The assessment of frailty in community dwelling older people

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Declaration of work by the candidate

I, Shahrul Bahyah Kamaruzzaman confirm that the work presented in this thesis is my own.

Some of the work conducted here in Chapter 3 and Chapter 6 on the development of the British Frailty Index and its comparison with another well known index has been condensed for publication which has recently been submitted and is currently under review. In this paper I led the interpretation of the data and wrote the first draft of the manuscript. Dr George Ploubidis provided statistical advice on this paper and Professor Shah Ebrahim and Professor Astrid Fletcher contributed to its final version.

For the work on the systematic review and meta-analysis in Chapter 2, I received assistance on the search strategy from Margaret Burke a search scientist from the Cochrane group. This work in addition to the predictive validity of the British Frailty Index in Chapter 5 is currently being drafted to be submitted for publication.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background: This thesis explores the concept of frailty, as a latent vulnerability in older people, with the aim of refining its measurement by generating a new measure of frailty – the British Frailty Index (FI). This index was developed and validated in a cohort of community-dwelling older women, the British Women's Heart and Health Study (BWHHS), in 23 towns in Britain. Findings were replicated in another large Medical Research Council (MRC) Assessment of Older People study.

Methods: A systematic literature review examined the evolution of the concept and definitions of frailty. A meta-analysis on the prognostic value of current frailty measures confirmed extensive heterogeneity in the prediction of all-cause mortality despite consideration of age, sex, type of measure and duration of follow up. A 'General Specific' model of frailty was derived from factor analysis in the BWHHS population and replicated in the MRC cohort. Construct, external criterion and predictive validity of the British FI were assessed and its performance compared to another widely used index – the Canadian Frailty Index – with single indicators of frailty.

Results: Frailty was explained by seven factors; physical ability, cardiovascular and respiratory disease and symptoms, visual impairments, other co-morbidities, psychological problems and physiological measures. Associations with frailty included increased age, female sex, smoking, living alone, not living in own home, poor social contact and low socioeconomic position. Frailty was an independent predictor of all-cause mortality in both cohorts and predicted

hospitalization and institutionalization in the MRC study, performing better than the Canadian Index.

Conclusion: This thesis provides better understanding of the multi-dimensional domains of frailty in older people. The British FI demonstrates validity in relation to adverse outcomes, provides a more reliable measurement tool and its application offers further opportunities for the prevention, detection and treatment of frailty at a clinical level.

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Lastly I dedicate this work to my grandmother who epitomized the meaning of frailty in her last years. She passed away peacefully and with dignity at home just prior to the submission of this thesis.

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Abbreviations

AUC	Area under the curve
BWHHS	British Women's Heart and Health Study
CFA	Confirmatory factor analysis
CSHA	Canadian Study of Health and Aging
CRP	C-reactive protein
ECG	Electrocardiogram
EFA	Explanatory factor analysis
FA	Factor analysis
FI	Frailty index
HR	Hazard ratio
ICF	International Classification of Functioning, Disability and Health
MeSH	Medical subject headings
MRC	Medical research council
NHS	National Health Service
PCA	Principal component analysis
PHA	Proportional Hazards Assumption
SEP	Socioeconomic position
SES	Socioeconomic status
SRH	Self rated health
ROC	Receiver Operating Curve
SAGE	Study of Global Ageing and Adult Health
TNF	Tumor Necrosis Factor
WHO	World Health Organization

Chapter 1: Frailty in older adults

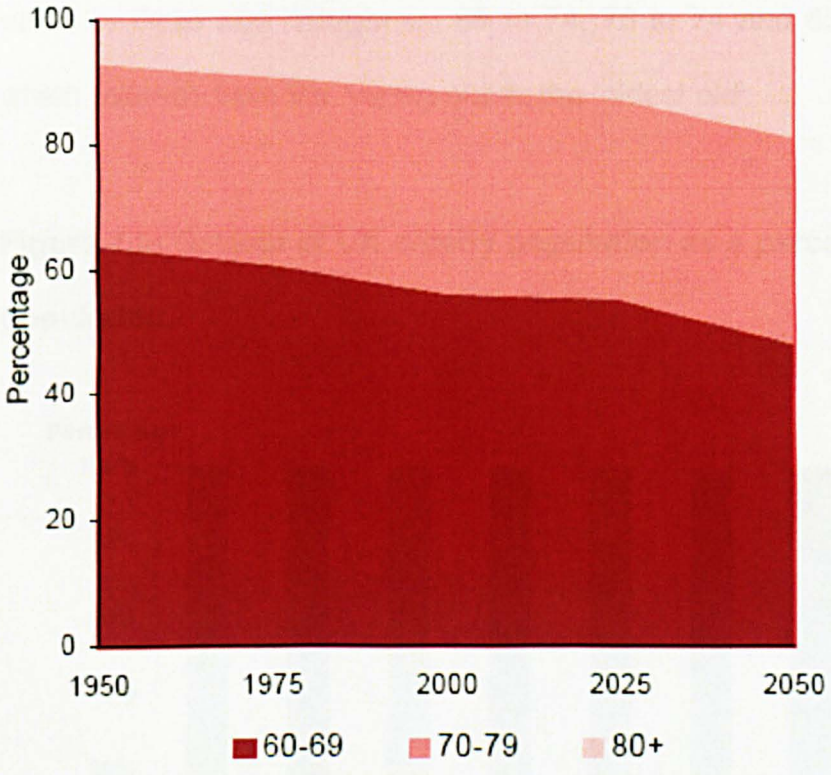
Background

The management of the frail older person has been the core of a geriatrician's existence since the specialty began. Geriatricians have long recognized the heterogeneity of the health status of older people in grappling with the complex care of these vulnerable individuals [1, 2]. However, it has only been in the past few decades that a special population of older adults had become a more prominent 'cause' among public health specialists and policy makers. They are known as the 'frail elderly' [3]. Identifying who they are, whether on an individual basis or population level, has presented a challenge to the care of older people. The numerous frailty measures published in recent years give an indication of the many approaches to meeting this challenge [4]. However, the drive to provide tangible means of defining this population more accurately arises from concerns about 'population ageing'.

The phenomenon of 'population aging' is possibly the biggest challenge to the world's population today. Underlying population ageing is a process known as the 'demographic transition' in which mortality and then fertility, decline from higher to lower levels [5]. As fertility rates move towards lower levels, mortality decline, especially at older ages, assumes an increasingly important role in population ageing. Particularly in developed countries, where low fertility has prevailed for a significant period of time, relative increases in the older population are now primarily determined by improved chances of surviving to old ages [6].

An important aspect of demographic transition is the emergence of the frail older population associated with a progressive ageing of the older population itself. For most nations, regardless of their geographic location or developmental stage, the 80 and over age group is growing faster than any of the younger segments of the older population [5](see *Figure 1.1*).

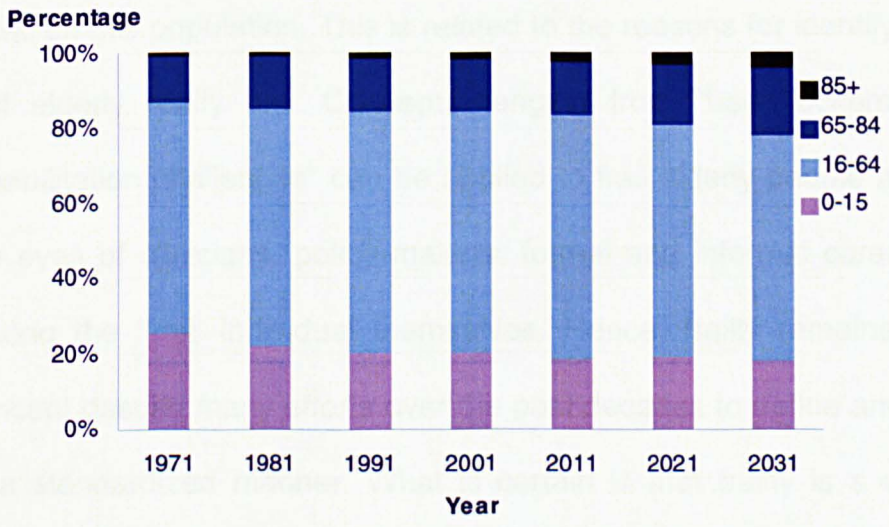
Figure1.1: Distribution of people aged 60 or over by age groups: world, 1950-2050.



Source: World population aging 1950-2050; Population Division, DESA, United Nations

In the United Kingdom (UK), it is projected that there will be more people of state pensionable age than under-16s (see ***Figure 1.2)***. This reflects a decline in the number of under-16s, which fell to 18.9 per cent of the population, compared with rising numbers of men aged 65+ and women aged 60+, who accounted for 19.0 per cent of the population at mid-2007.The oldest age group (80 and over) is the fastest growing, accounting for 5 per cent (2.7 million) of the total population in mid-2007 and has increased by more than 1.2 million between 1981and 2007[7]. The current and projected rise in the older United Kingdom population over the coming years in three age categories; 65 to 74, 75 to 74 and 85 years and above which extends from the 'young old' to the 'oldest old'.

Figure 1.2: Growth of UK elderly population as a percentage of total UK population.



Source: ONS censuses 1971-2001; National population projections: 2011-2031.

This demographic transition from a younger to older age structure has now reached global proportions among the world's populations. As population aging is progressing rapidly in developing countries that have lower socioeconomic development than their developed counterparts, there is less time to adjust to this change and its consequences. This has implications for each country's economy and its provisions allocated for health care services across all ages not just the old.

Arising from this growing and older population is a special group of older adults recognized as the 'frail elderly'. I traced their first emergence in the UK to the description of the 'frail ambulant' by JH Sheldon in 1960[8].This description was coined in the interest of 'administrative tidiness' and the hope of discovering the correct authority to provide care for the "enfeebled" old persons who were increasing the pressure on hospital beds in acute medical departments. Over the years, the types of individuals that make up this special group are very much determined by the view or assumption one takes on this population. This is related to the reasons for identifying who the frail elderly really are. Concepts ranging from "bed-blockers" to "major rehabilitation challenges" can be applied to frail elderly people and varies in the eyes of clinicians, policy makers, formal and informal carers and even among the 'frail' individual themselves. Hence, frailty remains an elusive concept despite many efforts over the past decades to define and measure it in a standardized manner. What is certain is that frailty is a controversial concept and its use in reference to the care of the older person has gained in popularity over the past few decades. These relate to particular questions such as whether a distinction should be made between frailty and ageing;

whether frailty is truly a syndrome or a series of age-related impairments that predict adverse outcomes; as well as what are its critical domains. A consensus on the concept and definition of frailty would play an important role in informing decision makers as to who among the older population are to be allocated care/access to health care services. A first step in this direction is to untangle the existing definitions of frailty that are used in general, among gerontologists and clinicians. This is explored in greater detail in Chapter 2 where I present a systematic literature review of the evolution of existing frailty definitions.

Who are the frail elderly?: Untangling the concepts

The development of the concepts and subsequent measures of frailty has been affected by the definition of frailty used. Brown et al[9] describes four problems with the way frailty has been used:

- 'frailty is usually used without definition, and without identifying any assumptions that might function as parameters to its use'
- 'frailty is used in a variety of ways; to fit with the thinking of the interests and perspectives of various authors'
- 'frailty in older persons is thought to be an undesirable state; a stigmatized and poorly thought of process; creating a self fulfilling prophecy for those considered frail'
- 'lack of strong instrumentation to measure and assess frailty'.

To a certain degree, general meanings of 'frail' and 'frailty' used in the context of daily living run in parallel to the world of gerontology and clinical practice. The Oxford English dictionary [10] provides a general meaning of the adjective 'frail' and the noun 'frailty'.

'Frail: adjective: weak and delicate, easily damaged or broken'

'Frailty: noun: the condition of being frail, weakness in character or morals'

The Webster's Ninth New Collegiate Dictionary 1985 [11] similarly defined;

'Frail: adjective: easily led into evil (~humanity), easily broken or destroyed; fragile, physically weak, slight, unsubstantial'.

'Frailty: the quality or state of being frail, a fault due to weakness especially of moral character'.

Other meanings along this negative vein are seen in Roget's International Thesaurus 4th Edition[12]:

'Frail: slight, delicate, dainty, delicately weak, puny, lightweight, womanish, effeminate ;(informal terms): namby-pamby, sissified, pansyish, fragile, breakable, destructible, shattery, crumbly, brittle etc.'

A Canadian based study investigating the view points of English speaking women on their experiences of frailty reported that older women describe frailty not only as an observable physical state such as 'looking small and skinny' but also as an emotional experience of vulnerability. As a socially constructed concept, frailty was related to judgments and negative assumptions of powerlessness and dependence[13]. These meanings depict frailty in actual daily use, as a negative state which introduces an inherent social devaluation. It is therefore of no surprise that older adults themselves, by and large, do not equate their health status with this general meaning[13].

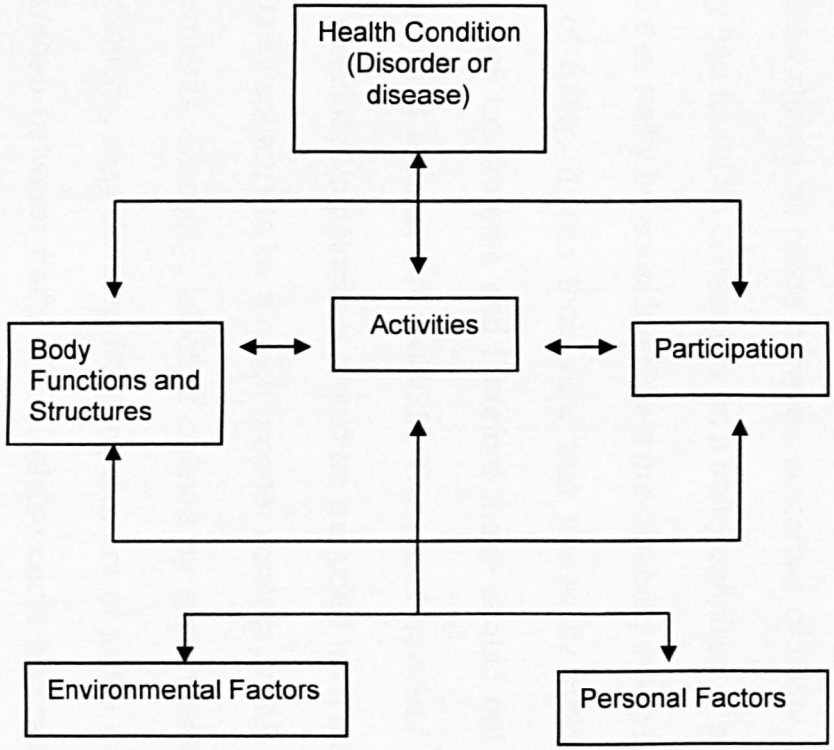
In clinical practice, the identification and management of the frail older person has been the mandate of geriatricians who have long embraced the complexity of the health status of older adults and perhaps *'it is in the management of frailty that the art of geriatrics is best expressed'[14].* However, from a clinical/geriatric perspective the frailty concept is not an easy one to quantify/translate into a tangible measure/tool. As one author explains, perhaps geriatricians *'have not been as good at articulating just how we embrace the complexity of our patients[15].* This could be due to the fact that frailty does not fit into a particular clinical slot and is often subtle and asymptomatic. Hence, it often goes unnoticed by most medical practitioners. Symptoms of chronic illness are also treated similarly by older adults and their family who tend to relate the changes to the normal aging process. This is probably because limitations and disease associated with aging are an inseparable part of frailty[16]. As with aging, frailty is an individual and qualitative experience. The indistinct line between normal and pathological aging (age-related disease) could explain why the experience of frailty differs from one person to the next. In fact, the difference between biological and chronological age in any one individual may be explained by their susceptibility to frailty. Hence, it has been suggested that using frailty as the criterion to select older persons for preventive interventions may be better than selecting persons based only on their chronological age[17].

Over the past few decades, growing uncertainty about the definition of frailty and the underlying reasons for making these measures is certainly reflected by the creation of many measures, scales and indices of frailty. Operational definitions of frailty vary widely according to the conceptual framework. Some

consider frailty in a broad sense (qualitatively), encompassing multiple domains of physical, social, cognitive, co-morbidity and psychological. This was proposed by Rockwood in the well validated Frailty Index developed for older Canadians[18]. This concept was replicated in the Comprehensive Geriatric Assessments (CGA)[19].Others define frailty more restrictively, (quantitatively) as seen in the well known 'Fried's physical phenotype of frailty' which focuses mainly on performance parameters, such as the measurement of gait speed, grip strength, weight loss, energy intake and physical activity[20]. Single physical measures of frailty have also been proposed and include the measurements of grip strength[21] and gait speed[22]. Although social and psychological domains have not been totally excluded from the concept of frailty, their importance has diminished over the years, making way for the more quantitatively measured definitions of physical frailty, with technological and superficially more objective science of measurement. However, there are those that resist a '*frailty equals physical frailty*' approach. One proposal to operationalize the definition as a clinical measure includes several features, such as cognitive, functional and social circumstances, that go well beyond just the physical aspects [23]. This view is in keeping with the aims of the World Health Organization's International Classification of Impairments, Disabilities and Handicaps (*ICIDH)* 1980, and the current International Classification of Functioning, Disability and Health (ICF). ICF is a classification of health and its domains that describe body functions and structures, activities and participation. [24] The domains are classified from individual and societal perspectives. Since an individual's functioning and disability occurs in a context, ICF also includes a list of

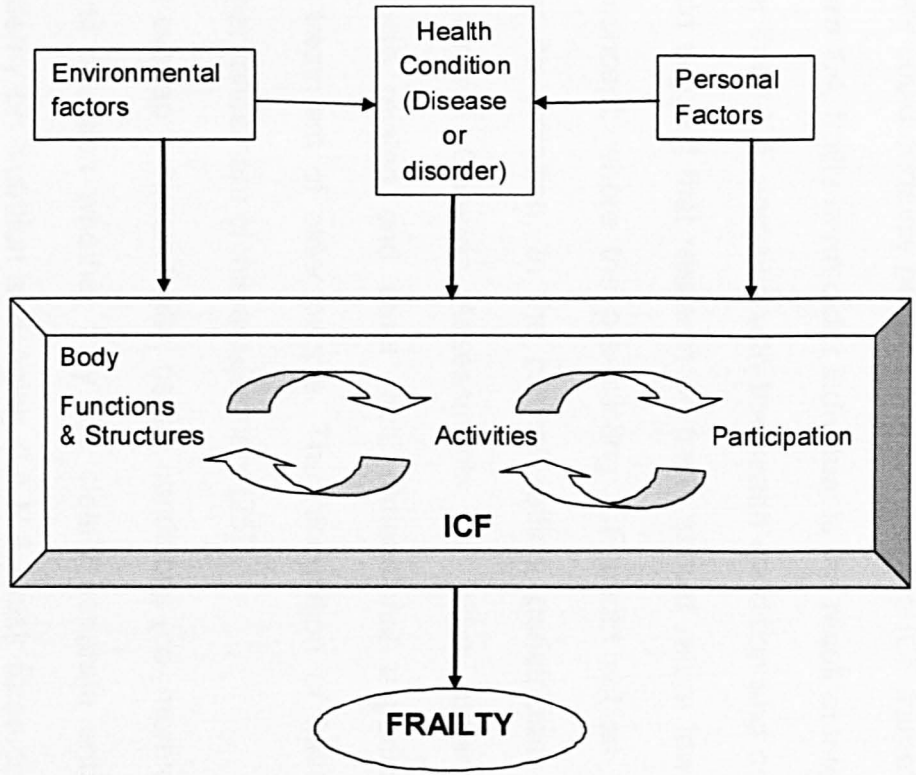
environmental factors, which include the physical, social and attitudinal environment in which people live and conduct their lives. The full health experience is described using all these components where an individual's functioning in a specific domain is an interaction between the health condition and contextual factors (i.e. environment and personal factors). *Disability* (now classified as activity limitation), *impairment, participation, handicap* (participation restriction) are key entities that form these associations (see ***Figure 1.3***).

