widely accepted, one particular study has questioned the temporal relationship between frailty and cognitive decline (Avila-Funes *et al.*, 2009). This group have in fact suggested that it is more likely the combination of frailty and a particular cognitive profile that accelerates the risk to dementia and AD. Thus, frailty per se could not be seen as a predictor of dementia, which suggests that it is a separate pathophysiological process, independent of cognitive decline. Rather it is the coincidence of frailty and cognitive impairment that potentially exacerbates the vulnerability of a subject, increasing the risk of developing dementia (Avila-Funes *et al.*, 2009). Therefore, due to the potential interaction between frailty and cognitive impairment, special attention should be paid to the subgroup of individuals showing the two phenomena simultaneously. Those most at risk of this interaction may display a specific cognitive profile.

Our findings contribute to the literature in this area by providing preliminary evidence that suggests, executive function impairment could perhaps play an important role in that cognitive profile. Further prospective studies could investigate whether poorer performance in executive functioning and frailty combined lead to poorer outcomes or more accelerated global cognitive decline in those who do progress to established cognitive impairment and dementia. Of further interest is the possibility of targeting executive dysfunction at an early stage if it does in fact constitute an important early biomarker of global cognitive decline when combined with co-existent frailty. There is some early evidence to suggest that behavioural interventions and computer

'games' improve cognitive function including executive function in older adults (Jobe et al., 2001; Sammer et al., 2006; Smith et al., 2001; Willis et al., 2006). Pharmacological therapy may also be an option with studies in older adults and those with Parkinson's disease demonstrating that methylphenidate may improve executive functioning (Auriel *et al.*, 2006; Ben-Itzhak *et al.*, 2007; Devos *et al.*, 2007).

8.3.5 Limitations

Clear limitations of this work include the cross-sectional nature of our data which prevents us from determining causality to any extent. Similarly given the convenience sample utilised we may have introduced a healthy participant bias, for example, which may have led to an underestimation of the aging effect using these data and certainly diminishes the generalizability of our findings.While we recognize that there is much more to cognitive processes, and to frailty, than what is described in this piece of work we do feel that there are some strengths worth noting also, in particular the detailed characterization of cognition using well established neuropsychological assessments in a large cohort of community-dwelling elderly with no known history of cognitive impairment.

8.3.6 Conclusion

We have found that the biological syndrome model of frailty even at the pre-frail stage appears to be closely associated with poorer global cognitive performance in a healthy non-demented elderly cohort. We have also identified a close correlation with frailty and impaired executive functioning in those without established cognitive decline. Any intervention targeting frail patients should consider the need for cognitive evaluation. Likewise, case management for a person targeting cognitive

performance should perhaps contemplate the possible co-existence of the biological syndrome of frailty with an attempt to coordinate interventions to address both conditions. It is important to deepen our understanding of the relationship between frailty and health outcomes such as cognition, both of which contribute to the loss of functional independence, increased health costs and decreased quality of life for our older population.

8.4 Frailty and Dementia

In this study we attempted to characterize frailty in a group of cognitively impaired community-dwelling elders and to enable a consideration of the relation, if any, between frailty and the domains of clinical heterogeneity in a group of patients with AD and MCI. Further aims were to determine the role of frailty in patient quality of life and as a driver of increasing economic cost and resource utilization in the context of cognitive impairment.

8.4.1 Frailty and its Correlates in AD and MCI

We present preliminary data that suggest frailty is a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity. An association between frailty and ageing has already been shown in older cohorts (Lipsitz, 2008). Our findings suggest that in the cognitively impaired it continues to be an important correlation, other factors notwithstanding. Increasing burden of comorbid illness inferring a higher likelihood of frailty is also consistent with current theory, where the cumulative effect of multiple age and disease related impairments leads to a degradation of physiologic systems. Frailty emerges from this vulnerable health state and may contribute to

further decline in functional performance and an increased risk of poorer outcomes (Boyd *et al.*, 2005; Rockwood, 2004). Optimized management of comorbid illness in dementia patients and adoption of stringent preventative health strategies in those at the stage of MCI may play a role in minimizing the health impact of frailty in this group.

The longitudinal association between frailty, incident mild cognitive impairment and AD has previously been reported in community dwelling older persons (Boyle *et al.*, 2010b; Buchman *et al.*, 2008). Further work however has shown the risk of developing dementia is five-fold in those with cognitive impairment irrespective of their frailty status (Avila-Funes *et al.*, 2009). This suggests frailty is not necessarily a predictor of dementia but may represent a separate pathophysiological process, independent of cognitive decline. Our results support this hypothesis. Markers of cognitive decline and illness severity did not retain significance with advancing frailty in our analysis. Other groups evaluating frailty beyond the biological syndrome model have included cognitive impairment as an inherent criterion for frailty. Our findings however show a high proportion of robust and intermediately frail participants within our cognitively impaired group. Not all cognitively impaired persons are frail. The importance of this lies in the modifiable nature of frailty and its potential role as a novel target for intervention. We hypothesize that the coincidence of cognitive impairment and frailty may accelerate the trajectory of decline in dementia. Preventive or treatment interventions focused on frailty independent of cognitive impairment could be effective at reducing poorer outcomes at a number of points on the pathway from mild cognitive impairment to end-stage dementia.

Limitations of our work include its cross sectional nature. The validity of our results and hypotheses need to be evaluated in a longitudinal context. Further limitation is our combination of both AD and MCI participants, MCI may never in fact transition to AD. However our interest lies in the investigation of frailty in those with established cognitive decline and our analysis identified the odds of frailty did not significantly differ between either group. This contributed to our rationale of combining both groups for evaluation. We also acknowledge our results may not be generalizable to a larger population. Findings from our population of patients with MCI and mostly mild to moderate AD may not be readily extrapolated to patients with more severe cognitive impairment. Similarly those persons who present to memory clinics may have more functional impairments or be frailer than other persons with MCI or AD. Another critical issue involves the assessment of dementia patients and the validity of the self-report measures used. To address this we cross-checked any self–report measures with primary caregivers to ensure the accuracy of our data prior to analysis.

8.4.2 Frailty and Quality of Life

This work has also identified an important correlation between advancing frailty and HR-QOL. When linear regression models were constructed, increasing neuropsychiatric symptoms and frailty were the key predictors of HR-QOL in the total sample. However when we evaluated the sample according to cognitive status we found that increasing frailty and neuropsychiatric symptoms were more significant determinants of HR-QOL in the earlier stages of disease whilst deteriorating functional ability was the most important determinant of HR-QOL as disease progressed. A key point to note in terms of our findings is that, in contrast with

current literature neither carer burden nor depression scores correlated with HR-QOL within our cohort. Conversely previous studies have found that both depression and burden are often associated with lower ratings of HR-QOL in dementia using proxy measures.(Logsdon *et al.*, 2002) Our negative finding may suggest lower levels of burden and depression within our carer group reflective perhaps of our sample of mostly mild to moderate cognitively impaired patients.

Other findings are more consistent with current literature. Similar to previous studies we have found no association between age or gender and HR-QOL (Hoe *et al.*, 2005; Wang, 2006). Nor did we find a significant correlation between HR-QOL and cognition as measured by the MMSE which is in agreement with work in the area to date (Hoe *et al.*, 2005; Logsdon *et al.*, 2002). Our results continue to reinforce the importance of behavioural and psychological symptoms in determining HR-QOL in the cognitively impaired. Neuropsychiatric symptoms (NPS) are common manifestations of AD. A consistent pattern is observed in the literature that increasing behavioural disorder is associated with decreased HR-QOL for caregiver ratings (Banerjee *et al.*, 2006). There is a belief that the prevalence of NPS increases as disease progresses, however recent studies indicate that a high proportion of subjects display clinically meaningful NPS as early as the stage of mild cognitive impairment (Feldman *et al.*, 2004). This is comparable with our finding that the association between NPS and HR-QOL appears to be most important in the milder stages of cognitive impairment compared to more moderate to severe disease. The pattern of association between activity limitation and HR-QOL in dementia in the literature to date has been somewhat less clear. It is known to be strongest for proxy ratings and in severe dementia (Hoe *et al.*, 2006; Hoe *et al.*, 2005). This likely underlies our finding

of functional limitations being retained as the optimal predictor of HR-QOL when we evaluated our subset of more severely cognitively impaired with an MMSE of <20.

In addition to reinforcing findings from the current literature, we introduce novel data suggesting that frailty represents an important predictor for HR-QOL in cognitively impaired patients particularly for those with mild impairment. In the past the term frailty has often been used interchangeably with disability and chronic disease. However as our knowledge of frailty grows the importance of defining it as a separate clinical entity is becoming more apparent. Frailty increases susceptibility to acute illness, falls, and disability, thus caring for frailer cognitively impaired older adults may represent a more challenging process due to their complex medical, psychological and social needs. This may underlie to some extent the association found between frailty in our cognitively impaired group and HR-QOL as assessed by a proxy measure. A further factor may be that at the earlier stages of cognitive decline increasing frailty could contribute to functional limitations for the patient thereby affecting HR-QOL. Frailty has previously been identified at the stage of mild cognitive decline.(Boyle *et al.*, 2010a) Recent work also indicates that in fact core components of frailty, including impaired grip strength, slowed gait, and low body mass index (BMI) may actually predict subsequent development of dementia (Rosano *et al.*, 2005; Stewart *et al.*, 2005). Therefore it is comprehensible that frailty may significantly influence HR-QOL even at the milder stages of impairment. The importance of identifying frailty as a key determinant of HR-QOL in dementia lies in the reversibility of frailty at an early stage and its potential role as a novel target for intervention (Fried *et al.*, 2004).

Limitations for these findings include the fact that findings from this population of patients with MCI and mostly mild to moderate AD may not be readily extrapolated to patients with more severe cognitive impairment. We may therefore have failed to capture those with a higher level of frailty and so lack the ability to generalize. Despite this it must be acknowledged that it is only the earlier stages of frailty that have been shown to be reversible and so have potential for interventional targeting.A further limitation is our use of a proxy report to measure HR-QOL. Recent studies indicate meaningful data on HR-QOL in dementia can be obtained using either subjective or proxy measures. Proxy reports however, only provide us with an evaluation of carer's views about how they believe the person with cognitive impairment would report on their own HR-QOL. In this way it is likely to reflect a different aspect of outcome than a self-report measure would (Logsdon *et al.*, 2002; Smith *et al.*, 2005).Yet the affective, cognitive and reality distortion aspects of dementia can belie a person's perception of their own QOL (Katschnig, 1997). Proxy-report is not directly influenced by deficits which may occur in those with cognitive decline (Gonzalez-Salvador *et al.*, 2000). Despite the numerous biases inherent in proxy-reporting it is often considered to be a preferable choice (Rabins and Kasper, 1997). Also the significance of proxy assessed HR-QOL must not be diminished. At the very least proxy reports provide complementary views of the same important construct. Moreover, the perspective of family carers regarding HR-QOL is of critical importance when clinical decisions are made on behalf of patients.

We must stress the cross sectional nature of our study does not allow us to draw any conclusions regarding causality. We do, however, extend prior work on HR-QOL in cognitively impaired patients by identifying frailty as a potential novel target

associated with HR-QOL that has not previously been reported. We have also examined the value of this physical syndrome as an independent predictor of HR-QOL in the context of already known determinants. A further strength of our work is the fact we have evaluated predictors of HR-QOL in two groups, those with mild impairment and those with moderate to severe impairment. Previous studies have indicated the importance of assessing QOL separately for mild, moderate and more severely impaired patients as predictors vary by cognitive severity.(Logsdon *et al.*, 2002)

AD and cognitive impairment represent a significant public health concern due to increasing prevalence and the serious consequences for patients, their families and health services. Health-related quality of life is an important resource in offering valuable information about the impact of cognitive impairment. Our data suggests that frailty and neuropsychiatric symptoms are the key determinants of HR-QOL in the earlier stages of cognitive impairment. Functional limitations represent the sole predictor of HR-QOL in the later stages of cognitive decline. Frailty may be a novel modifiable factor in early dementia that could represent a target for intervention to improve health-related quality of life for patients and their caregivers.

8.4.3 Frailty and Increasing Care Costs in Dementia

Finally within our work on frailty in the area of dementia we have attempted to identify whether frailty plays a role as a driver of increased costs of care for dementia and cognitively impaired patients. It has been debated whether the `welfare state' has the financial strength to cope with the increasing number of elderly people in general (Thorslund, 1988), and with dementia in particular (Wimo et al., 1996b). At a time

when countries across Europe including France, Norway, Malta, England, Scotland, Wales and Northern Ireland are each facing up to the global challenge of Alzheimer's Disease by developing national dementia strategies, Ireland currently has no national dementia strategy (Cahill, 2010). If no dramatic effects of new treatment methods occur, the costs of dementia care will increase considerably and the need for priority discussions will be even greater than today. The impact of demographic ageing is as important in the Republic of Ireland as in the UK and other European countries and the significance of Alzheimer's Disease and dementia in overall health and social care costs is huge and must now be given high priority in Ireland's national health and social care agenda (Cahill, 2010). A comparative analysis of dementia care in OECD countries shows that two policy principles in particular – to remain at home as long as possible and to support caregivers – appear to be universally accepted as desirable (Moise et al., 2004). Increasing our knowledge on the factors which drive costs of dementia care is becoming increasingly important for informing national policy. Few interventions for dementia have unambiguously demonstrated outcomes, but for many this is perhaps a matter of a proper evidence base being built (Sorenson et al., 2006).