Figure 1.3: Interactions between the components of the International Classification of Functioning, Disability and Health (ICF)



Source: International Classification of Functioning, Disability and Health-World Health Organization 2001

Figure 1.4: Interactions between frailty and the components of the International Classification of Functioning, Disability and Health (ICF)



Conceptually, frailty could certainly be incorporated into the ICF framework. As illustrated in ***Figure 1.4***, frailty in an older individual is the result of interactions within each of the three ICF domains with the health condition and contextual factors. This would suggest that research on frailty should return towards the holistic geriatric concept; where the pre-existing ICF could act as a useful guide/template for its definition. In the clinical setting, geriatricians already conduct Comprehensive Geriatric Assessments on older patients. This incorporates disease related and other multi dimensional aspects of the assessment and treatment of older people. The recognition of frailty would perhaps be a further refinement of this assessment [25].

As there is great overlap between frailty, health conditions (co- morbidity) and disability, we must question whether they are clearly separate entities. An International Academy on Nutrition and Aging (I.A.N.A.) task force combining evidence derived from a systematic review of literature along with an expert opinion of a European, Canadian and American Geriatric Advisory Panel stated that a distinction should be made between outcomes of frailty and frailty itself. Although they had found no consensus on a frailty definition or assessment tool, it was agreed that frailty be considered as a pre-disability stage as disability was an outcome of frailty. It was their view that the frailty syndrome does not include functional impairments and therefore these should not be included in frailty definitions and assessment tools[26]. The panel however, did not specify which type of functional impairments would be excluded from future operational definitions. Frailty appears to be a much broader concept as it is due to multiple system impairments. Disability, which is defined by impairments giving rise to functional limitations, may develop from impairment of just a single system or more. The overlap between frailty and disability could perhaps be greater in

older people at advanced ages. Therefore, the incorporation of functional impairments into a frailty assessment tool should still be a subject for debate[20].

Why focus on frailty?

Fortunately, there is unanimous agreement that frail older adults are indeed vulnerable and at high risk for a range of adverse health outcomes (acute and chronic illness, falls, disability, mortality). Despite the ongoing debate on the concept of frailty and its measurement, there is no doubt about the impact of frailty, be it on the frail individual, the family or primary caregiver, as well as on society as a whole. Identifying frail elderly people in clinical practice or in the wider population through various aspects of their health and social status is a challenge worth attempting as it would enable pre-emptive action to be taken that might avoid serious sequelae at individual and population levels. However, a vital step to consider before deciding on a standard measurement of frailty is the purpose behind its use [25]. The challenge would be to develop a standard frailty measure that could incorporate the different perspectives behind its purpose. These perspectives include a clinical, gerontological research or public health one.

A geriatrician's perspective would be for a frailty measure to refine the Comprehensive Geriatric Assessments and further improve the decision making process in terms of weighing the risk and benefit and cost of curative versus rehabilitative/palliative care services in the frail older person.

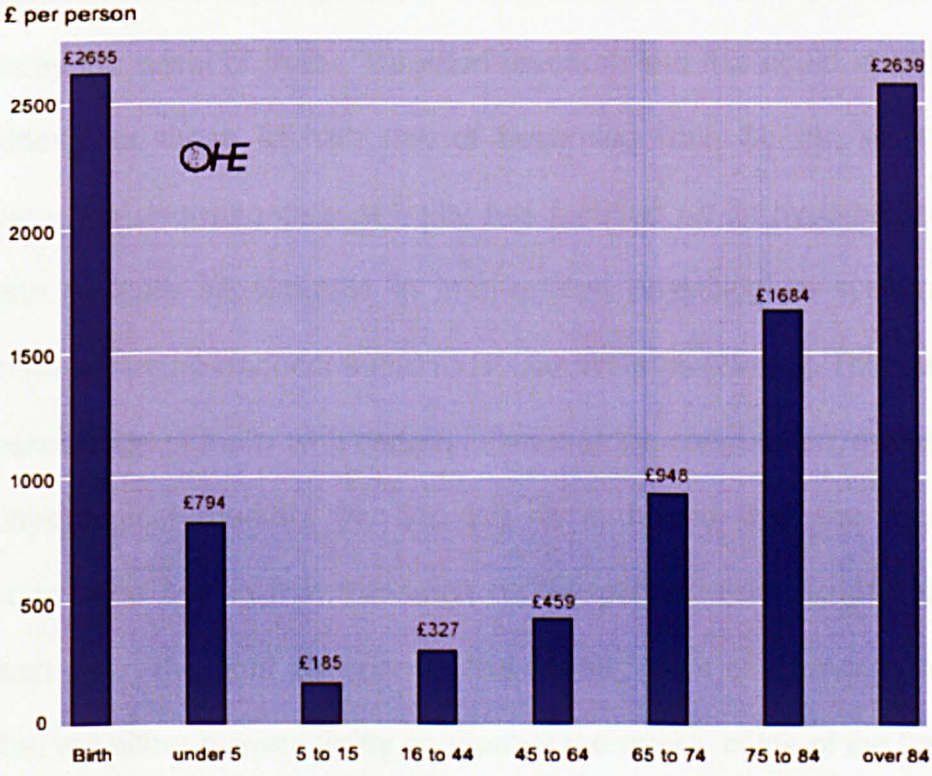
A research gerontologist would use a measure of frailty to assess the underlying causes of frailty so as to identify a pre-frailty stage and enable its

prevention. From a public health perspective, a standardized frailty measure could enable a more cost effective use of resources through population preventative measures and intervention. Briefly, there are three main reasons why it is useful to measure frailty:

i) To reduce the health care burdens associated with frailty

Frail older people are the major users of health care worldwide[19]. This is evident by their increased utilization of resources in the community, hospital as well as long-term care institutions[27]. These all relate to adverse health outcomes that commonly accompany frailty. In the United Kingdom, the NHS cost per age group is shown in ***Figure 1.5***. The NHS cost rises sharply in the 65 and over age group, with the highest owing to the 84 and over age group, who appear to cost the NHS as much as those just born.

Figure1.5: Estimated Health and Community Health Service (HCHS) per capita expenditure by age group, England, 2002/03



Source: The Government's Expenditure Plans 1999/00 (Department of Health)

A standardized measure of frailty could target the frail elderly people who are at increased risk of multiple hospital admissions, institutionalization and death. Their detection may reduce the incidence of frailty and the number of years of dependency through education, prevention and promotion of healthy lifestyles. Measuring frailty would be useful for informing not just clinical practitioners but also policy makers on how to detect, prevent and delay the onset of these frailty outcomes and enable more effective planning of the future needs, services and use of resource for elderly people.

Currently, the limitations in defining frailty make its prevalence uncertain[28] posing a barrier to targeting or allocating appropriate healthcare services to this vulnerable group.

ii) To understand the underlying causes of frailty.

Understanding the pathways that lead to frailty, its underlying causes and its association with ageing could enable the discovery of ways to detect, prevent or delay the onset of frailty. Targeted research into this could identify the 'pre-frail elderly' or those at high risk of becoming frail. So far, work on the early detection and diagnosis of frailty has focused on its hypothesized association with multiple impairments in inter-related physiological systems namely the immune, neuro-endocrine and muscular systems [29, 30]. This has revealed the association of frailty with certain inflammatory, coagulation, metabolic and other physiological markers [4, 31, 32]. It is hoped that the growing body of knowledge arising from research on the pathophysiology of frailty [32-34] will lead us in the right direction in the development of interventions or therapies that will either prevent frailty or improve the quality of life of the frail older adult.

iii) To target interventions on those who will become frail or those who are 'high risk frail'.

Targeting interventions would also be possible with a standardized measure of frailty to identify people at an early pre-frailty stage (i.e. those at high risk of becoming frail) and those who are already frail and therefore at risk of complications of frailty (e.g. falls, mortality). Such an approach would help with more cost-effective planning of services for older people.

These services would involve the implementation of specific primary or secondary intervention strategies which aim at reducing the chances of becoming frail and the adverse outcomes associated with frailty. We must acknowledge that much important work on the presentation and/or interventions for frailty (e.g.: Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) trials and interventional studies with Tai Chi) has been achieved without a precise definition being in place [35-37]. However, a standardized, reliable and accurate measure would more likely increase the effectiveness and reduce the costs of interventions by providing them to those who would really benefit most.

A successful definition of frailty

Unfortunately, the daunting array of available measures or scales of frailty in older persons pose a significant problem in generalizing or even comparing one set of findings to another. Hence, validation which is essentially a process of hypothesis testing [38], must be carried out on the various operational definitions to determine whether the 'test' is measuring frailty. The assessment of the measures used is based on several aspects:

Content validity: assesses the theoretical basis and degree to which the measure covers all the relevant or important content or domain for frailty e.g. multidimensional, dynamic, and is useful across different contexts.

Face validity: although related to content validity assesses whether a test appears to be a good measure or not. Hence judgment is made just on the 'face' of it

Construct validity: assesses whether the measure is associated with other variables in the expected direction: increased frailty with age, in women, in poorer socioeconomic groups, co-morbidity and poor self rated health. Two aspects of construct validity are ***convergent and divergent /discriminant validity.*** Convergent validity assesses the degree to which the measure is correlated with other measures or other variables of the same construct it should be related to. Divergent validity assesses the degree to which the measure does not correlate with dissimilar or unrelated variables.[38]

Criterion validity: assesses the correlation of a measure with ideally a reference or a 'gold' standard measure which is widely used and accepted in the field. It is usually divided into two types: ***concurrent and predictive validity***. Concurrent validity assesses the correlation of the measure with other measures/variables of the same construct that are measured at the same time. Predictive validity assesses this at a future time, testing the ability of the measure to predict adverse health outcomes including death, hospitalization, institutionalization, falls, morbidity etc, and whether it provides an age threshold that predicts when everyone is frail[15].

As a reference standard definition of frailty does not exist, predictive validity provided means of evaluating the ability of a frailty measure to demonstrate susceptibility to adverse outcomes.

The validity of any measure however does not imply its reliability. ***Reliability*** refers to the degree to which measurements can be replicated. It involves making judgements on the adequacy of the measurement by assessing the amount of error, both random and systematic[38]. Thus the inclusion of various directly observed or objectively measured variables into a frailty measure will affect its reliability as the more variables considered, the greater the problems of measurement error and missing data. The sources of variance in a measure are tested by examining the effect of ***inter-observer reliability*** where the error results from different observers' perceptions. Variations of the measure within an observer are called ***intra-observer reliability***. If there are no observers involved in the measurement, which is the case in many self rated questionnaire measures, its reliability can be tested using ***test-retest reliability***. This approach is concerned with administration of the measure within a sufficiently short time interval where it is assumed that what is being measured has not changed. The greater reliability of a measure can also be assessed by the degree of ***internal consistency or homogeneity.*** This 'speaks directly to the ability of the clinician or researcher to interpret the composite score as a reflection of the test's items'[39], where the variables included in the 'score' should be moderately correlated with each other, and each variable should also correlate with the total measure's score.

Hence, a successful operational definition of frailty should (as with any tool) be valid and reliable when used in different populations. In keeping with a more holistic view of the individual, it would also need to be multi dimensional, identifying the domains of the community dwelling older people.

Scope of the work

It is indeed a challenge to compare and validate the various definitions of frailty thus far as they were constructed for different purposes and for different elderly populations. Given the heterogeneity of this term when applied to older people, it is hoped that this compilation of various known definitions of frailty (***Chapter 2.1***) and their prognostic value (***Chapter 2.2***) in large elderly populations will help untangle the growing body of knowledge on the concept of frailty and perhaps bring us closer to a consensus definition. ***Chapter 3*** introduces the British Frailty Index (FI) which is based on a multidimensional concept of frailty and developed using factor analysis. This new measure of frailty was developed using the BWHHS cohort of women and this process was replicated in both men and women of the larger and older cohort of the MRC assessment study of older people. Its construct and external concurrent criterion validity were assessed in ***Chapter 4*** by examining associations with specific socio-demographic and lifestyle variables. Predictive validity of the British FI in relation to adverse outcomes such as all cause mortality, cause specific mortality, hospitalization and institutionalization was examined in ***Chapter 5***. ***Chapter 6*** reports results of the comparisons made between the British FI and a well known multi-dimensional frailty index-the Canadian Frailty Index - as well as single markers of frailty. The last chapter incorporates an overall discussion of the findings made from this study, its implications as well as recommendations for future work.

This study has the potential to generate frailty indicators that should not only be able to predict death but also indicate the health status, functional decline and use of health services in the target population of frail older people. These frailty indicators should reflect the multi dimensional domains that relate to the

wellbeing and independence of this vulnerable population. Developing a prognostic tool for prediction of adverse events, would, if sufficiently accurate, aid clinical decisions on place and type of care for older adults at risk (for example palliative versus acute care).This would also permit preventive targeting of care/services on modifiable risk factors. It should be practical and simple for use in a primary care or hospital setting as well as appropriate across many cultures and populations

It is anticipated that this work will have impact on the direction of future intervention and healthcare strategies for frail elderly people. This is in the hope of reducing both the burden of suffering in these people and also the economic 'burden' that the growing elderly populations pose to healthcare services the world over.

Aim and objectives

The aim of this study was to generate a measure of frailty that can be used to predict adverse events in a community dwelling older population.

Objectives:

- To review existing literature on concept of frailty, its measurement and its prognostic value in large study populations.
- To derive a model based measurement of frailty (the British Frailty Index) and examine its internal reliability in community dwelling elderly people.
- To assess the construct and concurrent criterion validity of the developed frailty measure i.e. whether the measure provides information on expected associations and is correlated with other variables of the same construct.
- To assess the performance of the developed frailty measure in predicting all cause mortality in the British Women's Heart and Health Study (BWHHS) population.
- Re-evaluation of the British Frailty Index (FI) in an independent cohort of the MRC assessment study of older people.
- Comparison of the performance of the British FI with a widely used frailty index and with simple approaches to measuring frailty in both cohorts.

Chapter 2.1: Definitions and concepts of frailty: a systematic literature review

Introduction

Efforts to quantify the experience of frailty in older people have resulted in a wealth of research which requires much appraisal and synthesis. These efforts have contributed to our understanding of the pathways to frailty, its aetiology and associated risk factors. However, the presence of a huge variety of frailty measures also reflects the growing uncertainty about its definition and the underlying reasons for making these measures. At present, despite the absence of a consensus definition, many conclusions continue to be drawn on 'frail' older people deemed at risk of adverse events [20, 40-42]. I embarked on this systematic literature review to investigate the rationale behind the concept and definition of frailty in older people by tracing its evolution from the earliest definition to its current definitions and use. This included assessment of the use of similar meanings to the term 'frailty' to include definitions and concepts relating to the same population prior to the current popularity of the term "frailty". The challenge posed here was to compare and validate the various definitions of frailty thus far, as they were constructed for different purposes and for different older people populations. It is hoped that this compilation of the various

definitions of 'frailty' will provide greater clarity to the growing body of knowledge on the concept of frailty. This may bring us closer to a consensus on what defines frailty in elderly people; alternatively it may result in questioning the necessity for defining a condition that in most instances is self-evident.

In this chapter I present two systematic reviews: a) the historical development of concepts and definitions of frailty; b) the associations of measures of frailty with mortality and other adverse outcomes.

Methods

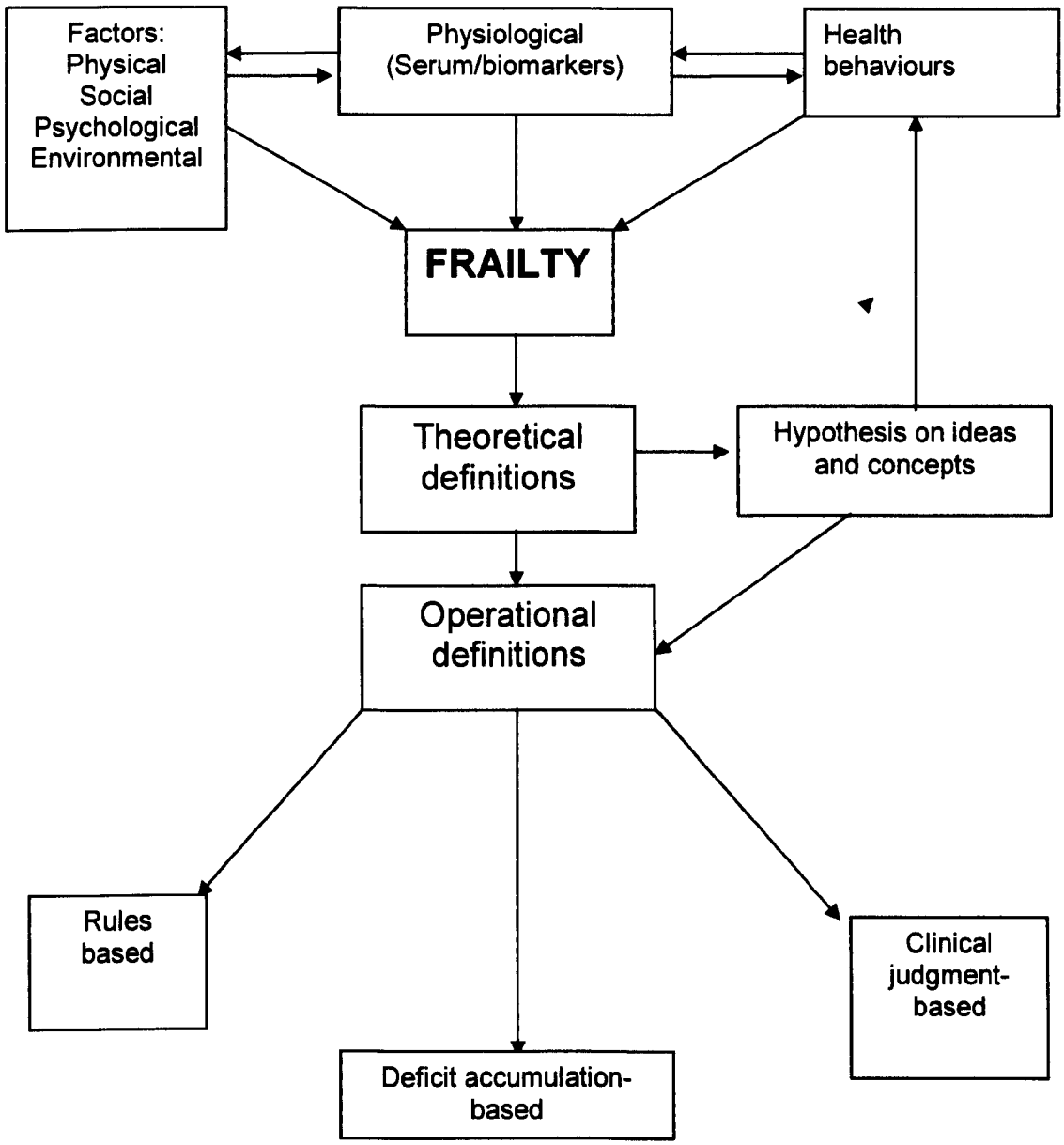
A systematic and comprehensive search strategy was designed with an information scientist to review the literature. Peer-reviewed journal articles were selected from the following databases: MEDLINE, Psych Info and Age Info (1950 to July 2009); EMBASE (1974 to July 2009) and Web of Science (1970 to July 2009). Gerontology textbooks were reviewed for earlier definitions and concepts of frailty. Citation tracking of key papers was also used. The search was limited to English language articles, humans and 'all aged 65 and over'. As frailty is yet to be defined, the search terms combined various Medical Subject Headings (MeSH) terms for *'frail elderly'* to broaden the scope of the search population *(see* **Table2.1***)*.

Table 2.1: Medical Subject Headings (MeSH) and other terms for frail elderly

exp Frail Elderly/
older old.tw.
(infirm$ adj3 elder$).tw.
(vulnerab$ adj3 (elder$ or old or older)).tw.
(weak$ adj3 (elder$ or old or older)).tw.
(function$ adj3 impair$ adj3 (elder$ or old or older)).tw.
(debilit$ adj3 (elder$ or old or older)).tw.
((sick or sicker) adj3 (elder$ or old or older)).tw.
((disabled$ or disabilit$) adj3 (old or older or elder$)).tw.
(socia$ adj3 frail$).tw.
(physical$ adj3 frail$).tw.
(mental$ adj3 frail$).tw.
(psychol$ adj3 frail$).tw.
(physiol$ adj3 frail$).tw.
(frail$ adj3 syndrom$).tw.

This produced literature which sought to define, conceptualize or measure frailty and its related terms as well as distinguished between theoretical and operational definitions of frailty. A proposed pathway to defining frailty is shown in **Figure 2.1**. As frailty in older people comprised of the interplay between associated factors, markers and health behaviours, articles which described frailty in terms of 'markers', 'associations', 'predictors' or 'contributing factors' were seen to be on the pathway to frailty and not truly providing a complete definition. Definitions were split into theoretical and operational.

Figure 2.1: Pathway to defining frailty



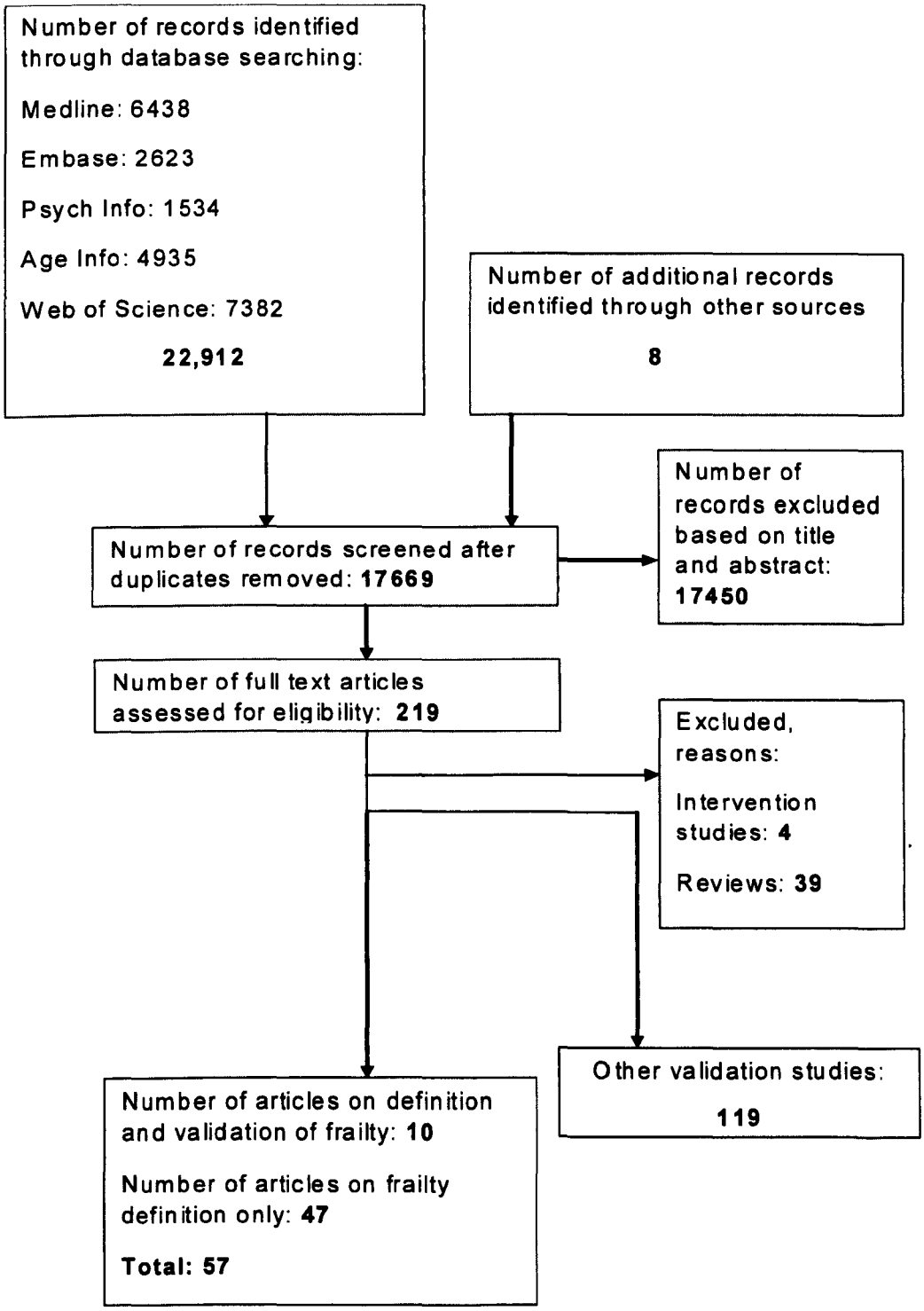
Theoretical definitions were those that proposed a hypothesis on the idea or concept of frailty. Operational definitions provided measures that defined frailty or its associated meanings and identified frail older people either by stating the

measures that fulfil the criteria for frailty and/or by providing scales or indices. The operational definitions were assessed by whether they fitted into physical, physiological, psychological or socially based criteria. Operational definitions were grouped into three categories as described by *Rockwood et al* : a) rules-based b) sum of deficit accumulation c) clinical judgment-based[35].

Results

Figure 2.2 demonstrates the flow of information through the different phases of the systematic literature review. The search for the relevant articles using the term 'frail elderly' and its associated meanings broadened the scope considerably. The combined database search resulted in a total of 22,912 citations of which only 219 potentially relevant articles were found. A total of 57 different definitions of frailty were identified (see ***Table 2.2***). Of this total, 47 articles focused on only defining frailty and 10 additionally validated frailty within the same population it was derived from. These definitions were tabulated chronologically and divided into theoretical and/or operational definitions (see ***Table 2.3***). Although 'frailty' or 'frail' was the major descriptive term used, this review revealed that other terms such as 'vulnerable'[43, 44], 'functionally impaired', 'functional limitations' or 'functional disability'[22, 45, 46] in older people were often used to describe or identify the same frail older population.

Figure 2.2: Flow diagram of the search strategy for the systematic literature review



The measures used to identify these vulnerable, functionally impaired or disabled older individuals were often the combination of variables included in or even similar to several known frailty measures[20, 22, 47-49]. Hence, regardless of the terms used, these measures appeared to have one common goal; the identification of the older persons at risk of adverse health outcomes. Other MeSH terms were later excluded as the articles screened did not attempt to identify or define the concept of frailty in the population under study.

Manual searching of old Gerontology textbooks [8, 50] unearthed two early descriptions from the 1960s which sought to define this subset of the older population. These provided broader qualitative and multi-dimensional definitions based on physical/functional, psychological and social criteria. Later year searches were derived from the databases mentioned. These yielded a varied selection of frailty definitions based on single, dual or multidimensional criteria. Prior to 1998, the majority of the definitions were theoretical and not validated. Operational definitions were mainly accompanied by a measure/test.

These can be:

- rules-based/phenotype of frailty, for example, a person may be defined as frail if 3 or more symptoms are present[20]
- Summing up of accumulated deficits (frailty index), is a proportion of all potential deficits considered for a given person[51]
- Reliance on clinical judgment, to interpret the results of history taking and clinical examination[41].

Table 2.2: Type of frailty definitions and the individual frailty domains.

Author	Physical	Physiological	Psychological	Social	Theoretical	Operational
Sheldon 1960	v		v	v	v	
Agate 1963	v		v	v	v	
OBrien,Wagner 1980				v	v	
Gadow 1983			v		v	
Brocklehurst 1985	v		v	v	v	
Wan 1986	v		v	v		v
Woodhouse 1988	v			v	v	
National Institute of Health 1988	v		v	v	v	
Berkman 1989	v				v	
Lachs 1990	v		v	v		v
Speechley&Tinetti 1991	v	v				
Buchner,1992		v			v	
Bortz 1993		v			v	
Rockwood 1994	v		v	v	v	
Kaufman 1995				v	v	
Brown, R 1995	v			v	v	
Campbell 1997		v			v	
Strawbridge 1998	v		v	v	v	v
Dayhoff 1995	v		v		v	v
Ranieri 1998		v				v
Fried & Walston 1998		v			v	
Carlson 1998	v		v	v	v	v
Rockwood 1999	v		v			v
Hammerman1999	v		v		v	
Chin 1999	v	v				v
Brown,M 2000	v					v
Fried 2001	v	v				v
Minitski 2001	v	v	v			v

Continued

Author	Physical	Physiological	Psychological	Social	Theoretical	Operational
Nourhashemi 2001	v		v	v		v
Saliba2001	v					v
Gill 2001	v	v				v
Steverink 2001	v		v	v		v
Bortz 2002	v	v			v	
Lipitzs 2002		v			v	
Gerdham 2003	v					v
Klein 2003	v	v				
Sydhall 2003	v	v				v
Fried 2004		v			v	
Gill TM 2004	v	v				v
Studenski 2004	v		v	v		v
Jones 2004	v		v	v		v
Minitski 2004	v		v			v
Cariere 2005	v	v				v
Scarcela 2005	v		v	v		v
Rockwood 2005	v					v
Puts2005	v	v	v			v
Klein 2005	v	v				v
Rolfson 2006	v		v	v		v
Carr 2006	v	v				v
Schultz-Larsen 2007	v	v				v
Amici 2008	v		v			v
Boxer 2008	v	v				v
Ensrud 2008	v	v				v
Varadhan 2008		v			v	
Ravaglia 2008	v		v	v		v
Guilley 2008	v	v	v			v
Buchman 2009	v	v				v

Table 2.3: The evolution of frailty definitions

Author/Year	Reference	Theoretical definitions	Operational definitions
Sheldon JH 1960	**8**	'frail ambulant' group of elderly 'belonging to the later period of old age, beyond 75 years with an increasing amount of breakdown in (physical and mental)health which is of long duration (chronic); who face domestic as well social problems.'	
Agate J ,1963	**50**	' a state of semi-dependence...the patient is not necessarily ill, and may have no specific disabilities; yet she cannot sustain an independent life with safety and success, even though willing to try and is mentally normal..'	
O'Brien J & Wagner DL 1980	**55**	> 75 years of age, living alone with sub-poverty levels of income	
Gadow S,1983	**54**	'a devalued phenomenon particularly identified with aging...	
Brocklehurst J,1985	**57**	'Model of Breakdown' using a balance between biomedical and psychosocial factors which were seen as 'assets' or 'deficits' that affect whether a person can live independently in the community.	
Wan TTH, 1986	**60**	measure of need for care conceptualized as 'a first order factor of four unobservable health related constructs, including self assessed health status, objectively evaluated functional status, perceived service needs and instrumental social support'	
Woodhouse,1988	**3**	'individuals over 65 years of age, dependent on others for activities of daily living...'	
National Institutes of Health 1988	**59**	'tend to exhibit great medical complexity and vulnerability; have illnesses with atypical and obscure presentations; suffer major cognitive, affective and functional problems; are especially vulnerable to iatrogenesis; are often socially isolated and economically deprived; and at high risk for premature or inappropriate institutionalization.'	

Author/Year	Reference	Theoretical definitions	Operational definitions
Berkman B, 1989	**56**	'Failure to Thrive (FTT)...functional ability to live with multisystem diseases, cope with the ensuing problems, and manage their own care was diminished and no longer responsive to health care interventions..'	
Lachs MS et al 1990	**46**		Frailty Staging System (FSS) was developed as an index of severity of functional impairment using a short approach focused on selected tests of vision, hearing, arm and leg function, urinary incontinence, mental status, instrumental and basic activities of daily living, environmental hazards and social support systems
Speechley M, Tinetti M.1991	**61**		9 variables correlating strongly with frailty; Age>80 yrs, balance and gait abnormalities, infrequent walking for exercise, decreased knee strength, lower extreme disability, decreased shoulder strength, decreased near vision, depression, sedative use. Subjects are frail if have at least four frail attributes and no more than one vigorous attribute
Buchner & Wagner 1992	**70**	'A state of reduced physiological reserve associated with increased susceptibility to disability.... frailty as a 'precursor state' to disability'.	
Bortz 1993	**68**	'Diminished energy flow (interaction) between the individual and their environment... when an organism is uncoupled from their environment...'	
Rockwood K,1994	**18**	'those in whom the assets maintaining health and the deficits threatening it are in precarious balance...dependence on others for activities of daily living..'	
Kaufman SR,1994	**64**	' socially produced and is a lived experience...reflects a societal view of aging, as a battle between independence and dependence...'	
Brown I, 1995	**9**	'A diminished ability to carry out the important practical and social activities of daily living'.	

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Campbell AJ & Buchner DM,1997	**69**	' condition/ syndrome resulting from multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure'	
Strawbridge WJ et al,1998	**62**	' a syndrome involving deficiencies in two or more domains involving physical, nutritive, cognitive and sensory capabilities'.	Classified as frail if problems/difficulties were reported in two of the following domains(16 variables): Physical function (4 items) Nutritive status(2 items) Cognitive functioning(4 items) Sensory functioning (6 items)
Dayhoff et al 1998	**48**	Diminished functioning combined with diminished self-rated health	Combined self reports of two measures: a) WHO Assessment of Functional Capacity (WHOAFC)-14 item measure of self sufficiency in performance of basic and instrumental activities of daily living. b) self report of health as fair or poor. Frailty classified by scoring 21 or more on WHOAFC and poor self report of health.
Ranieri P et al 1998	**84**		Low serum cholesterol as independent single marker of frailty; mean cholesterol levels were significantly lower in men; persons living with others; older individuals; and individuals with cognitive impairment, poorer somatic health, higher disability, and a higher level of malnutrition
Fried LP & Walston JM.1998	**16**	'A state of age-related physiological vulnerability resulting from impaired homeostatic reserve and a reduced capacity of the organism to withstand stress' Includes indicators such as sarcopenia neuro-endocrine dysregulation, nutritional and immune dysfunction in the 'cycle of frailty'.	

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Carlson JE et al 1998	**49**	Quantifies frailty in terms of 'functional homeostasis i.e. the ability of an individual to withstand illness without loss of function'.	Good or poor functional homeostasis defined by a 'Functional Independence Measure(FIM)' which ranges from 'Complete dependence(score 1 & 2) to Independence'(score 7). The FIM score is applied to the following areas: eating, grooming, bathing, dressing (upper body), dressing (lower body), toileting, bladder management, bowel management, transferring (to go from one place to another) in a bed, chair, and/or wheelchair, transferring on and off a toilet, transferring into and out of a shower, locomotion (moving) for walking or in a wheelchair, and locomotion going up and down stairs. It is also used for cognitive areas such as comprehension, expression, social interaction, problem solving, and memory.
Hamerman D,1999	**28**	Described as an evolving geriatric functional continuum; a midpoint between independence and pre-death.	
Rockwood K,1999	**71**		Geriatric status scale(GSS) ,classification of patients at four levels appropriate for people living in the community representing fitness to frailty: (0) those who walk without help, perform basic ADLs , are continent and not cognitively impaired. (1) Bladder incontinence only (2) One (two if incontinent) or more of needing assistance with mobility or ADLs, had CIND, or has bowel or bladder incontinence (3)Two or (three if incontinent) of totally dependent for transfers or one or more ADLs, incontinent of bowel and bladder, and a diagnosis of dementia.

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Chin A Paw MJ et al,1999	**63**		Frailty defined as 'Physical inactivity combined with low energy intake, 5-year weight loss, or low BMI (body mass index) Physical inactivity-<210min/week Low energy intake-<7.6MJ/day 5 year weight loss->4kg Low BMI-<23.5kg/m2
Brown M et al 2000	**47**		Frailty defined as scores obtained on a 36-point physical performance test (PPT): Not frail (32-36 points), mildly frail (25-31 points), or moderately frail (17-24 points)
Fried LP et al,2001	**20**		Frailty Phenotype 'a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity'
Minitski AB et al 2001	**72**		Frailty Index=The proportion of accumulated deficits (symptoms, signs, functional impairments and laboratory abnormalities)
Nourhashemi et al 2001	**45**		Frailty identified as having disability with one or more Instrumental Activities of Daily Living (IADLs) as measured by the IADL scale
Saliba D,2001	**43**	'vulnerable older persons as age 65 and older who are at increased risk of functional decline and death over 2 years.	Vulnerable Elders Survey (VES-13), a function based screen.
Gill TM et al 2001	**24**		Physical frailty was defined on the basis of slow gait speed and inability to stand from a chair with one's arms folded

Author/Year	Reference	Theoretical definitions	Operational definitions
Steverink N et al 2001	**81**		Groningen Frailty Indicator short 15 item screening instrument to determine level of frailty. Screens for loss of function or resources in the 4 domains of function; physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), social(emotional isolation), cognitive(cognitive functioning)and psychological(depressed mood and and feelings of anxiety
Bortz WM,2002	**66**	'A state of muscular weakness and other secondary widely distributed losses in function and structure that are usually initiated by decreased levels of physical activity	
Lipsitz ,2002	**67**	'Loss of adaptive capacity due to a loss of complexity...during resting conditions impedes an individual's ability to mount a focused response during stress.	
Gerdham et al.2003	**85**		'A subjective immediate impression of an individual's general health and appearance'...within 15s from first sight. This definition was transferred to an arbitrary scale (1-100).1=individual is not frail and 100=very frail or aged .
Klein BEK et al 2003	**82**		"index of frailty" consisting of highest quartile (slowest) gait time, lowest quartile of peak expiratory flow rate, lowest quartile of handgrip strength, and inability to stand from sitting in one try (for those not in a wheelchair)
Sydall H et al 2003	**21**		Grip strength as a single marker of frailty in older people of similar chronological age.
Fried LP et al,2004	**88**	' an aggregate expression of risk resulting from age or diseaseassociated physiologic accumulation of sub threshold decrements affecting multiple physiologic systems ...no single altered system defines this state,...multiple systems must be involved.'	