Our findings suggest that frailty is associated with increased costs of care in the context of dementia and cognitive impairment. Frailty retained a strong association with daily informal care costs even in the context of other known risk factors for increasing care costs such as dependence and co-morbid illnesses (Taylor et al., 2001; Zhu et al., 2008). Thus, interventions that reduce frailty as well as patient dependence on others may be associated with cost savings. Such information is of particular importance for clinicians and policymakers who are charged with planning for future care needs for patients with dementia in Ireland and elsewhere.

With projected increases in the number of persons at risk of developing Alzheimer's disease, its economic impact on future long-term care costs will be substantial. Since a higher proportion of the costs for institutional care are borne by the government than for community care, the costs to the public sector will be high. The roles and responsibilities of the public sectors in caring for Alzheimer's disease patients need to be carefully reassessed and must account for changes in the availability of potential informal caregivers. The cost of caring for people with the disease will increase dramatically for no other reason than the growth in the number of people at risk of developing the disease. The growing costs of providing care for persons with Alzheimer's disease highlights the importance of assessing the effectiveness and appropriateness of services targeted for persons with dementia. As specialized dementia services proliferate, the distribution of formal and informal costs may shift over time. The substantial cost to families providing informal care also has a direct impact on the financial viability of caregivers and may reduce the ability of the families to care for their family members at home.

We introduce novel preliminary findings that frailty may be an important driver of informal care costs in dementia that relate specifically to the provision of informal care. Given the potential reversibility of frailty at an early stage and our ability to identify and screen for it in the context of a comprehensive geriatric assessment it is an important factor to consider in terms of plans for future caregiver interventions that aim to be cost-effective. If medical interventions are discovered that slow the progression of Alzheimer's disease or cure it altogether, future public and private costs of caring for people with the disease may be reduced. Current knowledge does not indicate that therapeutic pharmacological, genetic, or other interventions to

substantially reduce or eliminate illness and death caused by the disease are likely to be developed in the immediate future. In the meantime, the public, private, personal, and social costs of Alzheimer's disease will continue to escalate. For this reason alone it is important to identify modifiable factors in the care pathway that can be addressed through practical and deliverable psychosocial measures that could be rolled out on a nationwide basis. This study contributes early findings that indicate frailty is an important and potentially modifiable factor that has an association with higher informal caregiving costs. Despite the limitations of our findings we do inform future research into replicating our results prospectively on a more representative sample and if successful piloting a frailty intervention to investigate its effect on informal caregiving costs and time to institutionalisation of dementia patients.

8.5 Frailty in Dementia Caregivers

We know that providing care to a family member suffering from Alzheimer's disease confers a significant health risk (Vitaliano, 2003). All cause mortality has been shown to be higher in caregivers than in controls (Schulz and Beach, 1999). Dementia caregivers have higher rates of both hypertension and coronary artery disease (Shaw *et al.*, 1999; Vitaliano *et al.*, 2002). Increased morbidity and mortality in dementia caregivers specifically suggests that the stress of caregiving in this context may be an important driver of ill-health. Frailty designates a decline in health function that is accompanied by an increase in disease vulnerability and

mortality (Walston and Fried, 1999). Our hypothesis in this study was that we would identify a clear association between increased caregiver stress and increasing frailty in caregivers. This was clearly the case, given that we found significantly higher perceived stress scores in both older (≥ 65) and younger (< 65) caregivers who could

be identified at an intermediate stage of frailty, when compared to those caregivers who were considered physically robust. High perceived stress was also retained as the only significant factor associatied with frailty in our older caregiver group once age, gender and co-morbid illness was controlled for. In younger caregivers higher perceived stress scores also increased the likelihood of being in a transitionary stage of frailty controlling for the same important factors.

8.5.1 Frailty and Caregiver Stress

Previous work in this area has identified that Alzheimer caregiver strain is related to markers of low grade systemic inflammation and coagulation activation, which are also part of the frailty syndrome . This study did not include a measure of the biological syndrome model of frailty however, merely measuring associated pro-inflammatory markers that have a known relationship with both frailty and the ageing process. We further advance this research by showing a clear association between perceived carer stress levels and increased risk of being in a transitionary stage of frailty – the pre-frailty or intermediate stage as measured using the biological syndrome model. We found this to be true in both younger and older caregivers even when controlling for age, gender and other co-morbid illnesses. Whilst only a cross-sectional association, we are unable to determine causality, yet our findings clearly suggest that the level of stress associated with dementia caregiving could play an important role as a driver of frailty. This certainly warrants replication and follow-up within a prospective study.

Spousal caregivers to patients diagnosed with Alzheimer's disease represent a chronically stressed population, and have been shown to have increased physical and

psychiatric morbidity (Mahoney *et al.*, 2005; Schulz *et al.*, 1995). The chain of biologic adaptations due to encountering environmental challenges might be an important mechanism linking chronic caregiving stress to adverse health outcomes. Past research suggests that distressed caregivers exhibit increased sympathetic-adrenal-medullary (SAM) arousal compared with non-caregivers (Aschbacher *et al.*, 2008; Mills *et al.*, 1997). If this system is frequently activated or sustained over time, one's risk for cardiovascular diseases may increase (Ross, 1999; Shaw *et al.*, 1999). Similarly a strong interplay between arterial vascular pathology, inflammation and coagulation has been identified. Factors which underlie a pro-inflammatory state that are common to both cardiovascular disease and frailty have been associated with chronic dementia caregiver stress (Kanel, 2003; 2006). We have contributed to this growing evidence base linking carer stress levels with emerging frailty.

Whilst these findings have to be validated longitudinally, their importance is clear. If caregiving stress truly does drive individuals towards a transition to frail health then potentially factors that alleviate this stress may also impact on physical frailty. As our population of dementia sufferers grows, so to does our pool of caregivers. If stressed caregivers are more at risk of a rapid transition to frailty then there is an increasing importance to address this to minimise the negative health impacts of dementia care provision. We identified a higher than anticipated proportion of carers which fell within the intermediate stage of frailty within our younger caregiver cohort, which suggests this phenomenon of an association between stress and frailty is not contained to older spousal carers. This begs the question whether commencing a 'caregiving career' at a younger age is more detrimental to health than providing care in your later

years. Our study cannot accurately answer this hypothesis, but it certainly is worthy of further investigation.

8.5.2 Frailty and the Younger Dementia Caregiver

Our evaluation of the relationship between both carer and care-recipient factors associated with frailty within the younger caregiver cohort revealed some other important findings. Notably less preparedness for the caregiving role, higher subjective burden and poor mutuality with their care recipient all increased the likelihood of younger caregivers being in a stage of pre-frailty. We also identified that poorer functioning in the area of activities of daily living as measured using a disability score, as well as a higher level of neuropsychiatric symptoms were two care recipient factors that also increased the likelihood of being at a transitionary state of frailty for younger caregivers.

Caregiver burden is a subjective measure of the physical, economic and psychosocial strain of care-giving and is considered the product of a dynamic interaction between caregiver resources, vulnerabilities and care demands (Vitaliano, 1990). Two models of factors leading to carer burden are most widely referred to. In the Poulshock and Deimling model, dementia leads to a burden of care which can manifest as strain in a number of ways that can be exacerbated (eg, by behavioural disturbance, physical or psychological ill-health in caregiver) or ameliorated (eg, by support, mature coping mechanisms) (Poulshock and Deimling, 1984). In Campbell and colleagues review of the model, the strongest predictors of caregiver burden were sense of "role captivity" (carer feelings of being "trapped" in their role), caregiver overload (eg, fatigue and

burnout), adverse life events outside of the caregiving role and relationship quality (Campbell *et al.*, 2008).

Dementia caregiver burden has been associated with increased risk of various health problems including cardiovascular problems, lower immunity, poorer immune response to vaccine, slower wound healing, higher levels of chronic conditions (such as diabetes, arthritis, ulcers, and anaemia), more doctor visits and use of prescription medications, poorer self-rated health, decreased engagement in preventative health behaviours such as exercise, and greater likelihood of smoking, drinking alcohol, and poor sleep patterns (Baumgarten *et al.*, 1992; Pruchno and Potashnik, 1989; Schulz and Martire, 2004; Schulz and Williamson, 1997). It is not surprising therefore that we have identified it as a significant factor associated with a stage of intermediate frailty in younger caregivers. A 2003 survey of 227 US dementia caregivers found that nearly one quarter provided 40 hours of care or more per week (compared with 16% for nondementia caregivers). This included personal care such as bathing, feeding, and assisting with toileting for 65% of caregivers. Over two thirds of caregivers sustained this commitment for more than 1 year and one third for 5 or more years. Younger caregivers may have other factors contributing to their burden of care such as work or family commitments outside the caregiver role. Whilst this is speculation on our part, our finding that carer burden could represent an important driver of deteriorating health in the younger caregiver, in the form of emerging frailty certainly warrants further evaluation in the context of a prospective study.

We have also identified that a reduced sense of preparedness for the caregiving role and an impaired relationship between carer and care-recipient as measured by

mutuality, may also be significant factors that contribute to a pathway to frail health. There are many reasons to be concerned about caregivers at the outset of their career. Though dementia sets in slowly and subtly, diagnostic disclosure confirms the irreversibility of the condition and marks the official entry into the caregiver role (Aneshensel *et al.*, 1995; Keady and Nolan, 2003; Quinn *et al.*, 2008) During this transition period, family members need to meet the challenges of becoming a caregiver, learn a host of things regarding their new responsibilities, and plan for the future (Keady and Nolan, 2003; Quinn *et al.*, 2008). Role transition represents the passage from one state or condition to another. Transitions are associated with life development stages or with specific situations, such as the passage toward new roles.

From the perspective of the role transition theoretical framework described by Meleis et al., the transition to a new role such as the caregiver role presents specific contextual characteristics (Meleis *et al.*, 2000). These include the necessity to develop self-confidence to deal with caregiving situations, to demonstrate a mastery of skills needed to manage the new situations, to acquire new knowledge of relevant formal services, and to feel connected with their informal social support network. It is necessary to understand the caregiving context in which this role transition occurs in order to guide practice and facilitate this role transition process. The challenges associated with becoming the caregiver of a person with dementia include, lack of informal support, lack of knowledge of formal services, lack of preparedness to provide care, and difficulty planning ahead for the relative's future care needs due to lack of knowledge of the disease process. Potential pro-active interventions from the outset of the caregiver career, such as early assessment of caregiver needs for support

and of caregiver preparedness to provide care, as well as psycho-educational interventions may foster a healthier transition to the caregiver role.

According to two literature reviews (Bamford *et al.*, 2004; Carpenter and Dave, 2004) and other studies (Connell *et al.*, 2004; Robinson *et al.*, 2005) caregivers receive little information about dementia and its prognosis at time of diagnostic disclosure. Robinson et al. pointed out that diagnostic disclosure alone did not prepare caregivers to plan for future care. It has also been reported that caregivers needed more information about formal services (Connell *et al.*, 2004; Robinson *et al.*, 2005). According to a survey conducted in four European countries (George and Gove, 2007), less than one third of caregivers were informed of services available to them. Laakkonen et al. revealed that half the spouse caregivers in their study felt that the follow-up care delivered to their partners with dementia was not well organized and expressed uncertainty about how to deal with future care (Laakkonen *et al.*, 2008). Other studies refer to caregivers feeling they were left to their own devices in order to meet their new caregiver responsibilities despite having to develop new skills to respond to their relative's behaviours (Ducharme *et al.*, 2009; Ducharme *et al.*, 2011).

A qualitative study evaluating the perceptions of preparedness and support during hospice care for informal caregivers of cancer patients showed caregivers interpreted preparedness in a variety of ways, such as being prepared for: specific caregiving tasks, the patient's diagnosis/prognosis, disease progression, and death and dying (Cagle *et al.*, 2010) Also related to preparedness, caregivers discussed their expectations about the illness and what they anticipated their caregiving role would entail. When the expectations of respondents were closely aligned with the actual experiences, caregivers expressed feeling better prepared. For example, being

provided with detailed information about the disease and dying process was frequently noted as a helpful way to prepare caregivers. Prior to the death, caregivers remarked about how unprepared they felt to confront the realities of caring for someone with cancer. Several described being caught "off guard" by the unexpected illness, which made preparation a difficult, if not impossible, task: These caregiver narratives reinforce the importance of preparing and supporting family caregivers for both the physical and emotional aspects of this role.

It is conceivable that the same importance could be applied to being prepared for the caregiving role of dementia patients. The findings from this qualitative study are consistent with a growing body of literature that identifies effective communication among patients, family members, informal caregivers, and health care professionals as a primary means of instilling a sense of preparedness (Herbert *et al.*, 2009; Waldrop *et al.*, 2005) Despite the fact that family-provider discussions on topics like potential responsiveness to treatment, disease progression, and prognosis all involve some level of uncertainty medical and allied health care professionals are in the position to help informal caregivers feel better prepared to deal with the many unknowns, while also reassuring them that they are not expected to handle unanticipated problems alone. The caregiving experience is more apt to be a positive experience if the caregiver has adequate physical, emotional, informational, and financial support, in other words, feels prepared to meet the multiple demands of providing good care, being prepared to take on specific care-related tasks or knowing how to anticipate the trajectory of the dementia process. Preparedness has a tangible dimension—knowing what to do—as well as an emotional dimension—being prepared to cope with the stressors and emotional demands of the role.