Author/Year	Reference	Theoretical definitions	Operational definitions
Gill TM et al 2004	**22**		Presence of absence of frailty defined on basis of gait speed: score of >10 seconds on the rapid gait test(walking back and forth over a ten foot course as quickly as possible)
Studenski S et al,2004	**23**	Global frailty includes intrinsic frailty and its consequences	Clinical Global Impression of Change in Physical Frailty includes 6 intrinsic frailty and 7 consequence domains. Intrinsic domains:-mobility, balance, strength, endurance, nutrition, neuromotor performance. Consequence domains: medical complexity, healthcare utilization, appearance, self-perceived health, ADLs, emotional status, social status)
Jones DM, Song X, Rockwood K,2004	**19**		FI-CGA was calculated as a count of the impairments identified at baseline Comprehensive Geriatric Assessment (CGA) ; scored and summed as a frailty index(FI).Consists of 10 standard domains: Cognitive status Mood Motivation Communication Mobility Balance Bowel function Bladder function IADLs Nutrition Social resources
Minitski AB et al,2004	**51**		Frailty Index using 40 variables based on Self report data, includes symptoms, health attitudes, illnesses and impaired function

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Cariere et al 2005	**91**		Measures frailty using a fitting method that establishes a hierarchy between components of physical frailty. -Mobility (gait speed and chair stand) -balance (tandem position test) -nutrition (BMI) -Muscle strength(grip test) -physical activity Also included is perceived health (self rated health and fear of falling) on probability of becoming dependent. Provides a predictive score using an integer-based linear combination of risk factors; can be used on subjects with apparent good health but are at risk of becoming disabled.
Puts MTE et al 2005	**77**		Frailty was defined as present when a subject had scores above the cut-off on three or more frailty markers, as described by Fried et al but was based on nine frailty markers. The static definition was based on the frailty markers at T2(1st follow up). The dynamic definition was based on the change in the frailty markers between T1(baseline) and T2. The nine frailty markers were body weight; peak expiratory flow; cognitive functioning (MMSE); vision capacity; hearing capacity; incontinence; sense of mastery; depressive symptoms; and physical activity.

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Scarcela P 2005	**95**		Identifies frail Italian elderly using Geriatric Functional evaluation(GFA) -modified from original version designed by Grauer and Birnbom (1975) Mental–physical Area (one question in each section with three possible answers with a score ranging from 0 to _20) Sight Hearing Mobility Respiratory functions Cardiovascular functions Diet Pathologies present (no scoring here —only the presence or absence is recorded) Disorientation Delirious psychosis Memory loss Energy and motivation Reasoning ability Hallucinations Socio-economical and functional area (each item has a score that varies from 0 to a maximum which differs according the specific weight established when designing the questionnaire) Functional status (7 items, total score 0–41) Community support (12 items, total score between 0 and 32) Housing (1 item, total score between 0 and 3) Relationship (1 item, total score between 0 and 15) Economical situation (1 item, total score between 0 and 8) The Final Synthetic Score, resulting from the sum of the scores in the 32 items, can vary from _118 to +91

Author/Year	Reference	Theoretical definitions	Operational definitions
Rockwood K et al 2005	**41**		CSHA Clinical Frailty Scale: 1 Very fit — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age 2 Well — without active disease, but less fit than people in category 1 3 Well, with treated comorbid disease — disease symptoms are well controlled compared with those in category 4 4 Apparently vulnerable — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms 5 Mildly frail — with limited dependence on others for instrumental activities of daily living 6 Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living 7 Severely frail — completely dependent on others for the activities of daily living, or terminally ill Note: CSHA = Canadian Study of Health and Aging.

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Klein BEK et al 2005	**78**		A frailty index combining poorer function for each characteristic was devised according to the following scheme: • highest quartile of gait-time (3.37 s in women, 3.19 s in men); • lowest quartile of peak expiratory flow rate (290 l/min for women, 440 l/min for men); • lowest quartile for hand grip strength for the dominant hand (18.5 kg for women,34.5 kg for men); • not being able to stand from a sitting position in one try (without use of arms) • visual impairment (best-corrected visual acuity of 20/40 or poorer in the better eye). Equal weight was given to each measure, further categorized into four levels: none (none of the characteristics), mild (1–2 characteristics), moderate (3 characteristics), and severe (4–5 characteristics).
Rolfson DB et al 2006	**87**		Edmonton Frail Scale ,samples 10 domains -2 performance based;clock test (cognitive performance) and 'timed get up and go'for balance and mobility. -mood, -functional independence, -medication use, -social support -nutrition, -health attitudes, -continence, -burden of medical illness -quality of life.

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Car DB et al 2006	**90**		Frailty defined as at least two out of three criteria: a) Score between 18 and 32 on the modified Physical Performance Test(PPT); b) Report difficulty or need assistance with two or more Instrumental Activities of Daily Living(IADLs) or one activity of daily living(ADL); c) Achieve a peak oxygen uptake (VO2) of less than 18Ml/kg body weight per minute.
Schultz-Larsen K,2007	**86**		Conceptualization of frailty based on a 2-dimensional perspective; 1) quantitative- an objective interpretation of frailty by a health professional; 2) a subjective perception and experiences of health by an older adult. 'Objective measure of physical frailty - maximal power in sustained work using a bicycle ergometer test - co morbidity assessed by thorough physician examination, ECG, Lab tests and the presence of 2 or more pre-defined chronic conditions such as diabetes, hypertension, bronchitis, osteoarthritis in lower limbs, arteriostenosis in lower limbs and myocardial infarction. Subjective measure of tiredness in daily activities measured by validated Mob-T scale. Participants were also asked if they felt tired after performing the same six activities as in the Mob-H scale. 1)transfer 2)walk indoors 3) get outdoors 4)walk out of doors in nice weather 5) walk out of doors in poor weather 6)manage stairs.'

Continued

Author/Year	Reference	Theoretical definitions	Operational definitions
Amici A et al 2008	**150**		Marigliano–Cacciafesta polypathological sc ale (MCPS): Eleven domains of pathology (Neurological, cardiopathy,respiratory,locomotor apparatus,sensory deprivation, metabolism and nutritional state,cognitive state and mood,peripheral vascular system,malignant cancerous and gastroenteritic disorders) -Slight polypathology <15 scores. - Medium polypathology 15–24 scores. -Medium-severe polypathology 25–49 scores. - Severe polypathology 50–74 scores. - Very severe polypathology >75 scores.
Boxer RS et al 2008	**83**		A 6 minute walking test (6MWT) may be useful to identify frailty and those in transition to frailty.
Ensrud KE et al 2008	**79**		A simple frailty index with the components of weight loss, inability to rise from a chair 5 times without using arms, and reduced energy l evel (Study of Osteoporotic Fractures [SOF index])
Varadhan R et al 2008	**65**	'...frailty..signifies a loss of resilience in homeostatic regulation	
Ravaglia G et al 2008	**94**		'Variables from six domains were considered as potential predictors of mortality: socio -demographic, lifestyle, medical status, physical function, nutrition, and mood and cognitive status'
Guilley E et al 2008	**151**	'..expanded working definition of frailty based on deficiencies in mobil ity, memory, energy, and physical or sensory capacities..'.	
Buchman AS et al 2009	**89**		A continuous composite measure of frailty based on four frailty components: • Grip strength • Gait-time to walk 8 feet • BMI • Fatigue Each of the four compon ents were dichotomized to represent categorical frailty; lowest quintile of >=2 component defined as frail.

The evolution of frailty

The 60s and 70s

The concerns regarding the increased number of elderly, bedridden and chronically sick patients, can be traced to early literature by Dr Marjory Warren who originated her pioneering work in a former Poor Law institution [52] and later helped found the British specialty of geriatrics. Following this, geriatric medicine had evolved from addressing the problem of 'bed blocking' by vulnerable older persons in acute medical wards to the teaching and implementation of geriatric assessments in the management and rehabilitation of the elderly patient. This greater rise in geriatric medicine during the 1960s and 70s could be seen as a response to the needs of the frail elderly.

In 1960 *J.H. Sheldon* published in the British Medical Journal the first description of the very old, enfeebled person using a special term; the *'frail ambulant'[8]*. It was coined in the interest of *'administrative tidiness'* in the hope of discovering the correct authority to provide custodial care for increasing numbers of very old people presenting to acute hospital departments.

They were described as 'belonging to the later period of old age, beyond 75 years with 'an increasing amount of breakdown in health.....imposing a special stress on the community'[8] by virtue of its long duration. Problems of physical health were seen to emphasize the importance of problems of social health, without which the discharge of ... 'these locally cured but constitutionally or mentally enfeebled old person may prove exceedingly difficult' [8]. This very first

definition of frailty was qualitative and broadly based on physical and psychosocial criteria, and also contained an important element of concern about the appropriateness or otherwise of frail people occupying acute medical resources.

In 1963,*J Agate* who based his definition on Sheldon's, described that after the age of 80, a state of general frailty was increasingly common. He defined frailty as *'a state of semi-dependence...the patient is not necessarily ill, and may have no specific disabilities; yet she cannot sustain an independent life with safety and success, even though willing to try and is mentally normal.....weakness and unsteadiness mean that she cannot shop for herself, nor do her own cooking, may need help with dressing, toilet and bathing, and someone at her elbow to give confidence in walking.'..... 'they do not need regular medical attention or nursing care; they do need gentle supervision and much domestic help.....the state of most of such people who live alone at home is precarious.'* [50] This definition was similarly based on physical, psychological and social criteria. It is interesting to note that the 'patient' here was described in decidedly 'feminine' terms. In the United States however, early official use of the term 'frail elderly' was later introduced in the 1970s through the work of Monsignor Charles F Fahey and the Federal Council of Aging. The heterogeneity of this older population was acknowledged and this term was selected to focus attention on those with 'physical debilities, emotional impairments and debilitating social and physical environments'[53].

The 80s

It was not until the 1980s that researchers began to elaborate on the term. In the early phase, the definitions of frailty were theoretical and hence mainly qualitative in nature. These definitions were coined for the purpose of identifying the characteristics of frail older people and provided the background for future description of frailty as having a single or multiple domains. A single domain definition by *Gadow* 1983 gave a psychological description in which frailty was seen as a *'devalued phenomenon'* particularly identified with aging and *'its negative value reflects a rationalist metaphysic in which body and self are adversaries'*.[54] In this context of frailty, the spirit or self is seen as indestructible; the body or flesh is frail. In 1980,another single domain definition on a social context by *O' Brien and Wagner* described a special population in Portland, U.S.A. of frail urban elderly with characteristics of having 'least capacity for self maintenance, for whom institutionalization or death are a very real potential occurrence'[55]. This study identified the frail as being over 75 years of age, living alone with sub-poverty levels of income. This early study not only stated the importance of the environment in which these older people lived, it also emphasized that they were very dependent on social ties (both formal and informal) for continued and functional community living.

In 1988 *Woodhouse* and associates followed with a social and functional definition of frailty defining the frail elderly as individuals over 65 years of age, dependent on others for activities of daily living, often in institutional care and not independently mobile[3]. Similarly, in 1989, *Berkman* described this group of

older people with the term 'failure to thrive'; having diminished functional ability to live with multisystem disease or cope with ensuing problems and manage their own care[56]. They were also deemed no longer responsive to health care interventions. This sparked the beginning of more functional definitions of frailty using measurable parameters of activities of daily living such as the Barthel Index and Katz's Instrumental Activities of Daily Living[45].

In 1985, *Brocklehurst [57]* formally described a multi-dimensional definition of frailty from a clinical geriatric perspective using his frailty 'Model of breakdown'. This model used a balance between biomedical and psychosocial factors which were seen as '*assets*' or '*deficits*' that affect whether a person could live independently in the community. On one side of the balance were assets which maintained a person's independence in the community: health, functional capacity, a positive attitude toward health and other resources. On the other were deficits which threatened independence: ill health (particularly chronic disease), disability, dependence on others for activities of daily living and burden on caregivers [58]. Later in this decade, a consensus multi-dimensional definition by the *National Institute of Health* described the frail elderly as individuals who '*tend to exhibit great medical complexity and vulnerability; have illnesses with atypical and obscure presentations; suffer major cognitive, affective and functional problems; are especially vulnerable to iatrogenesis; are often socially isolated and economically deprived; and are at high risk for premature or inappropriate institutionalization.'[59]*

A step towards more operational definitions was the construct of a frailty index by *Wan et al* in 1986 where frailty was described as a '*measure of need for care*' and conceptualized as '*a first order factor of four unobservable health related constructs, including self assessed health status, objectively evaluated functional status, perceived service needs and instrumental social support available among the elderly*' [60].This study proposed that the degree of frailty among elderly Bostonians can be explained by their use of formal health services. Other frailty indices that followed however focused primarily on self reports of health and functional status [19, 51].

The 90s

Combinations of single and multiple domains used to define frailty persisted into the nineties. These frailty measures were focused on combining domains of mainly physical frailty with other domains of nutrition, psychological (cognitive) and sensory functioning included [46, 61-63]. In 1994, *Rockwood et al* introduced a *dynamic model* of frailty in older people based on Brocklehurst's 'model of breakdown'. This model referred to frailty as a balance between biomedical and psychosocial domains and included those who were dependent on others for activities of daily living or those at risk of dependency[18]. Frailty was also described as a diminished ability to carry out important practical and social activities of daily living[9]. Purely socially based definitions elaborated further on how frailty is defined, framed and understood by older persons, their

family members, and their health care providers within the context of a multidisciplinary geriatric assessment service[64].

In this decade, the questions asked were purposely aimed at understanding the underlying pathways and mechanisms of frailty and its association with the aging process. This began the era of more physiologically based definitions which began to dominate the frailty scene and still do so today [65-67]. In 1993, *Bortz* proposed that a loss of cellular energy production was the key to underlying biological processes that led to the altered physiology of frail older adults. Using the concept of '*synmorphosis*', he suggested that frailty was a result of 'early disease in multiple systems leading to impaired muscle strength, mobility, balance and endurance'[68]. He also stated that frailty was largely separable from the process of aging and should therefore be susceptible to active intervention and reversal. Similarly, *Campbell and Buchner* defined frailty as a '*condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure*'[69]. This set the stage for further physiological definitions of frailty by *Fried* and *Walston* with their 'cycle of frailty' which moved future research towards the identification of the aetiologies of frailty. They hypothesized that multiple interrelated physiological systems such as inflammatory, skeletal muscle, endocrine, clotting and haematological changes that might underlie frailty [16, 23] were altered in the frail older person. These systems interact with one another and have the

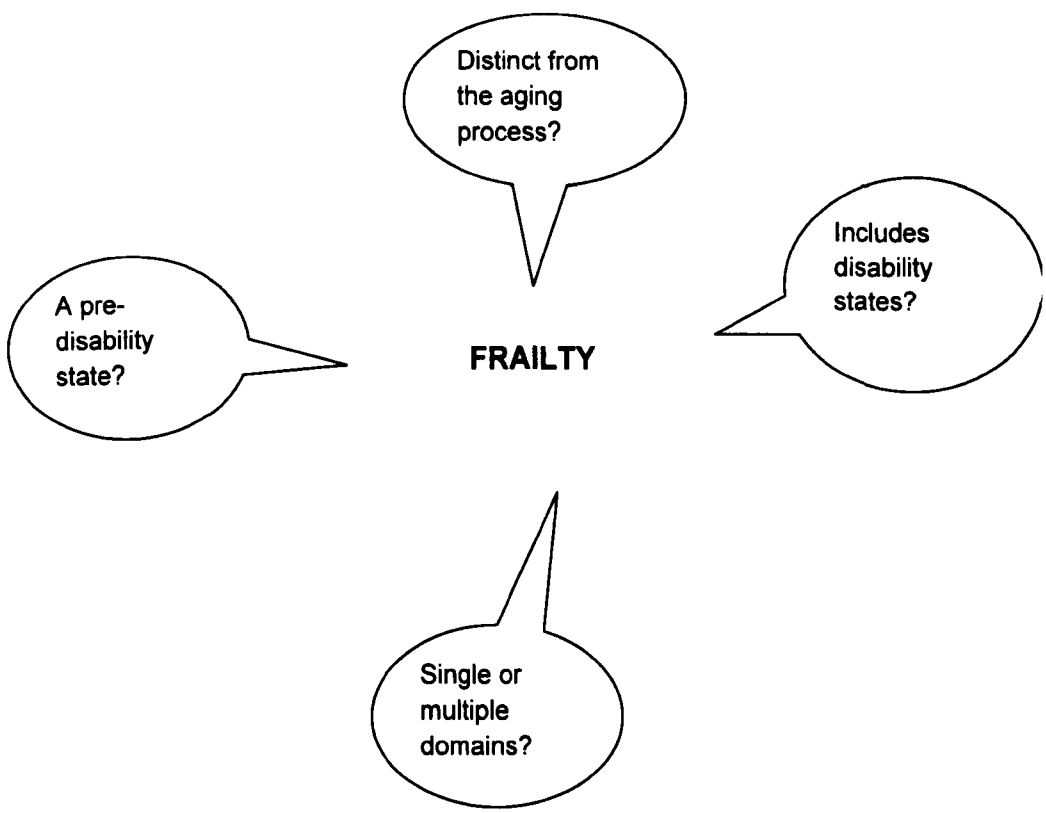
influence on overall health and well being. Although no unifying causal mechanism has yet been established, current research is focused on outlining the various components of frailty through these physiological and biological means.

Another question posed in this decade was whether frail older people were also disabled. In 1991, *Buchner and Wagner* reviewed the concept of frailty as '*losses of physiologic reserve that increase the risk of disability.*' They regarded frailty as a pre-disability state which '*represents a loss of physiologic capacity that is either not severe enough to interfere with major activities of daily living*' [70]. However, other research at this time defined frailty through use of physical performance measures to determine severity of functional disability in the older person [43, 46-49, 71] and therefore did not fully distinguish frailty from disability. Another operational definition was the *Geriatric Status Scale* (GSS) which combined a self reported measure of disability and test performance measures of cognitive impairment[71]. Frailty was defined here as a dependence on others for activities of daily living, and therefore suggested that those who were disabled could also be included in its definition.

By the end of this decade, there were several different opinions on frailty which continue on into the 21st century. Whilst most researchers agree that frailty was a process independent of aging, there is some confusion amongst those who emphasize on frailty as a pre-disability state and others who make it a state of

disability by including physical performance measures. Furthermore, there are also those who believe that frailty is best explained as a complex multi-dimensional state and others who feel a single domain would suffice. These differing opinions are illustrated in ***Figure 2.3***.

Figure 2.3: Questions arising from the various definitions of frailty



The 21st century

Two main frailty definitions formed the background for a considerable amount of research at the start of the twenty first century; Fried's phenotype of frailty[20] and Canadian Study of Health and Aging (CSHA) frailty index [72]. They were

developed as clinical tools used to identify frail older people in the clinical setting who were at increased at risk of adverse events. Both measures represent extreme ends of the various views on the frailty concept; one interprets frailty as a form of accelerated aging[72], the other as an entity with a distinct pathophysiological basis[20, 73]. In 2001, *Fried et al* proposed a *phenotype of frailty* which included key components of the hypothesized *'cycle of frailty'*. This was based on five domains; *(unintentional) weight loss , weakness, poor endurance and energy, slowness and low physical activity*'[20]. As a screening criterion for frailty; this definition required the presence of more than 3 of these clinical manifestations and was found to predict various poor clinical outcomes such as falls, development of disability, hospitalization and mortality. Other researchers have also validated this phenotype and added to the growing body of knowledge that focused solely on physical/physiological measures of frailty [1, 74-77].

Fried also proposed that although frailty frequently existed concurrently with co-morbid disease and disability, it was independent and distinct from these characteristics. This view of frailty was debated by experts from a European, Canadian and American Geriatric Advisory Panel at a recent International Academy on Nutrition and Aging task force meeting who agreed to consider frailty to be a pre-disability state. Although there was no consensus on a definition or assessment tool for frailty, they decided that as disability was not a cause but rather a consequence of frailty, it should not be included in a frailty definition or measure[26].

The second most frequently validated definition of frailty was the Canadian Study of Health and Aging (CSHA) frailty index (FI). Initially developed for elderly Canadians, was based on deficit accumulation which was counted using self reports or clinically designated symptoms, signs, disease and disabilities. This approach paid less attention to which variables were present, but rather assumed that the more people had wrong with them, the frailer they would be. The rationale behind this was that it made the assessment of frailty widely available without special instrumentation, while adhering to the standard view that frailty was multiply determined [40]. Different FI's have also been constructed under a similar assumption, with differing variables included in them [19, 40, 78-82].

Further measures developed in the past 10 years can be divided into single/dual domain or multidimensional measures. Single measures of frailty were purely physical/physiological ones such as slow gait speed[22] and/or inability to stand up from a chair[24], grip strength[21], six minute walk test[83], low serum cholesterol[84] or was simply a score based on a subjective evaluation of an individual's general health appearance[85]. Multi-dimensional measures included self report instruments such as the Vulnerable Elders Survey(VES-13) [43] and tiredness in activities of daily living (Mob T scale)[86] as well as the *Edmonton Frail Scale* which included domain of social support[87]. These measures provided subjective measures that identify vulnerable frail elderly requiring targeted strategies for prevention. These strategies for frailty

prevention also arise from more objective measures of frailty which have included other domains such as balance, motor processing (speed of movement, coordination), and cognition[23, 88].

A step towards translating the concept of frailty into a clinical entity was introduced in the *Clinical Global Impression of Change in Physical Frailty [23].* This measure deliberately restricted itself to physical frailty and emphasized the concept of structured clinical judgment as a foundation for the measurement of frailty. Another frailty measure which attempted to translate the measurement of frailty into a clinically sensible tool was the CSHA's *7- point Clinical Frailty Scale which* classified older persons from very fit to severely frail. This scale mixed items such as co-morbidity, cognitive impairment, dependency on ADLs and IADLs as well as disability [15].

In summary my main findings on this systematic literature review were as follows:

- The last decade had mainly focused on efforts to quantify frailty resulting in mainly physical/physiological definitions of frailty [20-22, 47, 83, 89-92].

- There was general agreement with the idea that an identifying feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resilience[66, 67, 88].

- Standardization of a frailty definition across populations is not, as yet, possible as present validated measures were based on different criteria and operationalized in different older populations.

- The measures that provide single domains or combine several different variables from self reports of health status, signs, symptoms of disease, to functional, sensory and cognitive impairments as well as poor social status into the same measure [71, 72] could introduce misclassification as they may not be measuring frailty itself but rather co-morbidity or even disability.

- Despite general agreement that frailty and disability were related but distinct concepts [26, 74, 88], there were still measures used today that include basic activities of daily living in their measurement of frailty [40, 43, 51, 93, 94].

- Despite the controversies and different viewpoints surrounding the literature on frailty, the unifying goal appears to be the identification of vulnerable older people so as to delay or prevent the onset of serious adverse events such as falls, institutionalization, hospitalization and death [20, 40, 41, 76, 95, 96].

Discussion

This systematic search of the various definitions of frailty provided me with an insight into how this concept was born and has now evolved into the more operational measures we see today. The numerous measures over the past few decades were a testament to the fact that clinicians and researchers did generally agree that frailty was a useful concept[73]. However, this in-depth review of the extensive literature revealed that there was little coherence in the many frailty studies conducted over the whole search period. Early theoretical definitions were multidimensional encompassing physical/functional, psychological and social criteria but were not operationalized to enable robust measurement. These operational approaches varied in the critical domains that made up the concept of frailty. The impact of the environmental in which old people live on frailty, which was initially deemed an important domain in the theoretical definitions[9, 55, 68, 69], alongside psychological and social domains dropped out of sight. Instead, the physical/physiological domains were the primary focus of operationalized definitions. The original concept of frailty as a multi-dimensional syndrome had been transposed to a focus on physical/physiological function and biomarkers of frailty reflecting the move away from holistic geriatric medicine practice and a patient-centred approach. This move may have arisen in response to more technological approaches and a need to be more objective in applying the science of measurement. This evolution of frailty concepts could be due to the physicians' desire for more

tangible and objectively confirmed evidence of patients' needs, which were more likely to be treatable by medical means.[97]

Whilst there are valid reasons to measure frailty (see ***Chapter 1***), until a consensus on a standardized definition is reached, we may be missing or denying the truly vulnerable in the community benefits of cost-effective prevention measures, acute treatment or rehabilitation. Currently although single measures may provide useful associations with frailty [21, 22, 84] focusing on one component of frailty alone (such as grip strength or gait speed) may result in a misclassification of those who are truly frail. On the other hand, they may turn out to be '*an adequate, practical screen for assessing vulnerability in non-disabled older people, and that the complexity of diagnosing frailty may be unnecessary*' [73]. To confirm this, more research is needed to further our understanding of underlying biological processes and pathophysiology of frailty. Until then, we may rely on classifications that are already in operation ,such as the ICIDH1 (International Classification of Impairments, Disabilities and Handicap 1980, and the current ICF (International Classification of Functioning, Disability and Health)[98] . The ICF is a classification of health and health related domains that describe body functions and structures, activities and participation. The domains are classified from body, individual and societal perspectives. Since an individual's functioning and disability occurs in a context, ICF also includes a list of environmental factors. This provides a scientific basis and a common language for describing,

understanding and studying health and health-related states, outcomes and determinants. According to the ICF, an individual's functioning in a specific domain is an interaction between the health condition and contextual factors (i.e. environment and personal factors) *Disability* (now classified as activity limitation), *impairment, participation, handicap* (participation restriction) are key entities that form these associations. The full health experience is described using all these components. This would indeed be a useful guide/template for defining frailty or serve as a good alternative as it is already in existence. However the ICF concept did not 'catch on' as the obvious approach to defining frailty. This is perhaps due to the surge in operational definitions which sought more tangible means of measuring frailty leading to a greater focus on physical domains.

In my opinion as a practicing geriatrician and student of epidemiology, a successful operational definition is one that is multi-dimensional, encompassing all the domains which constitute the whole patient. This would include all elements that represent the frail older person in terms of body (structure and function), person and societal levels. This includes not only the physical/physiological domains but also contributions from psychological, social and environmental domains. Frailty in the older person is also subject to time variations and is reversible, possessing the quality of changing status over time (dynamic) for example in acute illness and recovery[77]. An ideal concept of frailty should also translate as a multipurpose classification system designed to serve various disciplines and sectors across different countries and cultures.

However, we must recognize that as the experience of frailty is an individual and qualitative one, there may be latent qualities that may not be derived from directly observed or measured frailty indicators. This brings my concept of frailty closer to it being a 'latent vulnerability' in older people. This phenomenon is subtle, often asymptomatic and '*only evident over time when excess vulnerability to stressors reduces the older person's ability to maintain or regain their homeostasis*'[2]. This concept of frailty will be presented as a measurement model of frailty in ***Chapter 3*** of my thesis.

Chapter 2.2: Measures of frailty and their prognostic value in large study populations: a systematic review

Introduction

The search for a unifying definition of frailty in older persons is driven by the knowledge that they are a special group of individuals at high risk of adverse health outcomes such as falls, hospitalization, institutionalization, morbidity and death [62, 71, 99]. Improving and maintaining health care services for the growing frail elderly population whilst limiting the economic burden that it entails is indeed a challenge for all involved in their care as well as policy makers. A major obstacle though to impede targeted care and improvement of health outcomes of the older population has been the absence of a standardized method for screening those who are at risk in the community.

Frailty, a concept still yet to be defined, has evolved over the past few decades as the answer. Although consensus groups [2, 4] have called for a multi-dimensional definition of frailty, the focus has mainly been on the physical/physiological measures and biomarkers of frailty. This quantitative view of frailty in the older population was seen to provide tangible means of measurement and has been the focus of much literature on the subject [20, 30, 31, 33, 63].

The first part of this literature review revealed that the development of the existing measures of frailty had been affected by the definition used. The diverse views of clinicians and other health care professionals on the nature of frailty resulted in the current situation where "frailty" is used without definition, measured in a variety of ways and for a range of purposes [9].Henceforth, developers of these measures should make clear underlying assumptions regarding the meaning of frailty for the study population being assessed. As a 'gold standard' definition does not yet exist, predictive validity provides a means of evaluating the ability of a frailty measure to demonstrate susceptibility to adverse outcomes. The predictive value of the measure is of course dependent on the incidence of the adverse outcomes of interest. Many studies have attempted to individually validate the various concepts of frailty; none have compared all the different frailty measures in large populations. In this section of the systematic literature review I examined all the different measures of frailty used in study populations of over 1000 persons. My aim was to determine the accuracy of the various frailty measures and their prognostic value in determining adverse outcomes such as death, institutionalization, hospitalization, disability or falls.

Method

Search strategy and data extraction

Following the same search employed in **Chapter 2.1**, from the **219 articles** screened for eligibility, I selected studies which presented the prognostic/predictive value of their operational frailty measure. These operational measures were classified according to Rockwood et al's description of three types of frailty measure[35]:

- A rules-based/phenotype of frailty, for example, a person may be defined as frail if 3 or more symptoms are present[20]
- The summing up of accumulated deficits (frailty index),a proportion of all potential deficits considered for a given person[100]
- The reliance on clinical judgment, to interpret the results of history taking and clinical examination[41].

Articles were limited to the English language and community dwelling older persons aged over 65 years. Additional inclusion criteria for this part of the search were:

- studies with populations greater than 1000 were selected so as to provide greater likelihood of statistical power to the findings
- a fully defined description of the prognostic variable, in this case, frailty, which was available for all or a high proportion of the study population
- each study population included was followed up for longer than one year.

- the outcomes for each study were objective and fully defined with a status which was known for all or a high proportion of the subjects.
- the predictive value of the frailty measure was dependent on the incidence of the adverse outcome and the studies selected had clear estimates of the effect of frailty on the outcome of interest.

The exclusion criteria include:

- study population less than 65 years of age
- small study populations of less than 1000 people 3) duplicate measures on the same population
- cross sectional studies.

Of the 219 articles screened, 22 studies were based on operational definitions that fulfilled the inclusion criteria of age over 65 years and study population of over 1000. From these, 12 articles were validation studies and 10 were from operational definitions actually developed in their respective population (**see *Figure 2.4***).

Figure 2.4: Flow diagram of search strategy on the prognostic value of frailty measures in large study populations

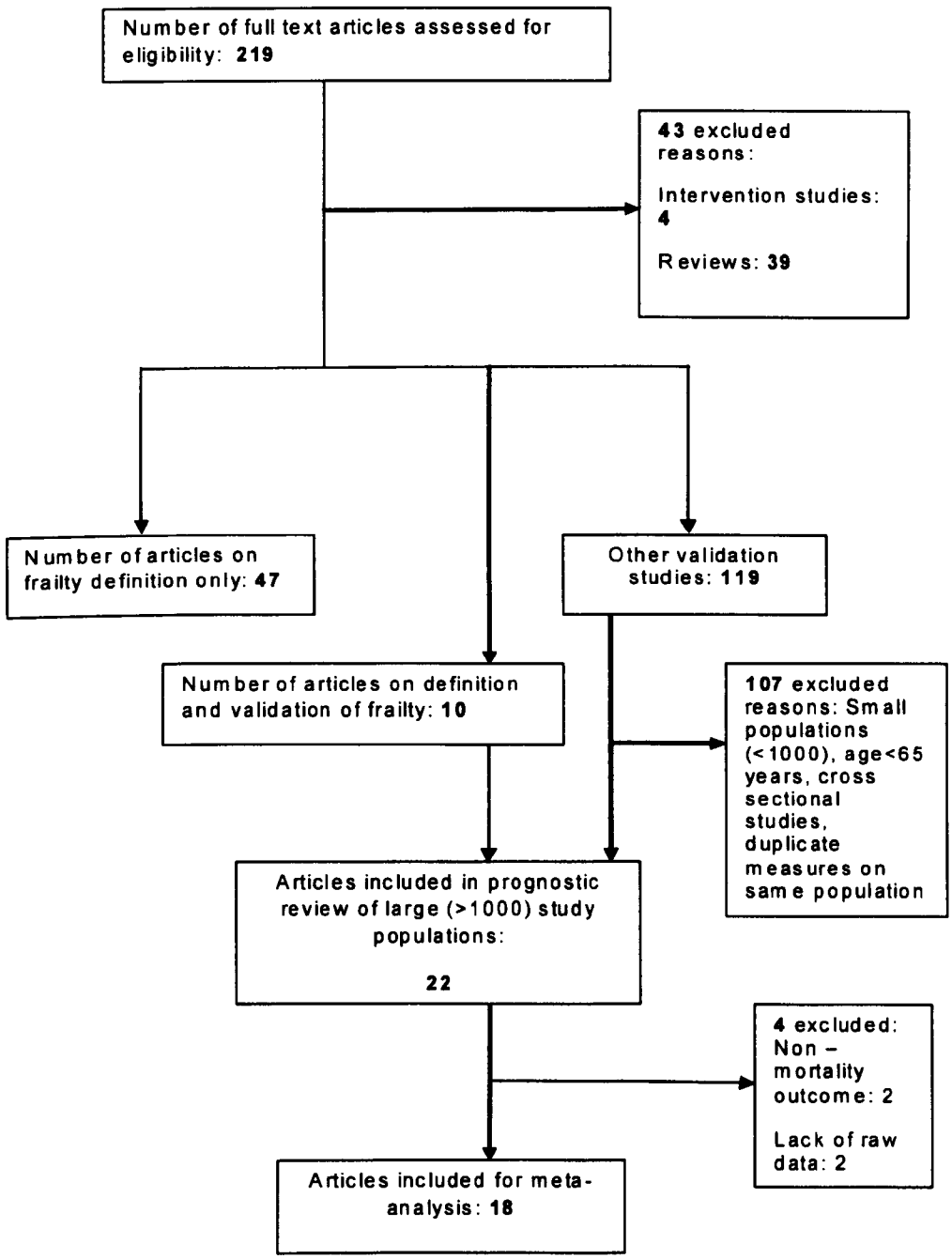


Table 2.4: Measures of Frailty in 22 large study populations according to predicted adverse outcomes.

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Fried LP et al 2001(20)	Phenotype of frailty - Presence of 3/>: • Unintentional weight loss • Self-reported exhaustion • Weakness (grip strength) • Slow walking speed • Low Physical activity	Cardiovascular Health Study (CHS) (longitudinal) **N=5317** community dwellers aged >65 Prevalence of frailty (overall) 6.9%	Rules-based	Predictive over 3 years: • Falls –(28%v 15%) • Hospitalization-(59% v 33%) • Worsening mobility and ADL disability-(39% v 8%) • Mortality-(18% v 3%)
Saliba et al 2001(43)	Vulnerable Elders Survey (VES-13) -a survey tool which includes age, SRH and function	**N=6205** Medicare beneficiaries aged>65 Cohort study Prevalence of frailty 32%	Rules-based	The vulnerable group has 4.2 times risk of death or functional decline over 2 years: • Mortality - 10% • Decline in ADL/IADL-14%
Rockwood K et al 2004(100)	Geriatric Status Scale (GSS) Mild, moderate or severe frailty	Canadian Study of Health and Aging (CSHA) **N=9008** community dwellers aged >65 Cohort study (72% response rate) Prevalence of frailty: 7% age 65-74 17.5% age 75-84 36.6% age>85	Rules-based	Death RRisk- adjusted (95%CI) • Mild frailty- 2.54 (1.92,3.37) • Mod/severe frailty- 3.69 (2.26,6.02) Institutionalization RRisk-adjusted (95%CI) • Mild frailty- 2.54 (1.67,3.86) Mod/severe frailty-2.60(1.36,4.96)

Continued

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Puts et al, 2005(77)	Presence of 3/> frailty markers: • Body weight • Peak expiratory flow • Cognition • Vision Problems • Hearing problems • Incontinence • Sense of mastery • Depressive symptoms • Physical activity	Longitudinal Study Amsterdam(LASA) **N=2257** (72.6% response rate) Prevalence of frailty men vs. women: Static frailty (17 vs18%) Dynamic frailty (18 vs14%)	Rules-based	Predictive of Mortality: (frail vs non frail) Static Frailty- 50% v 15% men 27% v 6% women Dynamic frailty- 34% v 17% men 25% v 7% women
Woods et al. 2005[1]	Phenotype of frailty: Presence of 3/>: • Unintentional weight loss • Self-reported exhaustion • Weakness (grip strength) • Slow walking speed • Low Physical activity	The Women's Health Initiative (WHI)Observational study **N= 40657** aged 65-79 Prevalence of frailty 16.3% Incident frailty 14.8%	Rules-based	Baseline frailty predicted risk using HR, 95% C.I. • Death 1.71 (1.48,1.97) • Hip fractures 1.57 (1.11,2.20) • ADL disability OR=3.15 (2.47,4.02) Hospitalization OR=1.95 (1.72,2.22)
Scarcella 2005(95)	Final Synthetic Score(FSS) originated from answers to a Geriatric Functional Evaluation questionnaire.	Sample of 3060 over 65 year old citizens of Ragusa(Italy) who lived in their own home.	Rules based	Predicted 5 year mortality: HR 2.91 (2.25,3.77) Use of public care services: 1.39(1.09,1.77)
Folsom AR 2007(34)	Phenotype of frailty(as above)	Four U.S. communities involving 4859 participants 65 years old and older.	Rules-based	Predictive of Venous Thromboembolism(VTE) RR:1.31 (95% CI:0.93-1.84). The comparably adjusted RR for idiopathic VTE: 1.79 (95% CI, 1.02-3.13).