We have identified that a lack of preparedness in younger caregivers may have a significant impact on their physical health. If preparedness is a factor relating to health outcomes in dementia caregiving as suggested by our findings then early interventions addressing caregivers' readiness to assume the caregiving role may promote a healthier transition. The assessment of preparedness throughout different stages of the caregiving role for dementia caregivers could better reflect the dynamic and temporal aspect of the caregiver trajectory and help pre-empt caregiver health decline contrasting the belief that supportive interventions become important only when caregivers are at risk of health problems. Family carers can be trained and supported to maintain their own well-being; interventions focussed on counselling and the provision of practical and psychosocial support have been shown to be cost effective, increase carer competence, and improve quality of life, mood and the health of both people with dementia and their carers (Graf *et al.*, 2003). Such interventions may also have a positive impact on emerging frailty if it is associated with reduced readiness for the caregiver role.

We also found an effect of reduced relationship quality as measured by mutuality on increasing the likelihood of younger caregivers being at an intermediate stage of frailty. Although stress-buffering resources in the context of the caregiving career are more often conceptualized as social support or coping effectiveness, a few researchers have begun to explore the moderating effect of interpersonal resources within the care dyad, such as the quality of the relationship between caregiver and care receiver. The majority of this work to date has been on caregivers of cancer patients. For example, Williamson and Schulz (1995) demonstrated that relationship quality (conceptualized

as a history of communal behaviour) moderated the linkage between caregiver burden and depressive symptoms in cancer caregivers. When relationship quality was low, caregivers experienced higher levels of depressed affect at both low and high levels of caregiver burden. More recent work looking specifically at mutuality as a measure of relationship quality in cancer caregivers has identified that with lowered mutuality caregivers were at risk for negative outcomes (Schumacher *et al.*, 2007; Schumacher *et al.*, 2008).

Caring for a loved one can be an integral part of many close relationships throughout life, but there are times when the care situation can come to dominate a relationship and offset previous interactions (Pearlin *et al.*, 1990). As care situations are increasingly unpredictable and result in many changes to the physical health and depression of the dyad, mutuality has been shown to deteriorate over the family care experience, understanding the association between changes in physical health and depression and changes in mutuality over time will advance our understanding of the well-being of the care dyad (Lyons *et al.*, 2007). We have shown a clear association between deteriorating relationship quality as measured by lower mutuality and an important physical health variable in emerging frailty for younger caregivers. Family relationships can be complicated by an illness experience and alter the way the older adult and family caregiver share information and communicate regarding well-being and the care situation (Druley *et al.*, 1997; Druley *et al.*, 2003). Yet, family caregivers, who report good relationship quality with the older adult have been found to have significantly lower role captivity (feeling of being trapped by the caregiver role) and overload (Lawrence *et al.*, 1998) and high family caregiver mutuality has

been associated with less frequent engagement in potentially harmful behaviours (Williamson *et al.*, 1998).

In this way it is not surprising we have found an association between lower relationship quality and emerging frailty. The fact that this association is specific to younger caregivers however is interesting. This may reflect the lower proportion of spousal caregivers in the younger category which we would hypothesise may have an influence on relationship quality in times of ill-health. This is merely speculative on our part and would have to be borne out in a larger comparative study as we do not have sufficient evidence to draw this conclusion. Nevertheless our finding of an association is supported by findings in other study groups who have identified that, one's own worsening physical health may interfere with the ability to sustain a good relationship with the other dyad member, whereas improving health may invigorate one's mutuality with the other dyad member. Although it might be assumed that physical health changes influence mutuality, rather than the reverse, it is possible that changes in mutuality, in turn, affect how physical health is rated (Lyons *et al.*, 2007).

We did not identify any care recipient factors that retained an association with frailty in our older caregiver group, indicating that there are likely other more important variables such as ageing and co-morbid illness contributing to the frailty pathway in this population. However that was not the case for our younger caregivers, where we found poorer functioning in the area of activities of daily living, as well as a higher level of neuropsychiatric symptoms increased the likelihood of this population being at a transitionary state of frailty even controlling for factors such as age and co-morbid illness. Functional decline and neuropsychiatric symptoms are already known

to be important factors associated with increasing carer burden (Black and Almeida, 2004; Coen *et al.*, 1997; Gallagher *et al.*, 2011). Our findings suggest they may also have an impact on other caregiver health outcomes such as emerging physical health decline in the form of frailty. Given our work is cross-sectional we are unable to draw direct conclusions as to causality however this findings is fitting with the wealth of evidence base available that suggests these care-recipient factors of functional decline and neuropsychiatric symptoms have an adverse effect on caregiver outcomes.

Evidence suggests that in the initial stages of disease time spent assisting and supervising the patient with instrumental activities of daily living may be more burdensome while neuropsychiatric symptoms impose increasing demands as the disease progresses (Gallagher *et al.*, 2011). Of course neuropsychiatric symptoms are significantly correlated with both functional decline and increasing patient dependence and it is likely that commonly occurring behavioural symptoms such as depression and anxiety undermine functional ability and increase dependence needs thereby presenting a therapeutic opportunity in a proportion of patients. Therefore our finding of an association between these factors and deteriorating physical health in younger caregiver may offer us an important window for intervention to minimise adverse effects. The reason as to why this association was identified in younger caregivers only remains unclear and cannot be elucidated from our study. However we would hypothesise that the impact of increasing age and multimorbidity in our older caregivers increase in importance as factors moderating the transition to frailty, whilst in younger caregivers it appears that both care-recipient and caregiver factors continue to hold weight as potential drivers along a frailty trajectory. Within the context of our study we cannot draw any conclusions on this hypothesis, instead our

findings pave the way for the relationship between caregiver and care-recipient factors driving frailty to be more closely evaluated in the course of a prospective study. Investigation of this area specifically within a younger cohort of primary caregivers may provide us with important information that could contribute to the minimisation of adverse health impacts on those embarking on a 'caregiving career' and positively impact on the already significant effort expended by informal caregivers.

8.5.3 Limitations

The primary limitations of this work have already been referred to throughout this discussion. Namely the cross-sectional nature of our study prevents us from infering causality in any identified association. Nonetheless we bring some interesting evidence to the fore in the important area of dementia care provision. Further limitations lie in the small number of caregivers evaluated and their variable spread in age. Yet our division of the sample into a category of younger and older caregivers addressed this particular issue. Whilst this may have negatively impacted our population size, we are of the opinion it is in fact an important distinction. As our pool of family caregivers continue to grow globally the importance of understanding the differences amongst caregiver types is becoing readily apparent. The impact of embarking on a caregiving pathway may be significantly different to a spousal caregiver in their seventies when compared to a younger child caregiver in their early fifties. The psychological, social and physical effects of caregiving may map out quite differently in these cohorts. So whilst our division of our caregiver population into two groups certainly poses a limitation in our sample size, it also infers a strength if the differences in types of caregiver are to be accounted for.

A further limitation of our sample however is the fact when the frailty characterization was applied an almost negligible amount of caregivers fell into the full-blown frailty category. Instead a larger than anticipated proportion fell into an stage of pre-frailty or intermediate frailty. This certainly may have influenced our findings in that we failed to capture a truely frail caregiver population. Regardless of this however the strength in our findings potentially lies in the increasing importance of identifying frailty at an early stage. Studies show that pre-frail elderly persons are more likely than non-frail elderly persons to develop the full syndrome (Fried *et al.*, 2001). Dynamic frailty is defined as a decline in the measurement of frailty markers over a 3-year period, with or without a diagnosis of frailty. Dynamic frailty, even when adjusted for age, education, disability, chronic disease, and static frailty markers, is associated with an increased mortality (Puts *et al.*, 2005a). This evidence therefore points us to the fact that there are stages of frailty transition that may have potential for intervention. The likelihood however of transitioning from a stage of full frailty to non-frailty is extremely rare however (Gill *et al.*, 2006). These findings highlight the importance of a focus in frailty research on early identification and intervention to optimise the chances of prevention or amelioration of full-blown frailty and adds strength to our findings in relation to factors associated with an emerging state of frailty in dementia caregivers both young and old.

8.6 Overall Conclusion

The number of people aged over 65 will rise from 390 million now to 800 million by 2025 - reaching 10% of the total global population. Increased survival leads not only to increasing numbers of healthy elders, but also frail and disabled elders. Researchers, policy makers, administrators and health care providers generally agree

that frailty will have a significant impact on affected individuals, their families particularly those involved in care-giving, the health care system and society as a whole.

This thesis has focused on contributing valid and sound research findings on novel clinical aspects of frailty, deepening our understanding of this phenomenon in order to facilitate future clinical and scientific work that is based on a broader and more in depth body of evidence than has been available to date. We have recruited and assessed over 600 community dwelling elders, over 100 cognitively impaired participants and over 100 dementia caregivers to participate in the studies described. Given the paucity of information available in certain areas of health associated with frailty, such as cognitive and psychological health we have primarily focused on these areas. We hope that the research findings generated from this study will enable new basic science hypotheses in frailty and direct future experimental and clinical research that might not necessarily be considered without our work.

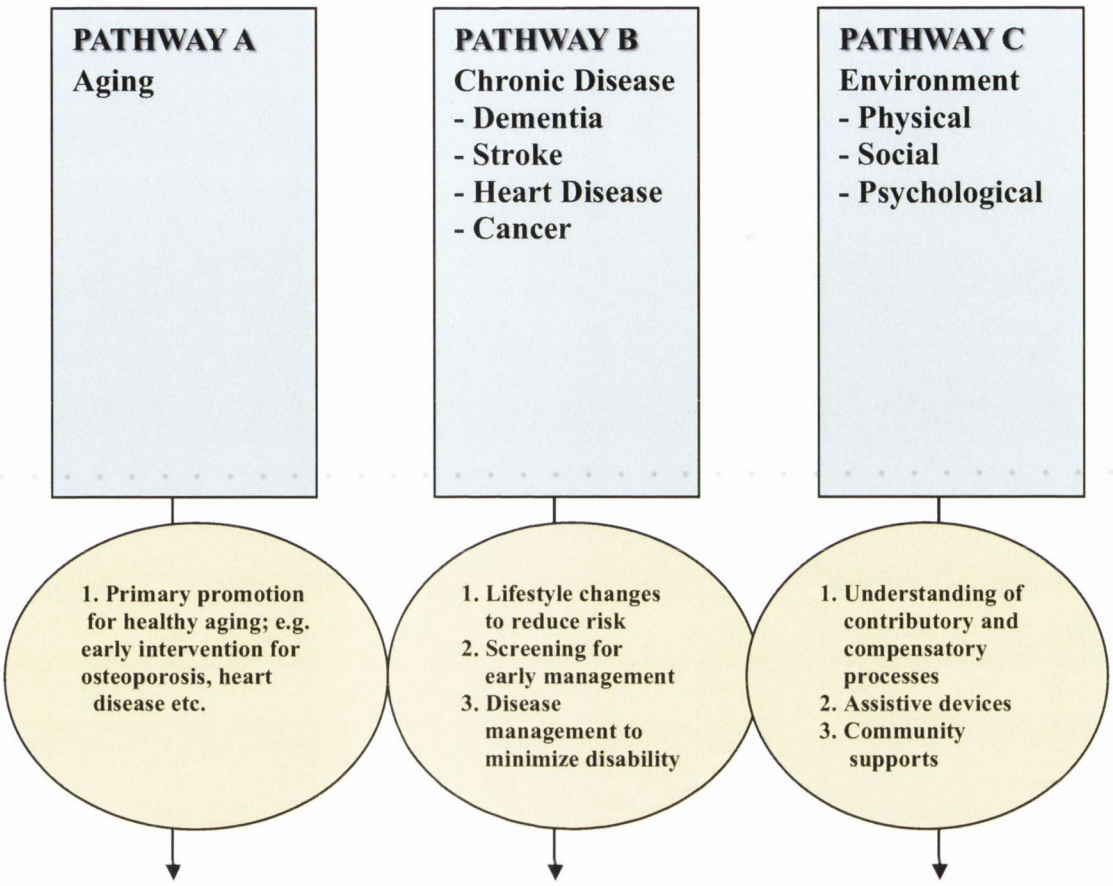
Our findings suggest that older persons who are becoming increasingly frail according to the frailty phenotype could be considered psychologically frail with an increased likelihood of emotional disturbance, notable anxiety and depressive symptoms. We have also found these psychological symptoms associated with frailty are important in determining the link between social isolation and loneliness and so may represent key targets in any interventions for frail and socially vulnerable elderly. Our work also makes an important contribution in the area of falls focusing specifically on the psychological phenomenon fear of falling. We provide preliminary evidence that

addressing depressive symptoms in fallers at a transitional level of frailty may be important to reduce fear of falling in this group.

We have also contributed to identifying and clarifying how cognition and frailty may be related, allowing us to target novel areas for future prospective and interventional studies. We have shown that global cognitive performance was poorer within both pre-frail and frail elderly, specifically within the areas of prospective memory, executive functioning and praxis and that the likelihood of having impaired executive functioning was increased fourfold if you were a pre-frail or frail elder. Our work also presents preliminary data that suggests frailty is a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity. Indicating that optimized management of co-morbid illness in dementia patients and adoption of stringent preventative health strategies in those at the stage of MCI may play a role in minimizing the health impact of frailty in this group. We have also identified an important correlation between advancing frailty and health related quality of life in cognitively impaired patients and similarly associated frailty with increasing informal health care costs which may have an important impaact not only on the dementia caregiver but on society as a whole given our rapidly aging population. We also explored frailty in the dementia caregiver, identifying perceived stress as a key factor increasing the likelihood of both younger and older caregivers being at a transitionary stage of frailty. These findings may prove beneficial in identifying areas for future intervention studies and rehabilitation programmes in which the aim is to improve health outcomes for caregivers.