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Bandeen-Roche K et al 2006(74)	Phenotype of frailty-presence of 3/>: • weight loss (>10% of weight at age 60 or BMI<18.5kg) • self report exhaustion • slowness • weakness(grip strength)	Women's Health and aging studies(WHAS) I&II >65 years, N=1438 women	Rules-based	Predictive over 3 years: Falls:adjusted HR 1.18 Severe IADL disability: adjusted HR 15.79 Hospitalization:adjusted HR 0.67 Permanent nursing home entry: adjusted HR 23.98 Death:adjusted HR 6.03
Cawthorn 2007(75)	Phenotype of frailty :Presence of 3 /> • Sarcopenia • Weakness • Self report exhaustion • Low activity level • Slow walking speed Similar but not identical measurements to CHS study	Osteoporotic Fractures in Men (MrOS) study. **N=5993** community dwellers aged >65 years Prevalence of frailty 4%	Rules-based	Age adjusted HR for mortality- Frail men 4.41(95%CI=3.43,5.67) Prefrail men 1.74 (1.47,2.07) compared with robust men.
Ensrud 2007(76)	Based on Fried's phenotype of frailty (as above)	Study of Osteoporotic Fractures (SOF) **N=6724** Caucasian community dwelling women aged >69 Prevalence of frailty 16.3%	Rules-based	Recurrent Falls –MOR=1.38(1.02-1.88) Death- 1.82MHR=1.82(1.56,2.13)

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Avila-Funes JA et al 2009(104)	Phenotype of frailty - Presence of 3/>: • Shrinking:weight loss > 3kg • Self-reported exhaustion • Slow walking speed • Weakness(difficulty rising from chair) • Low Physical activity	Three City Study (3-C) French community dwelling older people >65 years. N=6078	Rules - based	Predictlve over 4 years of: Incident disability (mobility,IADL,ADL): adjusted OR 1.58 (2.10,3.20) Hospitalization: adjusted OR 1.36 Death: adjusted HR 1.21
Ravaglia 2008(94)	Frailty score includes nine independent predictors of mortality	Conselice Study of Brain ageing(CSBA) N=1007 Italian subjects aged >65 years.	Rules-based	Predicted 4 year risk of Mortality: HR1.99 (1.82, 2.18) Fractures: OR 1.40(1.12, 1.73) Hospitalisation: OR 1.48 (1.26, 1.77) New disability: OR 2.21(1.73, 2.83) Worsening disability: OR 1.84(1.57, 2.16)

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Ensrud 2008/9 (79,103)	Study of Osteoporotic Fracture (SOF) index- Presence of 2/>: • Weight loss(>5% between examinations) • Reduced energy level • Inability to rise from a chair 5 times without using arms	Study of Osteoporotic Fracture N=6701 women aged>69 years N=3132 men >67 years	Rules-based	Predictive of: Falls: OR 3.03(men) 2.38(women) Fractures: HR 2.15(men, non-spine);1.79(women-hip/non-spine) Disability: OR 5.28(men); 2.17(women) Death: HR 2.53(men);2.37 (women)
Minitski et al 2004(51)	Frailty Index calculated from 40 self –reported variables	CSHA-wave1 cohort study **N= 8457** complete information on all 40 variables	FI	FI corresponding to a person's PBA (personal biological age) is predictive of death within 6 years.(p=0.017) as well as survival time
Goggins 2005(105)	Frailty Index-62 measures comprised of physical, psychological and socioeconomic variables.	Hong Kong cohort of 2032 persons >70 years (999 men and 1033 women)	FI	Predictive of death with age adjusted RR (based on 10 year increments: 2.04

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Klein et al 2005(78)	Frailty index calculated from markers: • Gait time • Peak expiratory flow rate • Hand grip strength • Inability to stand from sitting in one chair • Visual impairment Index range 0(no frailty) to 5 (max frailty)	Beaver Dam Eye cohort study **N= 2962** community dwellers aged 43-86	FI	Morbidity: Increase in age-adjusted odds ratio -35% for Cardiovascular disease 20% for hypertension 15-20% of cancer (excl.skin)-not significant. HR 1.69 (1.38-2.08) with Survival analysis
Cacciatore F 2005(93)	Frailty Staging System(FSS) consists of 7 domains of functioning: disability mobility, cognitive,visual and hearing function,urinary continence and social support.	'Osservatorio geriatrico regione Campania' study subjects N=1332 subjects aged >65 years.	FI	Predictive of mortality (over 12 year follow up): fully adjusted HR 1.62(with heart failure) and HR 1.24 (without heart failure)
Kulminski 2007(102)	Frailty Index of 32 measures self-rated health, disease, cognitive and functional impairments(BADL&IADL)	National Long Term Care Survey(NLTCS)	FI	Predictive of death at 1 & 21 years of follow up(men vs. women): 1 year mortality Men:RR 4.23 Women:RR 4.99 21 year mortality: Men:RR 2.53 Women:RR 2.24
Gu 2009(42)	Frailty Index of 39 measures from self reports of health status, cognitive functioning, disability, auditory and visual ability,depression, heart	Chinese Longitudinal Healthy Longevity Survey N=13861(7929 women,5932 men) aged 65-109 years.	FI	Predictive of 3 year mortality at advanced ages. Mortality was significantly higher in the 3rd and 4th quartile and higher in men at all age groups.

Author(reference)	Frailty measure	Population	Type of Measure	Frailty outcomes (frail vs. non frail)
Hastings 2009(101)	Deficit Accumulation Index(DAI)	1851 community-dwelling Medicare fee-for-service enrollees, aged 65 and older who were discharged from the emergency department (ED) between January 2000 and September 2002.	FI	Any adverse event (repeat outpatient ED visit, hospital admission, nursing home admission, or death): 27.4 vs.16.2% Risk of adverse outcome after ED discharge: HR 1.44, 95% CI: 1.06–1.96.
Rockwood et al 2005((41)	7-point Clinical Frailty Scale: • categorizes the very fit to severely frail	CSHA(wave 2) cohort study **N=2305** community dwellers aged >65	Clinical judgement based	Predictive validity for Death (HR=1.30, 1.27-1.33) Institutionalization HR=1.46,1.39-1.53) ROC analyses for adverse outcomes within 70 months

Table 2.4 summarizes the 22 studies according to type of measure and their outcome of interest. These 22 studies were selected by virtue of their respective adverse outcomes which varied across the different frailty measures, with the majority focusing on outcomes such as death and ADL disability and institutionalization. Of these, the **common adverse outcome** measured was **risk of death and/or survival** which formed the only basis of comparison of the prognostic value of the frailty measures reviewed here. Four studies were excluded ,two of which had non mortality outcomes[34, 101] one longitudinal survey lacked the raw data to enable calculation of a hazard ratio and confidence intervals[43] and the other study design was a mixture of a longitudinal and cross sectional survey. [102].

The final eighteen studies selected were all prospective cohort studies [1, 20, 41, 42, 51, 74-79, 93-95, 100, 103-105]. Twelve studies used a rules based definition of frailty [1, 20, 74-76, 79, 94-96, 100, 103, 104], six of which formed a phenotype of frailty. Although similar in theory to Fried's phenotype of physical frailty, some rules- based measures used different frailty markers to determine the criteria for frailty [74, 77, 79] whilst other rules- based measures included markers based on self reported health, instrumental activities of daily living (IADL) as well as social and psychological domains. Summing up of deficits using the frailty index was reported in five studies. The frailty index initially validated by Minitski in 2004 from the CSHA cohorts used only self reported variables. Later studies included other domains[42, 93, 105] whilst one calculated a frailty index only from accepted physical frailty markers[78]. Only

one study employed clinical judgment as a measure of frailty[41]. The CSHA population studies developed three frailty measures published in three separate studies which were derived from the same population of older Canadians [19, 41, 51]. The other fifteen measures were derived from different study populations.

Statistical analyses

A meta-analysis was carried out for each measure of frailty where data was available according to the criteria above. For each frailty measure, a pooled estimate (hazard ratio and relative risk) was calculated using the *random effects model*, along with a 95% confidence interval to measure the strength of the association between each measure of frailty and all cause mortality. The random effects model incorporates an estimate of between study variations (heterogeneity) into the calculation of the common effect, hence taking into account smaller studies[106]. Heterogeneity of effect or similarities between the studies was evaluated by the I-square statistic. Further exploration of heterogeneity among the studies was conducted by examining effect sizes by different subgroups. These subgroups include type of measure (rules-based or frailty index), age group (over or under 75 years), sex, number of variables included in each frailty measure (5 or less, 6 to 20 or more than 20 variables) as well as duration of follow up (more than or less than 5 years).

As with all meta-analyses, this review has the potential for publication bias. The Begg and Egger test [106] was conducted including all 18 studies to assess for evidence of publication bias. Data was analyzed using Stata version 10.

Results

The study populations mainly consisted of community dwelling older adults aged 65 years and older, from the Northern hemisphere with the exception of two Chinese population studies [42, 105]. Most of the populations were age stratified however one study[100] had over sampling of the two older cohorts respectively. Only one study population [76, 79] clearly excluded ethnic minorities in their sample population because of their low incidence of hip fractures. The ethnic groups were found to be frailer in these populations [1, 20]. Both sexes were included in the study populations with a majority of women in each population, except for four female [1, 74, 76, 79].and two male [75, 103] study populations.

Prevalence of frailty in the different populations varied greatly and ranged anywhere from 4 to 32%. Whether the measures were rules-based, clinical judgment based or a sum of deficits index, frailty was greater with increasing age in all the studies and was found to be higher in women compared to men except for one study population[78]. However, it was unclear whether frailty predicted a higher predicted mortality in men when compared with women, as this differed even when using the same type of measure [20, 79, 103]. All the

studies addressed appropriate and clearly focused questions which were mainly to measure or identify the frail elderly in their individual populations in relation to their risk for adverse outcomes which were also clearly defined. The selection of subjects was clearly stated as random in only 6 studies [42, 43, 51, 78, 96, 104]. All studies addressed the number of subjects studied at baseline and follow up but not all provided information on subjects who dropped out or were lost to follow up. Accuracy of performance of the individual frailty measures in predicting death using receiver operating curves (ROC) and area under the curve (AUC) was calculated in only six of the nineteen frailty measures[41, 43, 79, 103]. Three of these measures were developed in the same population of the Canadian Health and Aging study (the CSHA frailty index, the CSHA rules-based definition and the CSHA Clinical Frailty Scale) [41].All these measures reported an AUC ranging from 0.68 to 0.78 which show a moderately good performance in the prediction of all cause mortality.

Table 2.5: Frailty measures in eighteen large study populations with estimated risk of death (95% confidence interval) according to type of measure, gender and years of follow up.

Author	Type of Frailty Measure	Total N	Gender (%)	Adjusted Hazard Ratio (HR)	(95% C.I)	Follow up(years)
Fried2001	Rules	5317	57.9♀	2.24 1.63	(1.51, 3.33) (1.27, 2.08)	3 7
Rockwood2004‡	Rules	9008	59.5♀	1.17	(1.13, 1.20)	5
Puts2005	Rules	2257	52.9♀		(1.8, 3.8) (1.7, 3.2)†	3
Woods2005**	Rules	40657	100♀	1.71	(1.48, 1.97)	5.9
Scarcella 2005	Rules	3060	57♀	2.91	(2.25, 3.77)	5
Bandeen-Roche 2006	Rules	1438	100♀	6.03	(3.00, 12.08)	3
Cawthon2007**	Rules	5993	100♂	2.05	(1.55, 2.72	4.7
Ensrud2007**	Rules	6724	100♀	1.82	(1.56, 2.13	9
Ravaglia 2008	Rules	1007		1.99	(1.82, 2.18)	4

Author	Type of Frailty Measure	Total N	Gender (%)	Adjusted Hazard Ratio (HR)*	(95% C.I)	Follow up (years)
Avila-Funes 2008	Rules	6078	61.3♀	1.21	(0.78, 1.87)	4
Ensrud 2008**	Rules	6701?	100♀	Women: 2.37	(2.14, 2.61)	9
Ensrud 2009**	Rules	3132?	100♂	Men: 2.53	(1.75, 3.66)	3
Cacciotore 2005	FI	1139	56.4♀	1.24	1.04, 1.57	12
Minitski2004‡	FI	8457	59.5♀	1.26	(1.24, 1.29)	12
Klein2005	FI	2515	56.7♀	1.69	(1.38, 2.08)	4.5
Goggins 2005	FI	2032	50.8♀	2.04	(1.88, 2.22)	10
Gu 2009	FI	7901? 5960?	57.2♀ 42.8♂	Men: 3.86 Women: 2.94	(1.62, 6.09) (1.84, 4.04)	3
Rockwood2005‡	Clinical Judgment	2305	62.1♀	1.3	(1.27, 1.33)	5

* RR, HR based on adjusted rates on various confounders e.g.: age (all), sex, ethnicity, education, co morbid disease, self rated health, living alone, unmarried, cognitive impairment, smoking, functional status, socioeconomic status and disability, body mass index, estrogen use, femoral neck bone mineral density. **Single gender studies †RR based on static frailty ‡ CSHA studies

The risk of death between the frail versus non frail in their sample population was mainly calculated using the Cox proportional hazards method as shown in ***Table 2.5***, and based on a follow-up times between one to 12 years. These were grouped into rules based, FI and clinical judgment based definitions. Both adjusted and unadjusted rates for death were associated with frailty in all the study populations. Adjusted hazard ratios for death /survival ranged from 1.17 to 6.03 and 95% confidence intervals that did not include 1. All these studies typically adjusted for age and sex but differed with respect to the other covariates which were up to 25 in number. These include education, co morbid disease, socioeconomic status, smoking, ethnicity, self reported health status, living alone, being unmarried, functional status and disability. Single gender studies also included other confounders such as body mass index (BMI), femoral neck bone mineral density and oestrogen use.[1, 75, 76]

Meta-analysis

Figure 2.5: Forest plot comparing the risk of all cause mortality (Hazard ratios and 95% C.I.) between different frailty measures in large study populations

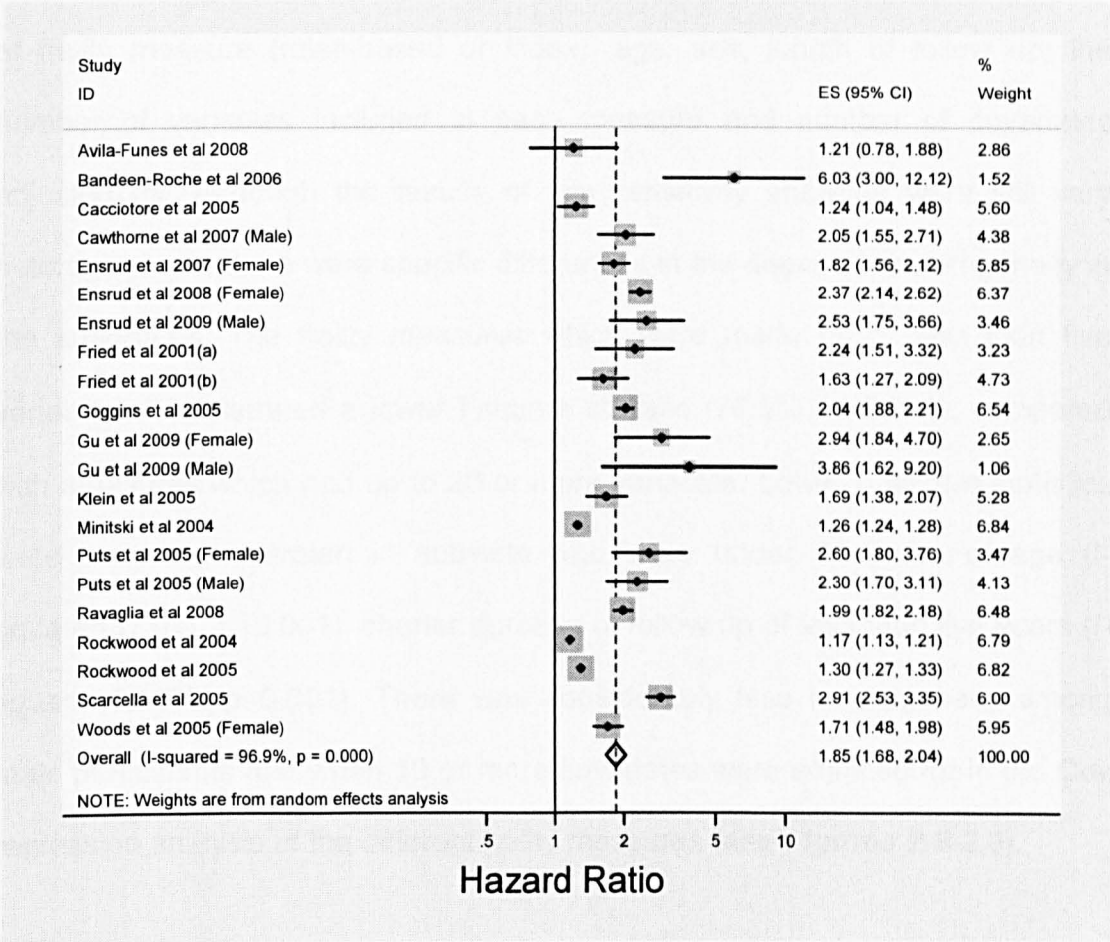


Figure 2.5 displays the results for the effect of each frailty measure as estimated by each of the 18 study populations. The results of each prognostic study are shown as hazard ratios with 95% confidence intervals, with a hazard ratio of more than 1 representing a risk of all cause mortality. Overall, the combined hazard ratio for the comparison of the estimated risk of death by the individual frailty measures was 1.85, 95%C.I.: 1.68, 2.04, $p<0.001$.There was

extensive evidence of heterogeneity between the hazard ratios in these study populations (I-squared=96.9%, p<0.001). The possible reasons for the heterogeneity was explored by examining the effect sizes in subgroups by type of frailty measure (rules-based or index), age, sex, length of follow up, the number of variables included in each measure and number of covariates adjusted for. Although the results of this sensitivity analyses were still very heterogeneous, there were specific differences in the degree of heterogeneity in the subgroups. The frailty measures which were made up of less than five variables demonstrated a lower I-square statistic (76.5%, p<0.001), compared with measures which had up to 20 or more variables. Lower I- square statistics were also demonstrated in subjects who were under 75 years of age (I-square=87.9%, p<0.001), shorter duration of follow up of less than five years (I-square=62.3%, p<0.001). There was considerably less heterogeneity among male participants and when 10 or more covariates were adjusted for in the Cox regression analysis of the different frailty measures (see ***Figures 2.6-2.9***).