We know frailty is a significant risk factor for disability, institutionalization and death. The evidence on frailty to date points us towards a multifactor aetiology which may be modifiable through multiple pathways. Figure 8.1 shows us a conceptualization of these pathways leading to frailty and the potential for intervention to minimize frailty and adverse outcomes. Interventions may include early health promotion and screening with rapid access interventions, community supports and assistive devices to address frailty. Our work on frailty has and will continue to significantly contribute to the current knowledge base regarding potential areas for health promotion and early intervention. We have contributed novel findings to the scientific literature improving our understanding of the contributory and compensatory process that may occur in the face of emerging frailty in vulnerable groups of elderly individuals. We are all in agreement that frailty and our aging demographics are an area of increasing public health concern that needs to be addressed. This thesis stands to contribute significantly to our expanding knowledge of frailty assisting researchers, health professionals and policy makers in addressing this complex syndrome in the future.

Figure 8.1 Pathways to Frailty



Appendix 1 - Bibliography

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Correlates of frailty in Alzheimer's disease and mild cognitive impairment†

SIR—The global prevalence of dementia is rising with Alzheimer's disease (AD) accounting for 50–60% of all cases and mild cognitive impairment (MCI) its precursor [1, 2]. Although the clinical hallmark of AD is progressive loss of memory and cognition, several studies have also shown changes in mobility and body composition suggesting frailty [3, 4]. Frailty represents age-related reduction in physiological reserve and resistance to stressors that can be delineated from comorbidity [5, 6]. It infers increased risk of health decline, disability and mortality regardless of concurrent illnesses. Intervention in the early stages may lead to reversal of frailty and prevent some of its adverse outcomes [6]. Individual components of frailty; impaired grip strength, slowed gait and low body mass index (BMI), have been shown to predict development of dementia and are associated with incident MCI [7–10]. The frailty syndrome within cognitively impaired patients may represent an important area for intervention that has yet been adequately investigated. A diagnosis of AD or MCI can mean considerable heterogeneity in terms of age, comorbidity, course of illness, cognitive impairment, functional limitations and abnormalities of behaviour. This study enables a consideration of the relation, if any, between frailty and these domains of clinical heterogeneity in a group of patients with AD and MCI.

Methods

Participants were recruited through the cross-sectional Enhancing Care in Alzheimer's Disease (*EC4D*) study at the memory clinic of St James's University Hospital, a Trinity College affiliated hospital in Dublin, Ireland [11]. Inclusion criteria were community-dwelling persons of age >55 years with a diagnosis of probable AD or amnestic MCI. Patients were excluded if they had a significant independent cause of disability (e.g. Parkinson's disease or dense hemiplegia). Ethics approval was obtained. Probable AD was diagnosed according to the NINCDS-ADRDA criteria and MCI according to international consensus criteria [12, 13]. Diagnoses were reviewed and Mini-Mental State Examination (MMSE) conducted at the time of recruitment [14]. Sociodemographic and medical details to include all known comorbid illnesses were collected as part of a structured questionnaire. Patient function was assessed with the Disability Assessment for Dementia scale (DAD) and neuropsychiatric symptoms with the Neuropsychiatric Inventory (NPI) [15, 16]. Severity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score [17].

†This work has been presented at the 6th Congress of the European Union Geriatric Medicine Society 2010 for which the President's Medal for best poster presentation was awarded.

Frailty

Frailty was measured using the Biological Syndrome Model [5, 18]. Shrinking was defined as a BMI of ≤ 18.5 kg/m^2. Exhaustion was defined by two questions from the Center for Epidemiologic Studies Depression scale (CES-D), 'I felt that everything I did was an effort', 'I could not get going' [19]. One of four responses were chosen, depicting frequency of occurrence in last week, giving a score of 0–3. Subjects answering '2' or '3' to either question were categorized as frail. Slowness was measured by usual pace walking speed and weakness by grip strength using cut points from the Cardiovascular Health Study [20]. Low activity was defined by kilocalories expended per week, <383 kcals for men and <270 kcals for women, based on responses to the Minnesota leisure time activity questionnaire [21]. Primary caregivers of the cognitively impaired participant confirmed all self-report criteria. Frailty score represented an ordinal variable of six categories ranging from 0 indicating completely robust with no frailty criteria present to five representing complete frailty. Participants with 0–1 criterion present could be determined as non-frail, those with two frailty criteria to be intermediately frail and those with three or more criteria to be fully frail [22].

Statistical analysis

The collected data were analysed using the SPSS 16.0 statistical package program. Frailty was included in all analysis as an ordinal variable with six categories from 0 to 5. Bivariate analysis using the Spearman correlation coefficient was performed to assess the strength of association between frailty and our explanatory factors which represented markers of clinical heterogeneity in our sample, to include; age, number of comorbid illnesses, cognitive impairment, a measure of global illness severity, functional limitations and neuropsychiatric symptoms. A proportional odds ratio model was then constructed to evaluate the relationship between frailty and the explanatory factors. Variables that on bivariate analyses were associated with frailty were entered into the model determined by the strength of their association. We set the critical value for significance in all analysis at $P < 0.05$. Test of parallel lines was completed to test the proportional odds assumption and the validity of our logistic regression model.

Results

A total of 115 patients were assessed, 44 men and 71 women. Ninety-five participants had a diagnosis of AD and 20 a diagnosis of MCI. Mean age was 74 years and mean MMSE was 20. Using the definitions of robust, intermediately frail and frail as described in the methodology, 51.3% of patients were classified as robust or not-frail, while 48.7% were at an intermediate or complete stage of frailty (29.6% intermediately frail, 19.1% fully frail). The only significant difference in frail criteria between groups

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was in the category of weight loss which occurred more frequently in the AD group (Fisher's exact test, $P = 0.04$). Given the pathology was a binary variable (patients either had MCI or AD) it was tested as an additional predictor variable for frailty using a proportional odds ratio model. Frailty was not significantly different in either group (OR = 2.15, CI 0.88, 5.23, $P = 0.092$). Therefore, it was deemed both groups could be pooled for the analysis.

There was no significant correlation between frailty and gender in our sample (Spearman's rho, $P = 0.353$). Table 1 shows the explanatory variables that were significantly associated with frailty on bivariate analysis. Deteriorating functional ability, increasing neuropsychiatric symptoms, a higher number of medical comorbidities, increasing illness severity, declining cognitive scores and advancing age all correlated with escalating frailty. Having identified these significant associations we conducted ordinal logistic regression. A proportional odds model was constructed to include the variables described in Table 1 to determine the key correlates of frailty in our cognitively impaired older cohort. (Table 2) Increasing number of medical comorbidities and advancing age were retained as the factors positively associated with escalating frailty. For each additional comorbid illness, the expected odds of increasing frailty were 1.69 greater. (CI 1.24, 2.31, $P = 0.001$) With each advancing year, the odds of increasing frailty were 1.07 times greater. (CI 1.02, 1.12, $P = 0.007$). Test of parallel lines was completed to verify the proportional odds assumption in our logistic regression model. No difference was identified in the coefficients between models and so the validity of our model was confirmed. ($P = 0.999$)

Discussion

We present preliminary data that suggest frailty is a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity. An association between frailty and ageing has already been shown in older cohorts [23]. Our findings suggest that in the cognitively impaired it continues to be an important correlation, other factors notwithstanding. Increasing burden of comorbid illness inferring a higher likelihood of frailty is also consistent with the current theory, where the cumulative effect of multiple age and disease-related impairments leads to a degradation of physiological systems. Frailty emerges from this vulnerable health state and may contribute to further decline in functional performance and an increased risk of poorer outcomes [24, 25] Optimized management of comorbid illness in dementia patients and adoption of stringent preventative health strategies in those at the stage of MCI may play a role in minimizing the health impact of frailty in this group.

The longitudinal association between frailty, incident MCI and AD has previously been reported in community-dwelling older persons [10, 26]. Further work, however, has shown the risk of developing dementia is fivefold in those with cognitive impairment irrespective of their frailty status [27]. This suggests frailty is not necessarily a predictor of dementia but may represent a separate pathophysiological process, independent of cognitive decline. Our results support this hypothesis. Markers of cognitive decline and illness severity did not retain significance with advancing frailty in our analysis. Other groups evaluating frailty beyond the biological syndrome model have included cognitive impairment as an inherent criterion for frailty. Our findings, however, show a high proportion of robust and intermediately frail participants within our cognitively impaired group. Not all cognitively impaired persons are frail. The importance of this lies in the modifiable nature of frailty and its potential role as a novel target for intervention. We hypothesize that the coincidence of cognitive

Table 1. Correlates of frailty on bivariate analysis

Variable	Spearman's Rho correlation coefficient	Significance
DAD score[a]	0.427	$P < 0.001$**
NPI score[b]	0.333	$P = 0.001$**
No. of comorbidities	0.285	$P = 0.002$**
CDR-SOB[c]	0.270	$P = 0.004$**
MMSE[d]	−0.223	$P = 0.019$*
Age	0.199	$P = 0.045$*

[a]Patient function was assessed with the Disability Assessment for Dementia scale.
[b]Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI).
[c]Severity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.
[d]Cognition was measured using the Mini-Mental State Examination.
*Correlation is significant at the 0.05 level (two-tailed).
**Correlation is significant at the 0.01 level (two-tailed).

Table 2. Proportional odds model depicting key correlates of frailty

Variable	Estimate	Std. Error	Sig.	OR	95% Confidence interval	
					Lower	Upper
No. of comorbidities	0.526	0.159	0.001**	1.69	1.24	2.31
Age	0.063	0.023	0.007**	1.07	1.02	1.12
DAD score[a]	0.013	0.028	0.648	1.01	0.96	1.07
NPI score[b]	0.010	0.009	0.233	1.01	0.99	1.03
CDR-SOB[c]	0.049	0.122	0.690	1.05	0.83	1.33
MMSE[d]	0.041	0.061	0.503	0.96	0.85	1.08

[a]Patient function was assessed with the Disability Assessment for Dementia scale.
[b]Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI).
[c]Severity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.
[d]Cognition was measured using the Mini-Mental State Examination.
**Correlation is significant at the 0.01 level (two-tailed).

impairment and frailty may accelerate the trajectory of decline in dementia. Preventive or treatment interventions focused on frailty independent of cognitive impairment could be effective at reducing poorer outcomes at a number of points on the pathway from MCI to end-stage dementia.

Limitations of our work include its cross-sectional nature. The validity of our results and hypotheses need to be evaluated in a longitudinal context. Further limitation is our combination of both AD and MCI participants, MCI may never in fact transition to AD. However, our interest lies in the investigation of frailty in those with established cognitive decline and our analysis identified the odds of frailty did not significantly differ between either group. This contributed to our rationale of combining both groups for evaluation. We also acknowledge our results may not be generalizable to a larger population. Findings from our population of patients with MCI and mostly mild to moderate AD may not be readily extrapolated to patients with more severe cognitive impairment. Similarly those persons who present to memory clinics may have more functional impairments or be frailer than other persons with MCI or AD. Another critical issue involves the assessment of dementia patients and the validity of the self-report measures used. To address this, we cross-checked any self-report measures with primary caregivers to ensure the accuracy of our data prior to the analysis.

Key points

- Detection of frailty at an early point is possible in dementia patients at various stages including pre-dementia states.
- Emerging frailty is closely associated with age and increasing comorbidity in cognitively impaired patients.
- Frailty may be a target for intervention to address adverse consequences of the combined effect of frailty and cognitive decline.

Conflicts of interest

None declared.

Funding

This study was part-supported by an educational grant from Elan Pharmaceuticals (Janssen acquired the Alzheimer Immunotherapy Program from Elan in September 2009). The sponsor had no role in the design, execution, analysis or interpretation of data.

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doi: 10.1093/ageing/afr066
Published electronically 25 July 2011

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Alcohol use of older adults: drinking alcohol for medicinal purposes

SIR—Of Finnish adults aged 65–84 years, 54% of females and 77% of males had consumed alcohol in the preceding year in 2007 [1–3]. Older adults are sensitive to the effects of alcohol as a consequence of the physiological changes associated with ageing, a high prevalence of diseases and the concomitant use of multiple drugs. Older adults also experience higher blood alcohol concentrations for a given amount of alcohol than younger adults due to changes in body mass [4].

Research on older people's use of alcohol has focused mainly on problem-drinking and consequent health problems [5, 6]. However, there is also public awareness about the possible health promoting effects of moderate alcohol consumption demonstrated in epidemiological studies [7–13]. Alcohol has been used throughout history for medicinal purposes; since antiquity, wine has been believed to stimulate appetite and digestion [14].

Very few studies are available on how older people perceive the health effects of alcohol, and how they use alcohol for medicinal purposes [15]. The aim of this study was to investigate the medicinal use of alcohol by individuals aged 65 years and older. We investigated (i) the prevalence of alcohol consumption as self-medication, (ii) associated factors and (iii) the reasons for which alcohol is used to self-medicate.

Methods

In May 2007, a postal questionnaire was sent to computer-generated random sample of 2,100 older persons (≥65 years) from the Espoo Population Register, and re-sent after 3 months to non-respondents. Espoo is a city with 240,000 inhabitants (10% >64 years olds). The number of the potential respondents was 1973 when those in permanent institutional care ($n = 92$), deceased ($n = 16$), with native language other than Finnish/Swedish ($n = 31$) or with unknown address ($n = 14$) were excluded. Altogether 1,395 individuals returned the questionnaire (response rate 71.6%). The local ethics committee approved the study protocol.

A structured questionnaire was piloted prior to the postal survey on 17 elderly individuals to ensure that the questions were easy to understand. The question items concerning demographics and health-related variables were retrieved from our previous epidemiological studies [16–18]. The questionnaire consisted of demographic and health-related variables. In addition, respondents were asked to list any medical diagnoses received from their doctors. Some categorisations were made for health-related factors and current use of medications. Charlson comorbidity index was constructed from medical diagnoses. It is a weighted index taking into account the number and severity of comorbid conditions [19]. To analyse the number of regularly prescribed drugs, participants were inquired to list their prescribed drugs.