Figure 2.6: Forest plot comparing the risk of all cause mortality (hazard ratios and 95% C.I.) between different frailty measures in large study populations stratified by the number of covariates adjusted for.

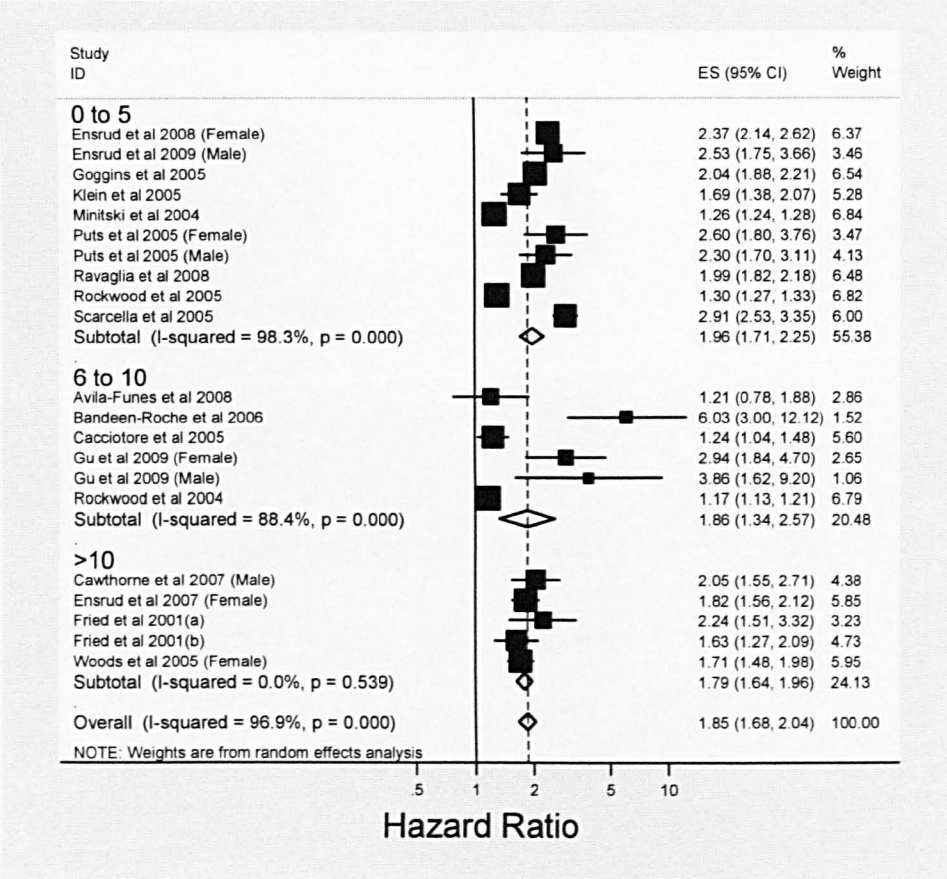


Figure 2.7: Forest plot comparing the risk of all cause mortality (hazard ratios and 95% C.I.) between different frailty measures in large study populations, stratified by sex.

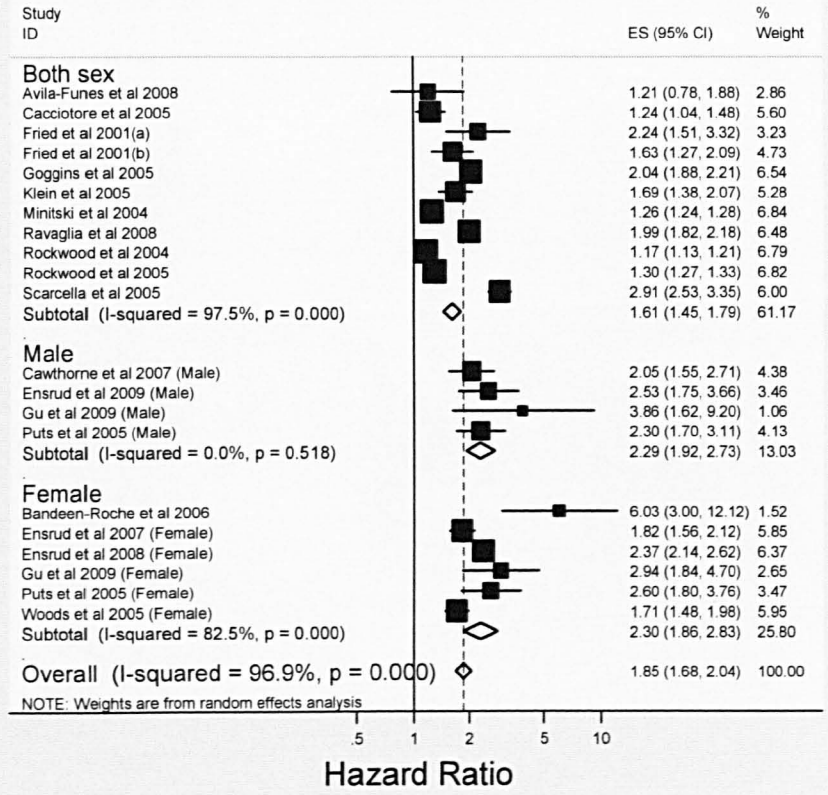


Figure 2.8: Forest plot comparing the risk of all cause mortality (hazard ratios and 95% C.I.) between different frailty measures in large study populations stratified by number of variables in each measure

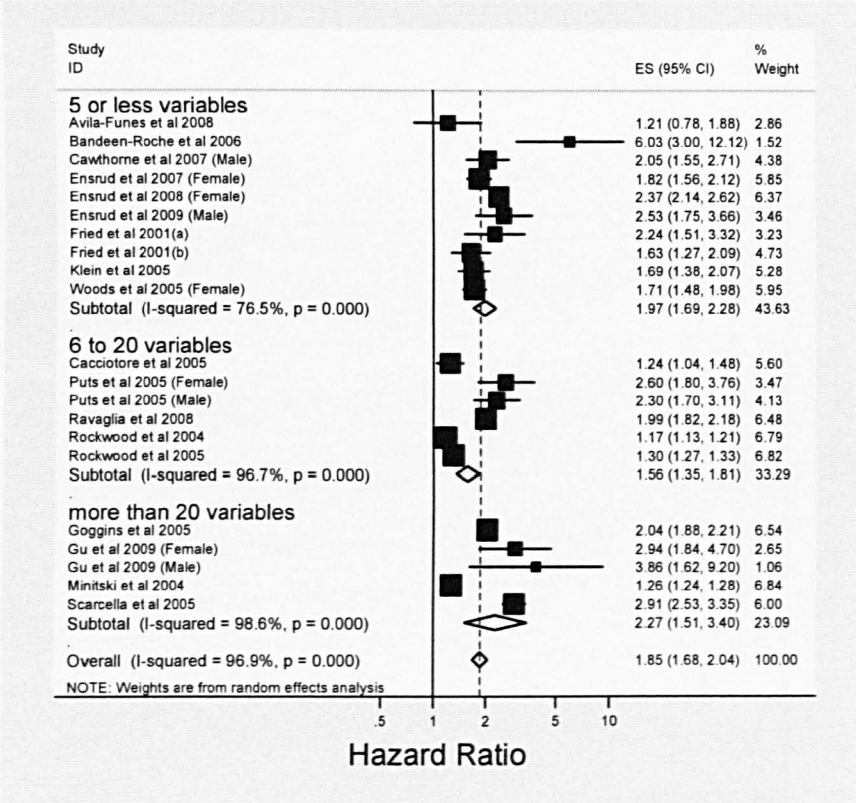


Figure 2.9: Forest plot comparing the risk of all cause mortality (hazard ratios and 95% C.I.) between different frailty measures in large study populations,stratified by duration of follow up period.

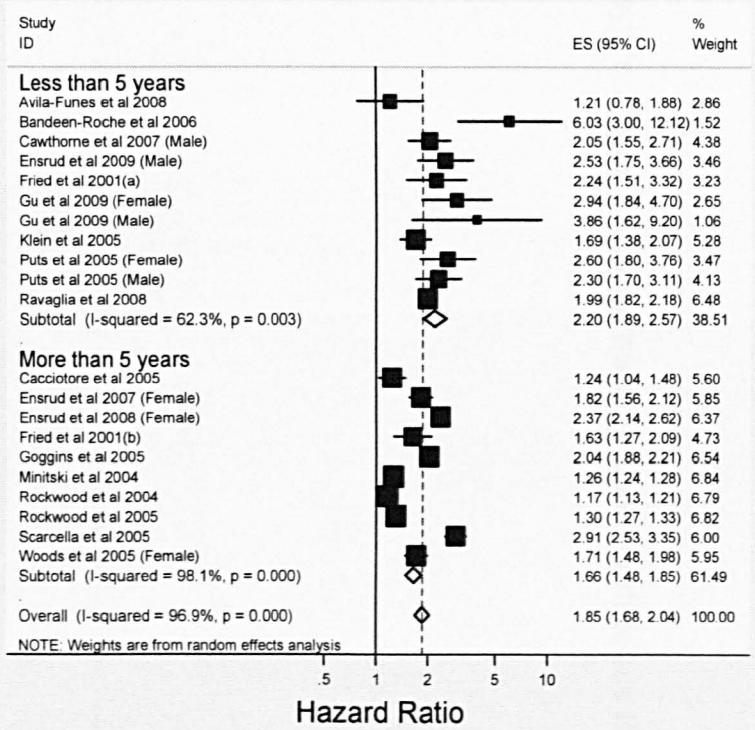
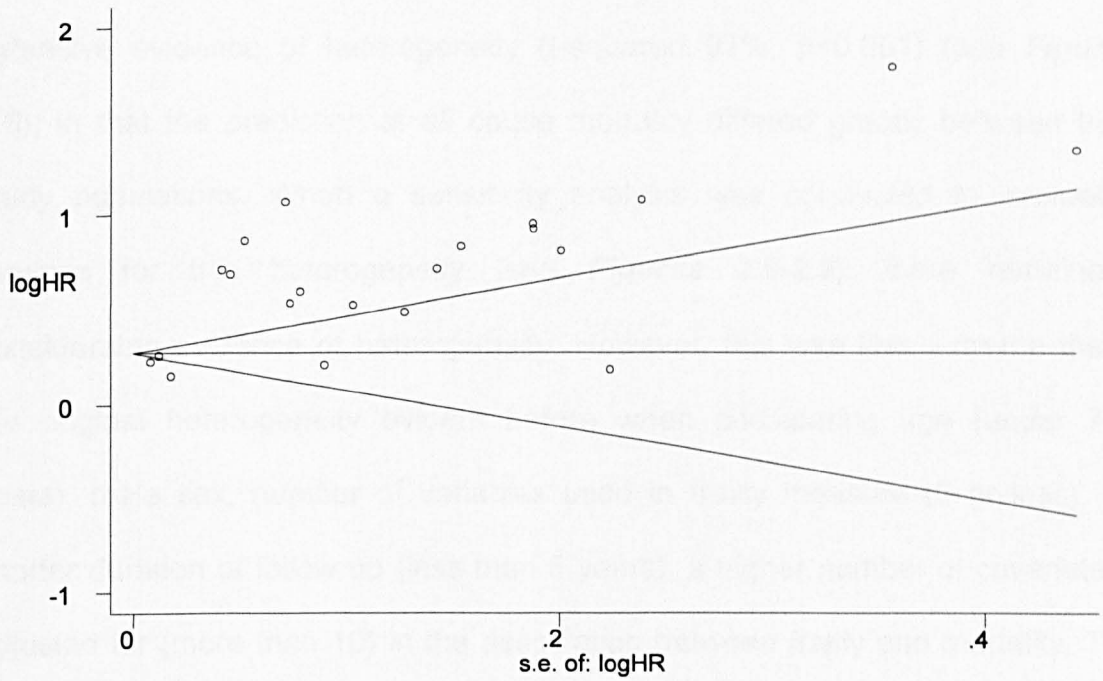


Figure 2.10 shows a Begg's funnel plot which is asymmetrical indicating a strong evidence of publication /small study bias(Egger's test's<0.001).

Figure 2.10: Begg's funnel plot with pseudo 95% confidence limits



Discussion

The prognostic value of various frailty measures were evaluated in 18 large study populations. A meta-analysis was conducted to enable a more reliable overall assessment of the validity of these measures in predicting all cause mortality. A direct comparison of all the different frailty measures showed extensive evidence of heterogeneity (I-squared 97%, p<0.001) (see ***Figure 2.5***), in that the prediction of all cause mortality differed greatly between the study populations. When a sensitivity analysis was conducted to evaluate reasons for this heterogeneity (see ***Figures 2.6-2.9***), there remained considerable evidence of heterogeneity. However, this was less extreme than the original heterogeneity evident before when considering age (under 75 years), male sex, number of variables used in frailty measure (5 or less), a shorter duration of follow up (less than 5 years), a higher number of covariates adjusted for (more than 10) in the association between frailty and mortality. To date, there has been no published meta-analysis comparing all the different types of frailty measures and their prognostic value. This may be due to the difficulty in identifying all the prognostic studies, the variations in study design, methods of analysis and measurement of frailty (using different cut-points) as well as differing statistical methods of adjustments for a wide range of covariates[106]

So far, comparisons made on different measures of frailty in large populations have been carried out by the CSHA group who had developed three types of measures [41, 51, 71]. They found that in a sample population of older Canadians, the predictive validity of the Frailty index and Clinical Frailty Scale (clinical judgment based) were indistinguishable, performing better than the

rules based definition, the Geriatric Status Scale [41]. Another article by the same group used the frailty index based on accumulation of health problems and their relationship with mortality in fourteen sample populations (N=36424) of four developed countries(Canada, Australia, United States of America and Sweden) [15].The findings were that women were frailer than men, and for both sexes, the mortality rate increased significantly ($p<0.001$) with increases in the frailty index. However, this should be interpreted with caution as some samples were cross sectional and not able to measure outcomes prospectively. This particular study was not included in this meta-analysis as it included clinical and institutional samples as well as cross sectional ones. Other comparisons studies have been based on two approaches to measuring frailty in the elderly [74, 79, 107]. This in effect tells us that any further comparisons should perhaps be saved for a time if/when a consensus is reached on the whole concept of frailty.

My decision to limit the studies to those with large populations of greater than 1000 narrowed the search to community dwelling older populations. Selection of large population studies should, to a certain extent, enable generalization of one set of findings to another. However, relating frailty to the community dwellers may only provide conservative estimates of the true population prevalence of frailty as those groups who are at greatest risk of being frail, such as the institutionalized elderly, those unable to walk, the oldest old as well as those with dementia will be excluded (or may be non-responders) in these study populations.

A limitation with meta-analysis is the combining of results of all the studies into one overall estimate is not recommended as a prominent component of

systematic reviews of observational studies as it could be misleading and lead to bias[106]. However, it does allow for a thorough investigation into all possible sources of heterogeneity (via sensitivity analysis) which could provide more insight into the reasons for this.

The Begg's funnel plot which is based on the precision of the effect of mortality will increase as the sample size of the component studies increases[106]. The asymmetrical plot produced in this meta-analysis may indicate small study or publication bias. This is in keeping with the very nature of prognostic studies which are more prone to publication bias than randomized trials[108] as their positive findings are more likely to be published. Another limitation was the lack of information on the percentage of ethnic minorities in the target population from which the study populations arise from. In this study, only two study populations presented separate results for differences of frailty with ethnicity, where ethnic minorities were found to be frailer than other Caucasian groups [1, 20].Inclusion of this information could provide a clearer picture of the generalisability of the results in this respect.

Conclusion and recommendations

Translating the existing frailty measures into a standard, clinically practical tool to precisely measure frailty has been a challenge for researchers working in the care of older persons. If a consensus definition is to be reached, more collaborative work is certainly required on what factors constitute frailty, its causes and associations and pathophysiology. However, a standard measure of frailty requires that it is actually measuring frailty *as an entity on its own*, rather than other factors such as co morbidity, disability or even proximity to death. I

will address this in **Chapter 3** in the development of an internally reliable measure of frailty.

This review highlights that there must be common ground in terms of types of population; numbers, study design, confounding factors and the adverse outcome studied. Although previous studies have revealed important information on frailty, new prospective cohorts created for the sole purpose of frailty research may enable a meta-analysis to be conducted in the future. The studies in this review were mainly cohort which offered a wealth of demographic and health characteristics useful for understanding the pathway to frailty but relied on baseline data which may have been collected for other purposes. Therefore, they were not designed to answer specific questions on frailty but a bigger research question. This indicates that perhaps the time had come to '*design new cohort studies that put frailty at the centre of their scientific paradigm*'[73]. A recommendation for the future may be to conduct a randomized controlled trial for frailty where the hypothesis is that screening for frailty will result in a better clinical outcome. This method would be used to compare different frailty measures with the number of adverse events (for example death) avoided as the outcome.

Until then, future studies could focus on detecting frailty in much larger populations, making comparisons between men and women, ethnic and socio-economic groups as well as on estimating the economic burden of frailty in older populations. Unless a consensus definition is reached, targeting preventative measures or care interventions in the pre-frail population using current non standardized measures may not be particularly useful for the older person or cost effective to health care systems. A novel approach would be to

channel our resources towards the identification of the very frail that are at greater risk of adverse outcomes so as to decide on the correct pathway of care needed; for example, palliative or rehabilitative care.

Summary:

- The systematic literature review identified studies that used various terms apart from 'frailty' to describe and predict adverse outcomes in the same population of frail older people at risk.
- Although the purposes behind identifying frailty in older people remains the same, its evolution from concept to measure has translated a holistic geriatric approach to a more tangible measurement which focus greatly on physical frailty.
- Two main types of operational frailty measures (rules based or deficit accumulation index) dominate the research publications on frailty with variations in the frailty indicators included in them.
- A formal meta-analysis on observational studies to assess the prognostic value of various frailty measures revealed extensive heterogeneity in the prediction of all cause mortality even after considering age, sex, number of variables used in frailty measure, duration of follow up, number of covariates adjusted for in the association between frailty and mortality.

Chapter 3: Development of a model based measure of frailty.

Introduction

Identifying frail elderly people in clinical practice or in the wider population through various aspects of their health and social status is a challenge worth attempting as it would enable pre-emptive action to be taken that might avoid serious sequelae at individual and population levels. Frailty has been measured using markers such as physical ability, self reported health indicators and well being, co-morbidity, physiological markers as well as psychosocial factors. Despite the efforts to quantify this experience, frailty in older adults remains undefined with no consensus about how it should be measured. This is evident from the numerous existing frailty measures presented in chapter 2, which were driven by a common goal of reducing the burden of suffering that frailty entails - hospitalisation[20, 94, 101, 104, 109] , falls [20, 45, 74, 75], institutionalisation [15, 19, 74] and death [1, 15, 19, 20, 43, 51, 74, 75, 93, 95, 96, 102, 104, 105]. A standardized definition and method of measurement could target health and social care for elderly people by enabling early detection and thereby reduce adverse outcomes and costs of care. Understanding the pathways that lead to frailty [31, 33, 95] is also valuable as it may lead to discovery of ways to prevent or delay the onset of frailty through interventions that target the 'pre-frail elderly' or those at high risk of becoming frail.