Alcohol consumption was charted with several questions developed from the clinical guidelines for alcohol use in older adults [20] and the AUDIT (alcohol use disorders identification test) [21]. Quantity and frequency were ascertained by asking: 'How often do you have a drink containing alcohol, including beer, cider, wine, or liquor; spirits?', and 'On a typical day when you drink, how many drinks do you have?' (1 drink = can or bottle (330 ml) of beer, 12 cl of wine, 4 cl of liquor; spirits (one shot-glass), or 8 cl of sherry or madeira or aperitif. Alcohol-related problems were inquired: (i) 'Have you forgotten to take your medication when you have used alcohol (never/sometimes/often)?'; (ii) 'Has any of your relatives or friends been

International Psychogeriatrics: page 1 of 10 © International Psychogeriatric Association 2012
doi:10.1017/S1041610211002110

Frailty, depression, and anxiety in later life

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ABSTRACT

Background: Anxiety and depression are common in older people but are often missed; to improve detection we must focus on those elderly people at risk. Frailty is a geriatric syndrome inferring increased risk of poor outcomes. Our objective was to explore the relationship between frailty and clinically significant anxiety and depression in later life.

Methods: This study had a cross-sectional design and involved the assessment of 567 community-dwelling people aged ≥60 years recruited from the Technology Research for Independent Living (TRIL) Clinic, Dublin. Frailty was measured using the Fried biological syndrome model; depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale; and anxiety symptoms measured using the Hospital Anxiety and Depression Scale.

Results: Higher depression and anxiety scores were identified in both pre-frail and frail groups compared to robust elders (three-way factorial ANOVA, $p \leq 0.0001$). In a logistic regression model the odds ratio for frailty showed a significantly higher likelihood of clinically meaningful depressive and anxiety symptoms even controlling for age, gender and a history of depression or anxiety requiring pharmacotherapy (OR = 4.3; 95% CI 1.5, 11.9; $p = 0.005$; OR = 4.36; 95% CI 1.4, 13.8; $p = 0.013$ respectively).

Conclusions: Our findings suggest that even at the earliest stage of pre-frailty, there is an association with increased symptoms of emotional distress; once frailty develops there is a higher likelihood of clinically significant depression and anxiety. Frailty may be relevant in identifying older people at risk of deteriorating mental health.

Key words: frailty, anxiety, depression, elderly

Introduction

One in four older patients treated in the community have severe emotional problems, predominantly anxiety and/or depression, which are often under detected (Olafsdottir *et al.*, 2001). A cost-effective way to improve detection is to facilitate early identification of those elderly individuals at risk of mental health deterioration. This would allow us to target vulnerable groups with preventive strategies and early treatment to minimize burgeoning mental health difficulties. Well-established risk factors for depression and anxiety include female gender, somatic illness, cognitive impairment, functional impairment, lack or loss of close social contacts, and a previous history of depression or anxiety (Vink, 2008). A number of studies have also identified links between chronic diseases, the medically unwell and mental disorders (Jones *et al.*, 2004).

Within the current literature, there is increasing interest in and focus on the concept of physical frailty in older populations as measured by a phenotypic definition, the biological syndrome of frailty (Fried *et al.*, 2001). There is increasing consensus that this frailty phenotype is a definable clinical state that exhibits associations consistent with a syndromal presentation (Fleg and Lakatta, 1988; Evans, 1995; Leibel, 1995; Tseng *et al.*, 1995; Buchner *et al.*, 1996; Morley, 1997; Bandeen-Roche *et al.*, 2006). It is a multidimensional construct of age-related reduction in physiologic reserve and resistance to stressors, associated with adverse health outcomes, which may be reversible at an early stage (Fried *et al.*, 2001). A frailty phenotype has been operationalized, with a critical mass of

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core "frail" elements: weakness, poor endurance, weight loss, low physical activity and slow gait speed. The use of this frailty phenotype to assess and measure frailty provides us with evidence of frailty as a medical syndrome. This allows us to characterize frailty in individual older adults in a way that supports early assessment and screening for the syndrome. It seems necessary then as frailty research progresses to better understand the strength of association between emotional health disturbance and phenotypic frailty as measured by the biological syndrome.

To date the biological syndrome of frailty has been associated with increased depressive symptomatology in those not using antidepressant medications (Fried *et al.*, 2001). However, no further studies have specifically evaluated the association between clinically significant depressive symptoms and the frailty syndrome, controlling for other known risk factors such as age, gender and a history of previous depressive illness. More surprisingly, to date, to the best of our knowledge no studies have specifically investigated the association between generalized anxiety in older adults and the frailty phenotype in any capacity. Clarifying any association between the frailty phenotype and elderly individuals who are emotionally vulnerable is worthwhile not least because of the known adverse health outcomes linked to both. Understanding the points of onset of frailty and/or emotional disturbance is vital to early identification of at-risk individuals and intervention in those components that are first affected, when reversal may be most possible. An important factor to consider is the potential reversibility of frailty at an early stage (Fried *et al.*, 2004). If its association with deteriorating mental health persists even in the presence of other known risk factors for emotional disturbance then it may represent a key target for intervention that we are under-utilizing.

The primary aims of this study were (i) to characterize the frailty phenotype in a group of community-dwelling elderly; (ii) to evaluate the relationship, if any, between frailty and emotional disturbance as reflected by quantified depression and anxiety within the group; and (iii) to investigate the strength of any association identified between frailty and emotional disturbance in the presence of other well-established risk factors for anxiety and depression in an older population

Methods

This study had a cross-sectional design. A convienience sample of 567 participants was assessed at the Technology Research for Independent Living (TRIL) Clinic in St James's Hospital, Dublin (http://www.trilcentre.org/). Exclusion criteria were: Parkinson's disease, a dementia diagnosis, and previous stroke. The TRIL Clinic offers a comprehensive geriatric assessment to community-dwelling people aged >60 years incorporating the use of various technologies. The clinic has a national scope and encourages referrals from all over Ireland, including self-referrals. Local research ethics committee approval was obtained.

Frailty

Frailty was measured using the Biological Syndrome Model originally described by Fried which includes five frailty criteria: reduced walking speed, impaired grip strength, minimal physical activity, subjective exhaustion, and weight loss (Fried *et al.*, 2001). The presence of 1–2 frail criteria indicates a state of pre-frailty, the presence of ≥3 criteria indicates complete frailty. The criteria of subjective exhaustion in the Fried model is determined by two questions – "I felt that everything I did was an effort" and "I could not get going" – taken from the Center for the Epidemiological Studies-Depression Scale (CESD). Respondents answering "yes" to either question for much of the time (≥3 days) during the previous week are defined as having subjective exhaustion. Given that we utilized the same CESD scale to measure depressive symptoms, the use of the exhaustion criteria was thought to be a potential confounder in our analysis as it was associated with both our exposure (i.e. frailty grouping) and one of our primary outcomes (i.e. clinically significant depression). We therefore omitted the "exhaustion" criterion and our measure of frailty consisted solely of the four other frailty criteria, with cut-offs for determining pre-frailty and frailty remaining the same. The effect of this exclusion would have only been to underestimate the extent of frailty within the group. We were able to maintain the cut-offs for determining pre-frailty and frailty as it is merely the cumulative presence of two or more of any of the frailty criteria that determines the pre-frail or frail syndrome. Our only futher adaptation of the frailty criteria was our definition of weight loss which was assessed objectively as a body mass index (BMI) of less than 18.5 kg/m^2, rather than a subjective report of weight loss of more than 10 pounds (4.5 kg). This was reflective of similar adaptations for the weight loss criterion from other large population-based studies validating the biological syndrome model of frailty (Cigolle *et al.*, 2009). Slowness was defined in terms of walking speed using the cut-points from the Cardiovascular Health Study (CHS), after adjusting for distance (Fried *et al.*, 2001).Weakness was defined by assessing grip strength, again using

Table 1. Population characteristics according to presence of clinically significant (case-level) depressive symptoms (CESD-8 ≥4)

PARAMETER (n %)	CESD-8 < 4 (n = 475)	CESD-8 ≥ 4 (n = 92)	P[a]
Gender (Female)	299 (71.4)	65 (70.7%)	0.899
Social Class I & II[c]	147 (35.1%)	25 (27.2%)	0.180
Educational Level			
• Primary	117 (28.6%)	33 (36.7%)	0.140
• Secondary	212 (51.8%)	46 (51.1%)	
• Tertiary	80 (19.6%)	11 (12.2%)	
Marital Status			
• Never Married	57 (13.8%)	10 (11.1%)	0.495
• Current Partner	211 (51.1%)	44 (48.9%)	
• Separated/Divorced	20 (4.8%)	8 (8.9%)	
• Widowed	125 (30.3%)	28 (31.1%)	
Retired	366 (89.5%)	82 (92.1%)	0.561
Living Alone	161 (39%)	41 (45.6%)	0.286
Urban Dweller	364 (87.9%)	78 (87.6%)	1.000
PARAMETER (MEAN ± S.D)	CESD-8 < 4	CESD-8 ≥ 4	P[b]
Age	72.16 (7.3)	73.40 (7.4)	0.14
MMSE[d]	27.70 (2.1)	27.35 (2.1)	0.15
Comorbid Illnesses[e]	3.54 (3.1)	4.57 (3.0)	0.004*
IADL Score[f]	25.89 (2.2)	24.77 (3.1)	0.001*
Adverse Life Events[g]	1.94 (1.5)	2.68 (1.7)	<0.0001**
Loneliness Score[h]	1.10 (1.2)	2.17 (1.6)	<0.0001**

* Statistically significant $p<0.05$, ** $p<0.001$.
[a] χ^2 test, [b] Student t-test, [c] Higher social class, [d] Cognition as measured by the Mini-Mental State Examination, [e] Age-Adjusted Charleson Comorbidity Index, [f] Lawton Instrumental Activities of Daily Living Scale, [g] Geriatric Adverse Life Events Scale, [h] de Jong Loneliness Scale.

the same cut-points as the CHS dependent on gender and BMI. Low activity was defined in terms of kilocalories expended per week, calculated using the Minnesota Leisure Time Activity questionnaire. Participants were categorized into three groups: robust (non-frail) with no criteria present, those with one or two criteria were pre-frail, and those with three or more criteria were frail.

Anxiety

Anxiety was measured using the seven-item subscale from the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond and Snaith, 1983). Scores ≥11 are indicative of a case of clinical anxiety, scores in the 8–10 range represent borderline cases.

Depression

Depression was measured using a shortened form (eight items) of the 20-item Center for the Epidemiological Studies-Depression (CES-D-20) scale (Turvey *et al.*, 1999). A cut-off of 4 or more has been used on the CESD-8 item to determine case-level depression.

Additional measures

Cognition was measured using the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). Any patient currently prescribed a selective serotonin re-uptake inhibitor (SSRI) or any other antidepressant regardless of class was grouped as having a potential history of depressive or anxiety disorder. Loneliness was measured using the short-item de Jong Gierveld Loneliness Scale (de Jong-Gierveld and van Tilburg, 2008) and adverse life events using the Geriatric Adverse Life Event Scale (GALES) (Devanand *et al.*, 2002). Comorbid illnesses were measured using the Age-adjusted Charlson Co-morbidity Index (AACI; Charlson *et al.*, 1994) and functional level using the Lawton Instrumental Activities of Daily Living Scale (IADL; Lawton and Brody, 1969).

Statistical analyses

The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0. χ^2 tests were used to compare demographic categorical variables. The difference between means was compared using one-way

Table 2. Population characteristics according to presence of clinically significant (case-level) anxiety symptoms (HADS-A ≥11)

PARAMETER (n %)	HADS-A < 10 (n = 523)	HADS-A ≥ 11 (n = 44)	P[a]
Gender (Female)	336 (70.3)	37 (84.1%)	0.056
Social Class I & II [c]	162 (33.9%)	11 (25%)	0.247
Educational Level			
• Primary	134 (28.8%)	19 (43.2%)	0.120
• Secondary	245 (52.6%)	20 (45.5%)	
• Tertiary	87 (18.7%)	5 (11.4%)	
Marital Status			
• Never Married	62 (13.2%)	7 (15.9%)	0.630
• Current Partner	244 (51.9%)	19 (43.2%)	
• Separated/Divorced	26 (5.5%)	3 (6.8%)	
• Widowed	138 (29.4%)	15 (34.1%)	
Retired	416 (89.3%)	42 (97.7%)	0.107
Living Alone	184 (39.1%)	21 (47.7%)	0.266
Urban Dweller	413 (87.7%)	40 (93%)	0.458
PARAMETER (MEAN ± SD)	HADS-A < 10	HADS-A ≥ 11	P[b]
Age	72.38 (7.3)	72.98 (7.1)	0.59
MMSE[d]	27.73 (2.0)	26.80 (2.3)	0.004*
Comorbid Illnesses [e]	3.65 (3.1)	4.66 (3.1)	0.036*
IADL Score [f]	25.77 (2.3)	24.90 (2.9)	0.062
Adverse Life Events [g]	2.04 (1.6)	2.49 (1.5)	0.082
Loneliness Score [h]	1.19 (1.3)	2.47 (1.7)	<0.0001**

*Statistically significant $p<0.05$, ** $p<0.001$.
[a] χ^2 test, [b] Student t-test, [c] Higher social class, [d] Cognition as measured by the Mini-Mental State Examination, [e] Age-Adjusted Charleson Comorbidity Index, [f] Lawton Instrumental Activities of Daily Living Scale, [g] Geriatric Adverse Life Events Scale, [h] de Jong Loneliness Scale.

and three-way factorial ANOVA. Odds ratio was used to describe the risk of clinically significant depression and anxiety using the established cut-off points described in the methodology. A multiple logistic regression model was built using a stepwise method; variables other than frailty entered into the regression model were based on known predictors of anxiety and depression in older populations to include age, gender and a history of anxiety or depression requiring pharmacotherapy. The critical value for significance in all analyses was $p<0.05$.

Results

Of the 567 participants, 166 (29.3%) were male and 401 (70.7%) were female; the mean age was 73±7.4 years; the mean MMSE score was 27 ± 2, social class I and II accounted for 32% of the cohort; almost 50% had received primary level education only; 90% were retired; and 40% lived alone. On application of the Fried frailty criteria using the modified frailty index where the criteria of exhaustion was excluded, 309 (49.5%) were classified as robust, 289 (46.3%) were classified as pre-frail, and 26 (4.2%) were completely frail. Had the exhaustion criteria been included, 283 (49.8%) would have been classified as robust or non-frail, 247 (43.5%) as being pre-frail, and 38 (6.7%) as completely frail. Using the already established cut-off scores for our assessment instruments the HADS-A and CESD-8, we established that 92 (16.2%) participants fulfilled criteria for clinically significant depression and 44 (7.7%) fulfilled criteria for clinically significant anxiety.

Demographic, lifestyle, and clinical characteristics of participants with and without clinically meaningful depression and anxiety scores are displayed in Tables 1 and 2. There was no significant difference in gender, social class, educational level, marital, working or residential status between participants with and without clinically meaningful depression or anxiety scores. Those who were depressed were more likely to have a higher number of comorbid illnesses (Student-t test: $p = 0.004$), to have lower scores on the independent ADL scale (Student-t test: $p = 0.001$), a higher occurrence of adverse life events (Student-t test: $p<0.0001$) and higher self-reported loneliness scores (Student-t test: $p<0.0001$). Those who had clinically

Table 3. Population characteristics according to frailty categories

PARAMETER (n %)	ROBUST (n = 309)	PRE-FRAIL (n = 289)	FRAIL (n = 26)	P[a]
Gender (Female)	202 (70.1)	183 (70.4%)	16 (84.2%)	0.421
Social Class I & II [c]	101 (35.1%)	75 (28.7%)	4 (21.1%)	0.168
Educational Level				
• Primary	73 (26.5%)	385 (34.6%)	9 (50%)	0.001*
• Secondary	141 (51.3%)	132 (53.7%)	7 (38.9%)	
• Tertiary	61 (22.2%)	29 (11.8%)	2 (11.1%)	
Marital Status				
• Never Married	28 (10%)	40 (16.3%)	4 (22.2%)	0.404
• Current Partner	160 (57.1%)	109 (44.3%)	6 (33.3%)	
• Separated/Divorced	16 (5.7%)	13 (5.3%)	1 (5.6%)	
• Widowed	76 (27.1%)	84 (34.1%)	7 (38.9%)	
Retired	243 (88%)	228 (93.1%)	16 (88.9%)	0.150
Living Alone	101 (36.2%)	105 (42.7%)	9 (50%)	0.208
Urban Dweller	246 (87.9%)	217 (88.2%)	17 (94.4%)	0.702
PARAMETER (MEAN ± SD)	ROBUST	PRE-FRAIL	FRAIL	P[b]
Age	71.21 (7)	74.57 (7.5)	75.3 (7.4)	<0.0001**
MMSE [d]	27.92 (1.9)	27.01 (2.8)	24.58 (2.9)	<0.0001**
Co-morbid Illnesses [e]	3.01 (2.8)	4.77 (3.2)	6.21 (2.9)	<0.0001**
IADL Score [f]	26.37 (1.3)	25.07 (2.8)	21 (4.2)	<0.0001**
Adverse Life Events [g]	1.86 (1.5)	2.27 (1.6)	2.41 (1.6)	0.008*
Loneliness Score [h]	1.21 (1.3)	1.34 (1.3)	1.65 (1.6)	0.276

* Statistically significant $p<0.05$, ** $p<0.001$.
[a] χ^2 test, [b] One-way ANOVA, [c] Higher social class, [d] Cognition as measured by the Mini-Mental State Examination, [e] Age-Adjusted Charleson Comorbidity Index, [f] Lawton Instrumental Activities of Daily Living Scale, [g] Geriatric Adverse Life Events Scale, [h] de Jong Loneliness Scale.

significant anxiety scores had lower mean MMSE scores (Student-t test: $p = 0.004$), had a higher number of comorbid illnesses (Student-t test: $p< 0.0001$) and higher self-reported loneliness scores.

Demographic, lifestyle, and clinical characteristics of participants according to frailty groups are displayed in Table 3. There was no significant difference in gender, social class, marital, working or living status between frailty groups. The frailest group, however, had a higher proportion of participants who had only completed primary level education when compared to other groups (χ^2-test, linear by linear association: $p = 0.001$). There was also a significant difference in mean age between groups, with the frailer participants being older (one-way ANOVA, $p<0.0001$) and having a higher burden of comorbidity (one-way ANOVA, $p<0.0001$). Frailer groups also had significantly lower mean MMSE scores (one-way ANOVA, $p<0.0001$), mean independent ADL scores and a higher incidence of adverse life events (one-way ANOVA, $p = 0.008$).

The unadjusted mean depression scores by frailty group are displayed in Table 4. The *F* and *P* values were derived from a three-way ANOVA. There was a significant difference in depressive symptoms according to frailty groups showing higher depression scores with increasing frailty. This difference was not apparent between groups defined according to either gender or age. A polynomial contrast indicated that the linear trend for depression scores to increase with frailty was significant at $p<0.0001$. Pairwise contrasts showed that the difference in marginal means between robust and pre-frail groups was statistically significant at 0.59 points (95% CI 0.23, 0.94; $p = 0.001$). The difference in marginal means was also significant between robust and frail groups at 2.1 points (95% CI 1.12, 3.02; $p<0.0001$) as well as between pre-frail and frail groups at 1.5 points (95% CI 0.53, 2.44; $p<0.002$).Profile plots indicated there was no interaction between frailty, age and gender in the analysis of depression scores.

Table 4 also shows the unadjusted mean anxiety scores by groups; again the *F* and *P* values were derived from a three-way ANOVA. There was a significant difference in anxiety symptoms according to frailty groups showing higher anxiety scores with increasing frailty. This difference was not apparent between groups defined according to either gender or age. A polynomial contrast indicated that the linear trend for anxiety scores to

Table 4. Mean depression and anxiety scores according to age, gender and frailty status

	N	CESD-8 SCORE MEAN (SD)[a]	*F*(df)[b]	*P* VALUE	*P* VALUE TREND
Gender					
Males	147	1.58 (2.03)	0.935 (1,503)	0.334	–
Females	364	1.80 (1.87)			
Age					
60–69 years	194	1.44 (1.76)	1.693 (2,503)	0.185	0.094
70–79 years	222	1.85 (1.98)			
80+ years	93	2.12 (2.04)			
Frailty					
Robust	311	1.42 (1.79)	12.522 (2,503)	<0.0001	<0.0001
Pre-frail	184	2.10 (2.04)			
Frail	16	3.62 (2.55)			
	N	HADS-A SCORE MEAN (SD)[a]	*f*(df)[b]	*P* VALUE	*P* VALUE TREND
Gender					
Males	149	4.89 (3.02)	1.316 (1,514)	0.252	–
Females	373	5.51 (3.78)			
Age					
60–69 years	195	5.42 (3.52)	2.218 (2,514)	0.110	0.066
70–79 years	230	5.24 (3.59)			
80+ years	95	5.38 (3.72)			
Frailty					
Robust	267	4.54 (1.79)	21.704 (2, 514)	<0.0001	<0.0001
Pre-frail	221	5.86 (2.04)			
Frail	34	8.09 (2.55)			

[a] One-way ANOVA.
[b] Three-way factorial ANOVA model.

increase with frailty was significant at $p<0.0001$. Pairwise contrasts showed that the difference in marginal means between robust and pre-frail groups was statistically significant at 1.4 points (95% CI 0.80, 2.08; $p<0.0001$). The difference in marginal means was also significant between robust and frail groups at 3.8 points (95% CI 2.53, 5.06; $p<0.0001$) as well as between pre-frail and frail groups at 2.4 points (95% CI 1.10, 3.62; $p<0.0001$).Profile plots indicated there was no interaction between frailty, age and gender in the analysis of anxiety scores.

To determine if frailty grouping was associated with clinically significant depressive and anxiety symptoms we conducted logistic regression analysis using a score equal to and above the established cut-off points on the CESD-8 (≥ 4) and HADS-A (≥ 11) questionnaires as our outcome measure. We also adjusted for the effect of other potential risk factors such as age, gender, and a history of depression or anxiety requiring pharmacotherapy within the regression models (Table 5). The adjusted odds ratio displayed in Table 5 shows that those participants falling within the robust group were less likely to have clinically meaningful depression scores and so being in the robust category represented a protective factor against depressive symptoms (OR = 0.47; 95% CI 1.3, 3.4; $p = 0.002$). The odds ratio for pre-frailty did not quite reach statistical significance; however, the odds ratio for frailty showed a significantly higher likelihood of clinically meaningful depressive symptoms even controlling for age, gender, and a history of depression or anxiety requiring pharmacotherapy (OR = 4.3; 95% CI 1.5, 11.9; $p = 0.005$). Using clinically meaningful anxiety scores as our outcome measure (HADS-A ≥ 11), no association was found for robust or pre-frail groups. However, participants falling within the fully frail group had a significantly higher likelihood of anxiety (OR = 4.36; 95% CI 1.4, 13.8; $p = 0.013$).

Discussion

We have found that both pre-frail and frail elderly people experience more symptoms of anxiety and depression than those who are robust. Older persons

Table 5. Multiple regression analysis of frailty and case-level depression and anxiety adjusting for age, gender and past history of depression or anxiety requiring pharmacotherapy

CASE-LEVEL DEPRESSION CESD-8 ≥ 4					
FRAILTY	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)	B	S.E	SIG.
Robust	0.444 (0.3, 0.7)	0.473 (1.3, 3.4)	−0.748	0.24	0.002*
Pre-frail	1.730 (1.1, 2.7)	1.594 (0.9, 2.5)	0.467	0.24	0.054
Frail	4.893 (1.8, 13.4)	4.305 (1.5, 11.9)	1.460	0.52	0.005*
CASE-LEVEL ANXIETY HAD-A ≥ 11					
FRAILTY	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)	B	S.E	SIG.
Robust	0.471 (0.2, 0.8)	0.520 (0.9, 3.7)	−0.653	0.34	0.054
Pre-frail	1.483 (0.8, 2.8)	1.337 (0.7, 2.5)	0.290	0.33	0.866
Frail	5.443 (1.8, 16.4)	4.364 (1.4, 13.8)	1.473	0.59	0.013*

* $p<0.05$ ** $p<0.001$, S.E = Standard Error, Sig. = Significance, OR = Odds Ratio.

with established frailty, fulfilling three or more frail criteria, were an at-risk population more likely to have clinically significant anxiety and depression even when risk factors such as age, gender, and a previous history of anxiety or depression requiring pharmacotherapy were accounted for. Our findings suggest that older persons who are becoming increasingly frail according to the frailty phenotype could also be considered psychologically frail with an increased likelihood of emotional disturbance.

Little previous research has systematically examined anxiety and depression and their association with the biological syndrome model of frailty using well-validated psychological measures. One previous study looked at self-reported psychiatric illness in older people and found that for each additional deficit defining frailty, odds of psychiatric illness increased (Andrew and Rockwood, 2007). A further large epidemiological study also identified a relationship between depressive symptoms and incident frailty (Woods *et al.*, 2005). This study utilized a measure for depression, however, that includes exhaustion as a symptom, which was also a key feature within their frailty measurement and may represent a confounding factor given its potential association with both exposure and outcome. To avoid this we ensured the exhaustion criteria for frailty was not included in our analysis. Whilst this may have underestimated the level of frailty associated with anxiety and depressive symptoms it ensured exhaustion was not a confounding factor in our results.

The current consensus to include a measure of exhaustion as a criteria for the frailty phenotype may in fact reflect the likelihood that there is a psychobiological component to the fraity syndrome as suggested by our findings. Mental fatigue could be described as a symptom of depressive illness. It may in part explain our finding of an association between increasing depressive symptoms and frailty at both a pre-frail and fully frail stage, as well as our finding that participants who were classified robust were significantly less likely to be depressed whereas those with full-blown frailty had a higher likelihood of clinically significant depression. Those who are depressed may be more likely to become frail secondary to disengagement from daily activities, psychomotor retardation, and poor nutritional intake. Or those who are frail may be more likely to develop depressive symptoms due to impairment of their functional abilities and social withdrawal. Drawing the conclusion as to which comes first – frailty or depression – is not possible in the context of this paper; however, given our findings this certainly warrants investigation within the context of a longitudinal study.

There is an even greater paucity of literature evaluating the relationship between frailty and quantified levels of anxiety in older persons. One recent study did examine health anxiety specifically and its correlation with varying degrees of frailty in a small sample of community-dwelling elders (Bourgault-Fagnou and Hadjistavropoulos, 2009). They identified that seniors with high levels of frailty experienced greater levels of health anxiety. The authors of this paper called for further studies investigating the association between frailty and generalized anxiety in older adults. Most cases of anxiety disorder in late life remain undiagnosed

and untreated despite the fact they often have increased contact with medical services (Kennedy and Schwab, 1997). Inadequately treated anxiety leads to distress, functional impairment, and increased medical morbidity and mortality (Jones *et al.*, 2004). In combination with increasing physical frailty anxiety is potentially an additional risk factor for poorer outcomes.

Within our study we have identified an association between increasing symptoms of anxiety as measured by the HADS-A and frailty at both the pre-frail and frail stages. We have also found an increased likelihood of clinically significant levels of anxiety in those who can be classified as completely frail fulfilling three or more frailty criteria. The use of the HADS-A scale may in part explain the strength of association found between frailty and symptoms of anxiety. The HADS is designed to be adept at picking up symptoms of anxiety in those with underlying physical comorbidities as it has been purposely designed with the omission of somatic indicators of anxiety and depression. In this way it may be particularly attuned to identifying anxious symptoms in those with a higher burden of comorbid illness such as our frailer participants. There is likely a complex interplay between anxiety and physical health decline, such as that seen in increasingly frail states. Real worry and pathologic anxiety could be consequences of comorbid physical illness, or chronic anxiety might itself contribute to deteriorating health and increasing medical morbidity or mortality and act as a driver for frailty. Unfortunately it is beyond the scope of this paper to determine cause and effect; however future work in the form of a prospective study is required to validate our findings and may enable us to disentangle why frailty is related to anxiety and to determine causality.

Limitations of our study include its cross-sectional design and the use of a convenience sample, which may have introduced a selection bias making the external validity of our findings questionable. Our sample included those who self-referred to the study; these participants may have certain characteristics that were over-represented. For example, many participants were independently mobile, healthy, and fell within a "younger old" age group. Therefore we may have failed to capture a higher level of frailty and so lack the ability to generalize. This is reflected in the lower level of full-blown frailty evident in our population and a significant proportion of participants who were defined as pre-frail rather than frail, again representing a somewhat "healthier" study population. Despite this the proportion of pre-frail individuals we identified is consistent with findings from the large Cardiovascular Health Study where up to 46% of the total cohort at baseline were considered to be intermediately frail (Fried *et al.*, 2001). A further limitation potentially contributing to a failure to capture a higher level of frailty is our use of a modified version of the frailty index with the exclusion of the "exhaustion" criteria in order to facilitate the analysis of frailty and symptoms of anxiety and depression. This led to an underestimation of frailty as reflected in our results and may have influenced our findings relating to frailty and our emotional health outcomes. We must also point to the limitation of our use of a proxy outcome measure (i.e. cut-points on an assessment scale) for the identification of clinically significant depressive and anxiety symptoms, rather than the use of a structured clinical assessment.

Despite these limitations our work provides preliminary cross-sectional results that suggest an association between frailty and the mental health of older people. Increasing symptoms of anxiety and depression were associated with the stages of pre-frailty and frailty independent of age and gender. In addition, full-blown frailty was associated with a higher likelihood of clinically significant anxiety and depression independent of age, gender, and a history of depression or anxiety requiring pharmacotherapy. Our findings suggest that even at the earliest stage of pre-frailty, there is an association with increased symptoms of emotional distress and, once frailty develops, a higher likelihood of clinically significant depression and anxiety. Frailty may be relevant in identifying older people at risk of deteriorating mental health.

Our study increases awareness of the potential links between frailty and emotional disturbance in older adults. It suggests that healthcare professionals who work with frail elderly people should consider the possible co-existence of depression and anxiety. We contribute further support to a possible psychosocial or psychobiological component of the frailty syndrome. In scenarios that predict future health service delivery in the Western world, the rapid increase in the frail elderly population is seen as one of the major challenges of healthcare (Bergman *et al.*, 2007). Further prospective research is needed to clarify causality and to determine if frailty may be a potential interventional target for those with symptoms of depression and/or anxiety who are at risk of the development of case-level disorders. In the context of a comprehensive geriatric assessment the psychological correlates of frailty could be easily screened for. Timely identification and appropriate intervention for anxiety and depression in frailer individuals may then translate to improved outcomes for this vulnerable group of older people.

Conflict of interest

None.

Description of authors' roles

Dr Aine M. Ní Mhaoláin was the primary author, established the specific study hypothesis and design, completed all analyses and interpretation of data, and prepared the paper in full. Dr Chie Wei Fan was involved with the set up and design of the research project, reviewed the analysis and interpretation of data, and undertook critical analysis of the final paper. Dr Roman Romero-Ortuno and Dr Lisa Cogan, who were contributing authors, were involved in the recruitment of all study participants, completed comprehensive geriatric assessments for all participants and were involved in the interpretation of all study data. Ms Clodagh Cunningham was responsible for direct liaison with all study participants, and was involved in the recruitment and assessment of participants. Professor Rose-Anne Kenny had a supervisory role and was involved in approving the study concept and design, reviewing the analysis and interpretation of data as well as critical analysis of the completed paper. Professor Brian A. Lawlor took on the primary supervisory role and was involved in approving the study concept and design, reviewing the analysis and interpretation of data as well as critical analysis of the project at all stages, from initial data analysis to completion of the final paper.

Acknowledgments

The Technology Research for Independent Living Centre focuses on the research of new technologies to enable people to live independent lives for as long as possible in the environment of their choosing. The Centre is a joint initiative between Intel and the Industrial Development Agency Ireland. The Centre is an active research collaboration between industry and academic partners including Intel, Trinity College Dublin, University College Dublin and the National University of Ireland Galway, and represents a multidisciplinary team of up to 70 researchers including ethnographers, designers, clinicians, economists and a range of scientists and technologists.

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RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Depression: a modifiable factor in fearful older fallers transitioning to frailty?

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Objective: Fear of falling is one of the most common fears among community-dwelling older people and is as serious a health problem as falls themselves. Understanding fear of falling in fallers transitioning to frailty may help us identify effective strategies to reduce it in this already vulnerable group of older people. Our aim was to evaluate the psychological factors associated with fear of falling in a group of fallers transitioning to frailty when compared with robust or non-frail fallers.

Methods: Cross-sectional design where 301 fallers underwent assessment at the Technology Research for Independent Living Clinic in Dublin (http://www.trilcentre.org/) is seen. Fear of falling was measured using the Modified Falls Efficacy Scale, and frailty was measured using the Biological Syndrome Model. Psychological measures included assessment of anxiety, depression, loneliness, personality factors and cognition.

Results: Frailer fallers had increased fear of falling when compared with robust fallers ($p < 0.001$). Age, female gender and lower cognitive scores were associated with greater fear of falling in the robust group. For frailer fallers, higher depression score was the only factor associated with fear of falling on multivariate analysis. The odds ratio of having case level depressive disorder (CESD-8 ≥ 4) if you were a frailer faller was significantly higher than if you were robust (OR = 2.6, CI 1.3–5.2, $p = 0.006$).

Conclusion: Fallers at a transitional level of frailty may represent a particularly vulnerable group psychologically who would benefit most from interventional stratagies with specific intervention components addressing depressive symptoms. Copyright © 2011 John Wiley & Sons, Ltd.

Key words: fear of falling; frailty; depression
History: Received 18 May 2011; Revised 6 July 2011; Accepted 11 July 2011; Published online 23 December 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/gps.2780

Introduction

Falls represent a serious problem for community-dwelling older people with approximately one third falling annually. They are the primary cause of injury-related death and the third leading cause of poor health, hospitalization and disability (Tinetti and Speechley, 1989). Even a single fall in an older person may result in fear of falling, one of the most common fears among community-dwelling older people, where it is experienced by approximately half of the population (Friedman *et al.*, 2002). Fear of falling is suggested to be as serious a health problem as falls themselves (Zijlstra *et al.*, 2007b).

Fear of falling has been associated with objectively assessed measures of balance (Maki *et al.*, 1991), gait (Maki, 1997) and falls (Cumming *et al.*, 2000; K Delbaere *et al.*, 2004; Friedman *et al.*, 2002), indicating it may simply reflect a rational appraisal of reduced functional abilities and consequent increased risk of falling. If this is the case, strategies aimed at reducing fear of falling may have the potential to increase falls

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risk if they result in inappropriately low levels of fear of falling and the older person taking undue risks beyond their physical ability to cope. However, of those older adults reporting fear of falling, up to 40% also report activity avoidance caused by fearfulness. This leads to restriction of activities, reduced physical fitness and increased risk for future falls, mortality, morbidity and premature nursing home admission (Cumming *et al.*, 2000). Fear of falling can also be a maladaptive and irrational fear leading to unnecessary activity restriction, physical deconditioning, psychological distress and reduced life quality (Cumming *et al.*, 2000; Yardley *et al.*, 2002; Li *et al.*, 2003; van Haastregt *et al.*, 2008). It seems important, therefore, that we have a clearer understanding of what factors contribute to fear of falling in older people. This knowledge may assist in developing intervention programmes that help older people establish a realistic appraisal of fall risk and address physical functioning in conjunction with other drivers of fear of falling.

Approximately 30–40% of falls are preventable, the most effective strategy being a multifactor approach targeting various risk factors for falling simultaneously in selected or unselected populations (Davison *et al.*, 2005). Most fall prevention trials have been targeted at reducing the physical risk factors of falling, such as poor balance, impaired muscle strength or the harmful side effects of medication. Fall-related psychological factors have gained less attention (Decullier *et al.*, 2010). Factors independently related to fear of falling are understudied, yet to identify the appropriate population for prevention strategies, knowledge of these factors is important (Kannus *et al.*, 2005). Psychological risk factors for falling and fear of falling may go unrecognized and be omitted from falls prevention interventions, hampering their success. In fact, a recent systematic review indentified that out of 19 randomized, controlled trials evaluating the effectiveness of an intervention on fear of falling in community-living older people, only two included a cognitive restructuring component focused on addressing the psychological changes and factors that may underlie fear of falling in older people (Zijlstra *et al.*, 2007a).

Fallers are a heterogeneous group; there are different faller profiles. Assessing fallers within such profiles could be helpful to develop new dedicated fall prevention programmes (Fried *et al.*, 2004). Frailty is a multidimensional construct that represents an age-related reduction in physiological reserve and resistance to stressors; it is widely recognized to be associated with adverse health outcomes including falls (Fried *et al.*, 2001). The clinical correlates of frailty manifest as increased vulnerablilty, impaired capability to withstand intrinsic and environmental stressors and limited capacity to maintain physiological and psychosocial homeostasis. A frailty phenotype has been operationalized, based on the presence of a critical mass of core 'frail' elements, with the core entities being weakness, poor endurance, shrinking, low physical activity and slow gait speed (Fried *et al.*, 2001). This phenotype represents the biological syndrome of frailty. It is clear that frailer fallers would differ significantly in physical performance when compared with other types of fallers, which may influence how we target falls preventions in this group; however, they may also differ psychologically. Understanding the psychological factors associated with fear of falling in fallers who are transitioning to physical frailty may help us clarify whether additional psychological interventions may be effective in reducing or preventing fear of falling and, ultimately, subsequent falls in this vulnerable group of older people.

Objective

To evaluate the difference, if any, in psychological factors that are associated with fear of falling in a group of fallers transitioning to frailty when compared with fallers that could be considered physically robust or non-frail.

Methods

This study had a cross-sectional design where a convienient sample of 301 older fallers were assessed at the Technology Research for Independent Living (TRIL) Clinic in Dublin between August 2007 and July 2009 (http://www.trilcentre.org/). To be defined, a faller there had to be a minimum of one self-reported fall in the preceding 12 months. The TRIL Clinic offers an outpatient clinical service to community-dwelling people older than 60 years in the form of a comprehensive geriatric assessment that incorporates the use of technologies to measure risk factors for falls, cognitive decline and lack of social connectedness. TRIL Clinic participants must be community dwelling, older than 60 years, able to mobilize independently with or without mobility aid and be able to provide informed consent. Local research ethics committee approval was obtained.

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Defining frailty

Frailty was measured using the Biological Syndrome Model originally described by Fried with five frailty criteria (Fried *et al.*, 2001). Our only adaptation to these criteria being the definition of shrinking, which was assessed objectively as BMI of less than 18.5 kg/m^2, rather than a subjective report of weight loss of more than 10 pounds. This was reflective of similar adaptations for the shrinking criterion from other large population-based studies validating the biological syndrome model of frailty (Cigolle *et al.*, 2009). Poor endurance was determined by two questions, 'I felt that everything I did was an effort', 'I could not get going'. Respondents answering yes to either question for much of the time (≥ 3 days) during the previous week were defined as having poor endurance. Slowness was defined in terms of usual pace walking speed using the same cut points as in the Cardiovascular Health Study (after adjusting for distance) (Fried *et al.*, 2001). Weakness was defined by assessing grip strength, again, using the same cut points as the CHS dependent on gender and BMI. Low activity was defined in terms of kilocalories expended per week, based on responses to selected items from the Minnesota Leisure Time Activity questionnaire (Taylor, 1978). For the purposes of our analysis, we categorized the participants into two groups: fallers who were completely robust (non-frail) with 0 criterion present, and a frailer group consisting of fallers with one or two frailty criteria who were intermediately or pre-frail and those with three or more criteria considered to be fully frail. We pooled intermediate level of frailty with full frailty, within our analysis, as this best represented a group transitioning to frailty. Being at a pre-frail or intermediate stage of frailty has consistently been shown to infer risk of developing full-blown frailty and also a high risk of poorer outcomes when compared with non-frail individuals (Fried *et al.*, 2004).

Psychological measures

Fear of falling was measured using the Modified Falls Efficacy Scale (MFES); this is a self-report measure of falls efficacy, a validated measure of fear of falling (Tinetti *et al.*, 1990). The subject is asked to rate their confidence in performing 14 activities without falling on a 0–10 scale, with lower scores indicating fear of falling. Anxiety was measured using the Hospital Anxiety and Depression Scale, which contains a seven-item subscale for anxiety (Snaith, 1990). Depression was measured based on a shortened form (eight items) of the 20-item Center for the Epidemiological Studies-Depression scale (Radloff, 1977). Loneliness was measured using the de Jong Gierveld short-item loneliness scale (de Jong-Gierveld, 1987). Adverse life events were assessed using the Geriatric Adverse Life Event Scale (Devenand *et al.*, 2002). A measure of neuroticism was taken using the Eysenck Personality Inventory (Eysenck and Eysenck, 1964). An assessment of cognitive status (MMSE) was also included.

Statistical analysis

The collected data were analyzed using the SPSS 16.0 statistical package program. $\chi 2$-test was used for comparing demographic categorical variables dependent on frailty. The difference between means was compared using one-way analysis of variance (ANOVA). Sequential linear regression models were constructed to determine which psychological measures best predicted fear of falling in both groups of fallers and to adjust for potential confounding factors in the analysis, such as age, gender and cognition. Variables that on bivariate analysis were associated with fear of falling were entered into the model determined by the strength of their association with the outcome variable, fear of falling as measured by the MFES. We set the critical value for significance in all analysis at $p < 0.05$.

Results

Table 1 displays the population characteristics of the 301 older fallers. On application of the Fried frailty criteria to the faller group, 98 (32.6%) could be classified as robust or non-frail, 163 (54.2%) could be classified as being at an intermediate stage of frailty (pre-frail) and 40 (13.3%) were defined as completely frail. There was no significant difference in frailty dependent on gender ($\chi 2$, $p = 0.232$). There was a significant difference in mean age between groups of fallers with the frailer groups being older (one-way ANOVA, $p = 0.003$). There was also a higher burden of comorbid illnesses within both pre-frail [5.5 ± 3.1] and frail fallers [8 ± 3.2] when compared with robust fallers [3.7 ± 2.9] (one-way ANOVA, $p < 0.001$). There was a significant difference found in the mean MFES score within both pre-frail [8.7 ± 1.5] and frail [6.2 ± 2.3] groups of fallers with lower scores reflective of an increased level of fear of falling, when compared with robust fallers [9.2 ± 1.4] (one-way ANOVA, $p < 0.001$). To ascertain which psychological correlates were independently associated with fear of falling in both the robust and frailer faller groups, we

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Table 1 Population characteristics Subjects ($n = 301$)

Parameter *N* (%)	Total sample (%)	Robust (%)	Pre-frail (%)	Frail (%)	p[a]
Gender (females)	76.3	80.6	74.7	72.5	0.46
Social class 1 & 2	29.5	36.7	19.6	25.0	0.01
Lives alone	43.5	38.1	48.0	53.8	0.08
Parameter (mean [SD])	**Total sample**	**Robust**	**Pre-frail**	**Frail**	p[b]
Age	75 (7.5)	72 (7.5)	76 (7.3)	79 (6)	<0.001
MMSE	26.7 (3)	27.7 (2.1)	26.4 (3.2)	25 (2.8)	<0.001
Timed Up and Go	12 (5.7)	9 (3)	12 (5)	18 (6)	<0.001
Berg Balance Score	49 (8)	53 (4)	49 (8)	41 (8)	<0.001
Depression Score[d]	2.1 (2)	1.5 (2)	2.2 (2)	3.7 (4)	<0.001
Anxiety Score[e]	6 (4)	5 (3.3)	6 (4.1)	8 (5.5)	<0.001
IADL[f]	24.5 (3.4)	26.1 (1.5)	24.4 (3.3)	21.1 (4)	<0.001
AACI[g]	5.5 (3.3)	3.7 (2.9)	5.5 (3)	8 (3.2)	<0.001

[a]Pearson Chi-square
[b]One-way ANOVA
[c]Folstein Mini-Mental State Examination
[d]Center for the Epidemiological Studies-Depression (CES-D-8) scale
[e]Hospital Anxiety and Depression Scale-Anxiety Subscale
[f]Lawton Instrumental Activities of Daily Living Scale
[g]Age-adjusted Charleson Comorbidity Index

conducted sequential multiple regression analysis to include measures of depression, anxiety, cognition, neuroticism and loneliness, also accounting for factors such as age and gender (Table 2). Age, female gender and lower cognitive scores were associated with lower MFES scores reflective of greater fear of falling in the group of fallers considered robust. However, for those fallers who fulfilled either pre-frail or frail criteria, higher depression score was the only factor associated with lower MFES and greater fear of falling on multivariate analysis. A separate subanalysis identifed that the odds ratio of having case level depressive disorder (CESD-8 ≥ 4), if you were a frailer faller fulfilling any of the frailty criteria, was significantly higher than if you were classified as a robust faller. (OR = 2.6, CI 1.3–5.2, $p = 0.006$)

Discussion

When compared with robust fallers, pre-frail and frail individuals displayed a greater fear of falling as indicated by a significantly lower mean MFES. On multivariate analysis accounting for a number of psychological factors, only age, female gender and poorer cognition were retained as the factors significantly associated with fear of falling in robust fallers in an optimal model accounting for around 30% of variance. This is consistent with current literature where older females and those with poor cognition have been found to have higher rates of fear of falling (Arfken *et al.*, 1994). In our group of pre-frail and frail fallers, however, depression score was the only significant psychological factor associated with fear of falling in an optimal model accounting for 12.2% of the observed variance. The odds ratio of having depression

Table 2 Stepwise multiple regression models of psychological correlates and MFES in robust and frailer fallers

	Beta	Significance	R2
Model 1: Robust fallers ($n = 98$)			
Age	**−0.319**	**$p = 0.011$***	0.309
Gender	**0.451**	**$p < 0.001$***	
Cognition[a]	**−0.270**	**$p = 0.035$***	
Depression[b]	−0.002	$p = 0.987$	
Anxiety[c]	−0.172	$p = 0.221$	
Neuroticism[d]	0.044	$p = 0.768$	
Loneliness[e]	0.008	$p = 0.942$	
Model 2: Pre-frail/Frail fallers ($n = 203$)			
Age	0.004	$p = 0.965$	0.122
Gender	0.054	$p = 0.567$	
Cognition[a]	0.110	$p = 0.235$	
Depression[b]	**−0.286**	**$p = 0.026$***	
Anxiety[c]	−0.033	$p = 0.783$	
Neuroticism[d]	−0.011	$p = 0.927$	
Loneliness[e]	0.033	$p = 0.753$	

*Statistically significant $p = <0.05$
[a]Folstein Mini-Mental State Examination
[b]Center for the Epidemiological Studies-Depression (CES-D-8) scale
[c]Hospital Anxiety and Depression Scale-Anxiety Subscale
[d]Eysenck Personality Inventory
[e]de Jong Gierveld Short-item Loneliness Scale

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consistent with probable case-level disorder was increased 2.6-fold if you were a frailer faller when compared with those fallers considered robust.

Of the limited evidence available to us in the current literature on fear of falling and frailty, our findings are consistent with one other study, which evaluated activity related fear of falling in a cohort of older individuals defined as transitioning to frailty according to criteria established by Speechley and Tinetti in 1991 (Kressig *et al.*, 2001). They report that individuals fearful of falling and transitioning to frailty were more likely to be depressed than non-fearful individuals. A confounding factor in this study was the fact that depression is one of the criteria used by the Speechley and Tinneti index to define frailty (Speechley and Tinneti, 1991). Within our study, we have utilised a more recent and well-validated measure of the biological syndrome of frailty identified by Fried *et al.* The identification of those at an intermediate level of frailty using this measure has been robustly shown to infer risk of developing full-blown frailty and the multiple adverse outcomes associated with frailty also. Theoretically, this transitional stage is the last opportunity to affect frailty as it is at this point that it may be reversed (Fried *et al.*, 2004).

Previous studies have identified that fear of falling is independently associated with depression, and that older persons who report being very afraid of falling have the highest levels of depression (Chou and Chi, 2008). In those who are depressed, fear of falling has also been shown to be the only factor strongly associated with activity restriction, other factors only showing marginal associations (Deshpande *et al.*, 2008). A more recent study has also confirmed that high levels of perceived fall risk as measured by fear of falling are likely to result in future falls, independent of physiological risk, and the disparity between physiological and perceived fall risk contributes to risk mainly through psychological pathways with a propensity towards neuroticism, a higher prevalence of irrational fears and increasing depressive symptoms (Delbaere *et al.*, 2010). The importance of psychological factors such as depression associated with fear of falling is therefore supported by current literature. Mixed findings in relation to the causal direction between fear of falling and depression have been reported however. Two recent prospective studies suggest that fear of falling most likely contributes detrimentally to depressive symptoms through the mediating effect of social withdrawal but that this effect is not reciprocal (Murphy *et al.*, 2003; Chou and Chi, 2008). Emerging frailty may contribute to activity restriction and social withdrawal leading to adverse psychological consequences such as fear of falling and subsequently depression, or vice versa; depression may lead to social withdrawal, activity limitations and the development of frailty and subsequent fear of falling. Determining this level of causality is beyond the scope of this study because of its cross-sectional design. However, our findings suggest that the association between depression and fear of falling may be specific to those older fallers that can be placed on the frailty trajectory according to the biological syndrome model. This has implications for the development of future fall prevention strategies that also wish to target fear of falling.

Addressing co-morbid depression and fear of falling in frailer older fallers may reduce the morbidity associated with falls in this vulnerable group. The use of antidepressants, however, may increase the risk of further falls, although the evidence remains conflicted as to whether this risk is the same across all classes of antidepressants, and whether this effect is independent of concurrent mental health morbidity (Arfken *et al.*, 2001). Dependent on the severity of the depressive episode, pharmacotherapy should be considered; however, additional methods to address both depressive symptoms and physical frailty may be worth considering. Progressive resistance training has shown to be an effective approach to treat both depression and frailty in older adults (Singh *et al.*, 2005; Binder *et al.*, 2005). Similar programmes targeting the combined effect of increasing physical frailty and depressive symptoms may impact upon fear of falling and fall prevention. Similarly, psychotherapeutic approaches may play a role. Multicomponent cognitive behavioural intervention has already been shown to have positive and durable effects on fear of falling and associated activity avoidance and recurrent falls in older people (Zijlstra *et al.*, 2009). It has also been shown to be as efficacious as pharmacotherapy in the treatment of mild to moderate depressive disorder and depressive symptoms in older adults (Hollon and Ponniah, 2010). As mentioned previously, however, few randomized controlled intervention trials evaluating fear of falling as an outcome measure have included specific cognitive restructuring techniques known to be efficacious in the treatment of depression and anxiety (Zijlstra *et al.*, 2007a).

Our findings suggest that minimization of fear of falling within groups of fallers transitioning to frailty may be achieved through interventions, which address depression specifically. We suggest that fallers at a transitional level of frailty may represent a particularly vulnerable group psychologically who would benefit

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most from interventional stratagies that have specific intervention components based on a cognitive behavioural intervention approach as well as targeted exercise and physiotherapy interventions to address frailty. Our recommendations then would be that health care professionals who work with frail seniors who have fallen or are at risk of a fall should consider the possible co-existence of depressive symptomatology. The multidisciplinary team approach to falls assessment particularly in older persons should consider that frail or even pre-frail elders have an assessment of emotional health. Multifactor interventions may require specialist intervention to address any underlying affective disorders to ensure adequate rehabilitation.

The major limitation of this study is that discussion is based on a cross-sectional design. A longitudinal study is warranted to substantiate causal relationships. We have also focused our analysis solely on a group of fallers categorized according to their level of physical frailty. Our specific focus on fallers is caused by the fact that, fear of falling is a known phenomenon that occurs subsequent to even one fall. Fall interventions are also most often directed at those individuals who have previously experienced a fall. Our objective in this study was to contribute to the current knowledge on targeted falls intervention by evaluating whether there was any difference in the psychological factors underlying fear of falling in fallers when they differed in terms of their physical frailty, thereby, improving our ability to address fear of falling in frail fallers specifically, who are already known to be increasingly vulnerable. Nonetheless, fear of falling does occur in older persons who have never experienced a fall, and we acknowledge that our work could be expanded by also examining the psychological factors underlying fear of falling in frail and robust non-fallers. Breaking the vicious cycle between fear of falling and recurrent falls is crucial; despite any limitations in this study, we contribute important information that may assist in the provision of more targeted falls intervention programs that address physical and psychological health improvements. We have identified an increased likelihood of depressive symptoms and associated fear of falling in older fallers transitioning to frailty that may facilitate the focus of falls interventions in this group.

Conclusion

In view of the growing importance of fear of falling as an area of increasing public health concern, our study makes an important contribution. Depressive symptoms are associated with fear of falling in frailer older fallers, and these fallers transitioning to frailty have an increased likelihood of depressive disorder compared with their more robust counterparts. Our study suggests that addressing depressive symptoms in fallers at a transitional level of frailty may be important to reduce fear of falling in this group.

Conflict of interest

None declared.

Acknowledgements

The TRIL Clinic is funded by Intel Corporation, the Industrial Development Agency (IDA) Ireland and GE Healthcare, with operational support from St James's Hospital, Dublin. The financial sponsors played no role in the design, execution, analysis and interpretation of data or writing of the study.

Key points

- Depressive symptoms are specifically associated with fear of falling in older fallers transitioning to frailty.
- Frailer older fallers have an increased likelihood of depressive disorder compared with robust or non-frail fallers.
- Fear of falling interventions should address the coexistence of depression in frail fallers to facilitate rehabilitation.

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