The current situation has evolved where "frailty" is used without a standardized definition, measured in a variety of ways and for a range of purposes [9]. This had resulted in three types of measures that exist in literature – rules based, clinical judgement and indexes [35].The first determined that frailty was made up of a set number of criteria. Fried's rules-based frailty criteria, as validated by other studies [1, 74-76, 104], gave primacy to physical measures of frailty. Other measures assume a multi-dimensional form [17, 23, 62] or, at the other extreme, a single component physical/physiological measure such as grip strength[21],walking speed[22, 83], functional reach[110] and blood markers[32, 84, 111].Frailty measures relying on clinical judgement to interpret results of history taking and clinical examination are unlikely to be repeatable and will vary from clinician to clinician making them of little value for research or audit purposes[15]. The frailty index approach was based on a proportion of deficits accumulated in an individual in relation to age [40, 51]. The problem with this measure was the use of '*unweighted*' variables which assumed that deficits such as 'cancer' and 'arthritis' were of equal importance to one another in indexing frailty. Also, in large indexes (40 or more variables) a smaller subset of items, selected at random, were similarly associated with the risk of adverse outcomes as the whole set of items[40] .The more variables considered, the greater the problems of measurement error and missing data. Despite its reproducibility, [78, 105] and high correlation with mortality [40, 51], the index measure is time consuming and not widely used clinically. Additionally, all three types of measures may not be measuring frailty alone but also comprise other

entities that overlap with frailty such as morbidity or disability. Despite defining apparently useful frailty markers from clinical and physiological characteristics and showing strong correlation with the risk of adverse outcomes, none of these frailty measures have provided adequate evidence to inform policy and clinical practice.

To date, no model of frailty based on defining and quantifying frailty on a purely data driven approach has been produced. Thus, I propose a frailty model developed from factor analysis (FA), a robust analytical technique which uses latent variables as a means of data reduction to represent a wide range of attributes/variability among observed variables on a smaller number of dimensions or factors[112]. These latent variables are not directly observed but rather inferred (through a statistical model) from directly observed or measured variables[113]. This mirrors the concept of frailty as a *'latent vulnerability'* in older adults, subtle, often asymptomatic and only evident over time when excess vulnerability to stressors(e.g. acute illness) reduces the older person's ability to maintain or regain their homeostasis[2]. This model's advantage over previous frailty measures is that it corrects for measurement error and assigns relative weights in the association of each indicator with frailty. In this chapter I present a model- based measure of frailty and examine its reliability for use in a community dwelling elderly population. This new model of frailty was developed using the British Women's Heart and Health Study (BWHHS) population and was replicated using data from the "usual care" arm of

a large randomised trial of health care in general practice for people aged 75 and over.

Description of the British Women's Heart and Health Study (BWHHS) population

The British Women's Heart and Health Study (BWHHS) cohort of women provide the dataset for the construct of frailty. This study was based on the British Regional Heart Study which recruited men aged 40-59 years in 1978-80 from 24 towns throughout Britain. The British regional heart study framework was used to randomly select women aged 60-79 from general practice lists in 23 towns in England, Scotland, and Wales. No women were excluded from the study, and all 7166 women in the age range, regardless of whether they normally lived in private accommodation, a residential home, or a nursing home, and irrespective of medical conditions, were invited to participate. Transport to examination centres was offered to immobile and frail women. Invitations were sent to the women, and two reminders were sent to non-responders. A total of 4286 women (60% of those invited) participated. Baseline data (from a self completed questionnaire, interviews by a research nurse, physical examination, and review of primary care medical records) were collected between April 1999 and March 2001[114]. At the interview participants were asked about diagnosed diseases and underwent a medical examination which recorded blood pressure, waist and hip circumference, height and weight. The women completed a

questionnaire collecting behavioural and lifestyle data, including smoking habit, alcohol consumption and indicators of socio-economic position. The indicators used in my secondary analysis of this dataset were based on those collected at baseline.

Description of the MRC trial of assessment and management of older people in the community.

This study was a cluster-randomised factorial trial in 106 general practices (43219 eligible patients aged 75 years and older, 78% participation), comparing (1) universal versus targeted assessment and (2) subsequent management by hospital outpatient geriatric team versus the primary-care team[115]. General practices from the MRC General Practice Research Framework were recruited to the trial. The sampling of practices was stratified by tertiles of the standardized mortality ratio (mortality experience of a local area relative to the national mortality) and the Jarman score [116] (a measure of area deprivation) to ensure a representative sample of the mortality experience and deprivation levels of general practices in the United Kingdom. Practices were randomly assigned to two groups receiving targeted or universal screening. All participants received a brief multidimensional assessment followed, in the universal arm by a nurse led in-depth assessment while in the targeted arm the in-depth assessment was offered only to participants with pre-determined

problems at the brief assessment. The in depth assessment included a wide range of health related, social and psychological factors while in the targeted arm only elected patients had a full assessment. The baseline assessments were performed between 1995 and 1999. Referrals to the randomised team (geriatric management or primary care), other medical or social services, health-care workers, or agencies, and emergency referrals to the general practitioner were based on a standard protocol at the in-depth assessment. In this analysis I used data only from participants in the universal arm (53 practices) as they were considered a representative sample of community dwelling older people receiving "usual" care. People living in nursing homes were not eligible for the trial. The frailty indicators extracted from this dataset was matched closely to the ones extracted from the BWHHS dataset. ***Table 3.1*** summarizes the frailty indicators extracted from both datasets.

Construct of frailty using the BWHHS indicators

A multidimensional view of frailty incorporating its physical, physiological, psychological and social aspects was represented by the frailty indicators listed in ***Table 3.1.*** These frailty indicators included those in existing literature [17, 35, 51, 62, 74, 77, 88, 107] that was also available in the dataset. These included variables derived from self reports of health status, diseases, symptoms and signs, physical activity, activities of daily living, social as well as lifestyle

indicators. Blood investigations were deliberately ***excluded*** to create a measure which was *non- invasive* and *practical* to identify older people at risk in a primary care setting. These were extracted from the BWHHS database and recoded into binary categorical variables, coded as '1' if the indicator was present and '0' of it was absent. The indicators chosen in this dataset were limited to those available to the MRC Assessment study so that a comparable measure could be replicated. The development and testing of my hypothesis on frailty was conducted with factor analysis (MPlus version 4.21 software appropriate for binary data) using these chosen indicators from which 35 indicators were derived and confirmed by the data. This method is explained in detail in the following sections.

Table 3.1: A summary of the questions representing indicators chosen from both the BWHHS and MRC Assessment study datasets.

BWHHS frailty indicators	MRC Assessment of Older People Study frailty indicators
Living with someone else?	Does someone else live at home with you?
Any contact with others i.e. relatives, friends, siblings, children, neighbours?	Do you see relative, friend or neighbour (other than those you live with)? (daily→ rarely)
How would you describe your health at present?	Compared with other people your age would you say your health is generally: excellent, good, fair or poor?
Have you had a fall in past year?	In last 6months, how many falls have you had at home? (None0,1,2,3,4,>4)
Compared with your activity level 3 years ago, are you doing more, same or less?	Compared with other people your age, would you describe yourself as....(v physically active not at all)
Do you have problems washing or dressing? (no problem, some problem ,unable to wash and dress)	Wash all over, include bath and shower. Dress yourself including. zips /buttons (no difficulty, some, unable but help available, unable and no help)
Is your present state of health causing you problems with household chores? Y/N	Do light housework or simple repairs? (no difficulty, some, unable but help available, unable and no help)
Difficulty in carrying out activity on their own: going up and downstairs	Go up and down stairs(if necessary using frame, tripod or stick) (no diff, some, unable but help available, unable and no help)
Difficulty in carrying out activity on their own: walking about/going out of house/walking 400 yards?	Walk 50yrds down the road(if necessary using frame, tripod or stick) (no difficulty, some, unable but help available, unable and no help)
Do you have trouble with your hearing?	Do you have difficulty hearing & understanding what a person says to you in quiet room, even with hearing aid? (no difficulty, a little, a lot)

Continued

BWHHS frailty indicators	**MRC Assessment of Older People Study frailty indicators**
Do you have trouble with your eyesight?(not simply needing specs)	Do you have difficulty in seeing newsprint, even when wearing glasses? (no difficulty, a little, a lot)
Compared to five years ago, is your memory: improved, same, almost as good, worse, much worse? Dementia on medical exam.	Do you have problems with your everyday memory?(never, occasional, often, always)
Your health over all: are you anxious or depressed, not, moderately, extremely.	Do you feel sad depressed or miserable?(never, occasional, often, always)
Do you smoke cigarettes currently/ if so how many?	Do you smoke cigarettes? Y/N If yes, how many do you smoke a day?
Would you describe your intake as:(1.dailymostdays2.weekends only3.one/twice a mnth,4.special occasions)	During the last year, have you taken an alcoholic drink? Y/N During past week (include 0, how many drinks have you had of each of the following? Spirits(number of singles),wine, sherry or port, beers(number of half pints)
Type of accommodation? (owner occupier, renting from local authority, renting privately, other)	What kind of accommodation do you live in?(Council→ private nursing home)
Do your ankles swell up regularly?	n/a
Do you ever have any pain or discomfort in your chest?	Have you ever had any pain or discomfort in your chest? Y/N
Have you ever had a severe pain across the front of your chest lasting for half an hour or more ?	Have you ever had severe pain across front of your chest lasting >1hour? Y/N
When you walk at an ordinary pace on the level does this produce the pain?	Do you get it on walking at an ordinary pace on the level? Y/N
When you walk uphill or hurry does this produce the pain?	Do you get this pain when walking uphill? Y/N
Do you usually bring up phlegm (spit) from your chest first thing in the morning in the winter?	Do you usually bring up phlegm first thing in the morning in the winter? Y/N
Do you bring up phlegm on most days as much as 3 months in the winter each year?	Do you bring up phlegm like this on most days for as much as 3 months each year? Y/N

BWHHS frailty indicators	**MRC Assessment of Older People Study frailty indicators**
In the past four years, have you ever had a period of increased cough and phlegm lasting for 3 weeks or more?	In the past 3 years, have you had a period of increased cough and phlegm lasting 3wks or more? Y/N
Does your chest often sound wheezy (on most days or nights?)	Does your chest sound wheezy or whistling on most days (or nights)? Y/N
Do you get short of breath with other people of your own age on level ground?	Do you get short of breath walking with people of your own age on level ground? Y/N
Have you ever been told by a doctor that you have or have had asthma?	Has your doctor ever told you that you had any of the following? Asthma?
Have you ever been told by a doctor that you have or have had bronchitis or emphysema?	Bronchitis or emphysema?
Have you ever been told by a doctor that you have or have had arthritis?	Arthritis/Rheumatism?
Have you ever been told by a doctor that you have or have had high blood pressure?	High blood pressure?
Have you ever been told by a doctor that you have or have had thyroid disease?	Thyroid trouble?
Have you ever been told by a doctor that you have or have had a cataract?	Cataract?
Have you ever been told by a doctor that you have or have had glaucoma?	Glaucoma?
Have you ever been told by a doctor that you have or have had gout?	Gout?
Have you ever been told by a doctor that you have or have had depression?	Depression?
Have you ever been told by a doctor that you have or have had diabetes?	Diabetes?

Continued

BWHHS frailty indicators	**MRC Assessment of Older People Study frailty indicators**
Have you ever been told by a doctor that you have or have had gastric or peptic ulcer?	Stomach ulcer or other digestive ulcer?
Have you ever been told by a doctor that you have or have had heart attack (MI)?	Heart attack?
Have you ever been told by a doctor that you have or have had angina?	Angina?
Have you ever been told by a doctor that you have or have had a stroke?	Stroke?
Have you ever been told by a doctor that you have or have had cancer?	Cancer?
Have you ever fractured your hip?	Fractured hip?
Have you ever been told by a doctor that you have or have had Cardiovascular disease (diagnosed angina, mi, stroke)	n/a
Body mass index: high or low	Body mass index: high or low
Postural hypotension: according to 1996 consensus definition	Postural hypotension: according to 1996 consensus definition
Hypertensive (>140/90)	Hypertensive (>140/90)
Waist hip ratio (>/<0.85	Waist hip ratio (>/<0.85
Sinus tachycardia (>100 bpm)	Sinus tachycardia (>100 bpm)

*All indicators listed were ones originally included in the factor analysis (exploratory factor analysis) from which 35 indicators were derived and confirmed by the data.

Missing data

Table 3.2 lists the BWHHS frailty indicators included in the measurement model with the percentage of missing data present for each indicator. All the BWHHS indicators were included in the exploratory part of developing the hypothesis for frailty. In the BWHHS cohort, 80% of the indicators had less than 10% missing data whereas in the MRC Assessment study, all of the indicators had less than 5% missing data ***(see Table 3.3).*** This analyses were conducted under the assumption that the data was missing at random (MAR)[117].

In both cohorts, a complete case was defined as those respondents with complete data on all 35 frailty indicators. There were 4286 women respondents from the BWHHS database of whom 1568 had complete data. People in the MRC replication data set comprised 9032 women (6709 complete data) and 5622 men (4486 complete data).

Table 3.2: BWHHS frailty indicators included in exploratory factor analysis with percentage of missing data.

BWHHS Indicators	Present	Absent	Missing	Percentage missing (%)	Total
Arthritis	1832	1962	492	11.48	4286
Asthma	474	3406	406	9.47	4286
Anxiety/depression	992	2879	415	9.68	4286
Angina	642	3644	0	0	4286
Ankle oedema	1730	2102	454	10.59	4286
Bronchitis	738	3145	403	9.40	4286
Cancer	556	3730	0	0	4286
Cataract	527	3304	455	10.62	4286
Depression	678	3169	439	10.24	4286
Diabetes	220	4066	0	0	4286
Hypertension	1572	2411	303	7.07	4286
Dementia	59	3919	308	7.19	4286
Heart attack (MI)	199	4087	0	0	4286
Glaucoma	144	3639	503	11.74	4286
Stroke	125	4161	0	0	4286
Cerebrovascular disease	763	3523	0	0	4286
Thyroid disease	457	3383	446	10.41	4286
Ulcer	299	3546	441	10.29	4286
Falls	676	3371	239	5.58	4286
Hip fracture	59	3576	651	15.19	4286
Memory	784	3215	287	6.70	4286

Continued

BWHHS Indicators	Present	Absent	Missing	Percentage missing (%)	Total
Chest discomfort	1233	2736	317	7.4	4286
Ever had chest pain	205	3764	317	7.4	4286
On level pain	145	3767	374	8.73	4286
On uphill pain	494	3417	375	8.75	4286
Short of breath	754	3192	340	7.93	4286
Morning phlegm	626	3313	347	8.1	4286
Most days phlegm	399	3475	412	9.61	4286
Increased cough	1569	2377	340	7.93	4286
Often wheeze	353	3399	534	12.46	4286
Eyesight trouble	746	3077	463	10.8	4286
Hearing trouble	879	3105	302	7.05	4286
Postural hypotension	647	3132	507	11.83	4286
Waist hip ratio	1225	2721	340	7.93	4286
Low BMI	112	3845	329	7.68	4286
High BMI	1378	2908	0	0	4286
Sinus tachycardia	122	3831	333	7.77	4286
High blood pressure	2329	1635	322	7.51	4286
Difficulty going out	205	3245	836	19.51	4286
Walkabout	987	2966	333	7.77	4286
Difficulty walking 400 yards	517	2990	779	18.18	4286
Go up down stairs	848	2784	654	15.26	4286
Household chores	850	3044	392	9.15	4286
Wash & dress	375	3582	329	7.68	4286

Continued

BWHHS Indicators	Present	Absent	Missing	Percentage missing(%)	Total
Status activity	2395	1351	540	12.6	4286
Present health	127	3924	235	5.48	4286
Lives alone	1341	2750	195	4.55	4286
No contact others	956	2108	1222	28.51	4286
Accommodation	92	3990	204	4.76	4286
Current smoker	444	3516	326	7.61	4286
Alcohol	647	3261	378	8.82	4286

Table 3.3: MRC Assessment Study frailty indicators showing percentage of missing data.

MRC Assessment Study indicators	Present	Absent	Missing	Percentage missing (%)	Total
Arthritis	8167	6338	149	1.02	14654
Asthma	1484	13046	124	0.85	14654
Anxiety/depression	1251	13167	236	1.61	14654
Cancer	1480	13008	166	1.13	14654
Cataract	4316	10207	131	0.89	14654
Depression	1608	12887	159	1.09	14654
Diabetes	1146	13508	0	0.00	14654
Hypertension	4887	9612	155	1.06	14654
Emphysema	314	14214	126	0.86	14654
Heart attack (MI)	1561	12962	131	0.89	14654
Glaucoma	941	13561	152	1.04	14654
Stroke	1300	13242	112	0.76	14654
Thyroid disease	1335	13185	134	0.91	14654
Ulcer	1758	12747	149	1.02	14654
Falls	3044	11530	80	0.55	14654
Hip fracture	548	13962	144	0.98	14654
Memory	1358	13132	164	1.12	14654
Chest discomfort	2495	12114	45	0.31	14654
Ever had chest pain	1076	13263	315	2.15	14654
On level pain	425	13267	962	6.56	14654
On uphill pain	1328	12466	860	5.67	14654

Continued

MRC Assessment Study indicators	Present	Absent	Missing	Percentage missing (%)	Total
Short of breath	3089	11062	503	3.43	14654
Morning phlegm	3706	10753	195	1.33	14654
Most days phlegm	2234	11918	502	3.43	14654
Increased cough	2036	12378	240	1.64	14654
Often wheeze	1936	12598	120	0.82	14654
Eyesight trouble	4776	9699	179	1.22	14654
Hearing trouble	6304	8183	167	1.14	14654
Postural hypotension	3105	10244	1305	8.91	14654
Waist hip ratio	9593	5061	0	0.00	14654
Low BMI	830	12489	1335	9.11	14654
High BMI	3535	11119	0	0.00	14654
Sinus tachycardia	451	14071	132	0.90	14654
High blood pressure	9236	5239	179	1.22	14654
Walk 50 yards	4299	10070	285	1.94	14654
Go up down stairs	6021	8188	445	3.04	14654
Household chores	4124	10330	200	1.36	14654
Wash & dress	4757	9763	134	0.91	14654
Status activity	3414	11099	141	0.96	14654
Present health	312	14201	141	0.96	14654
Lives alone	7741	6758	155	1.06	14654
No contact others	657	13769	228	1.56	14654
Accommodation	1285	13237	132	0.90	14654
Current smoker	1431	13153	70	0.48	14654
Alcohol	11013	3457	184	1.26	14654

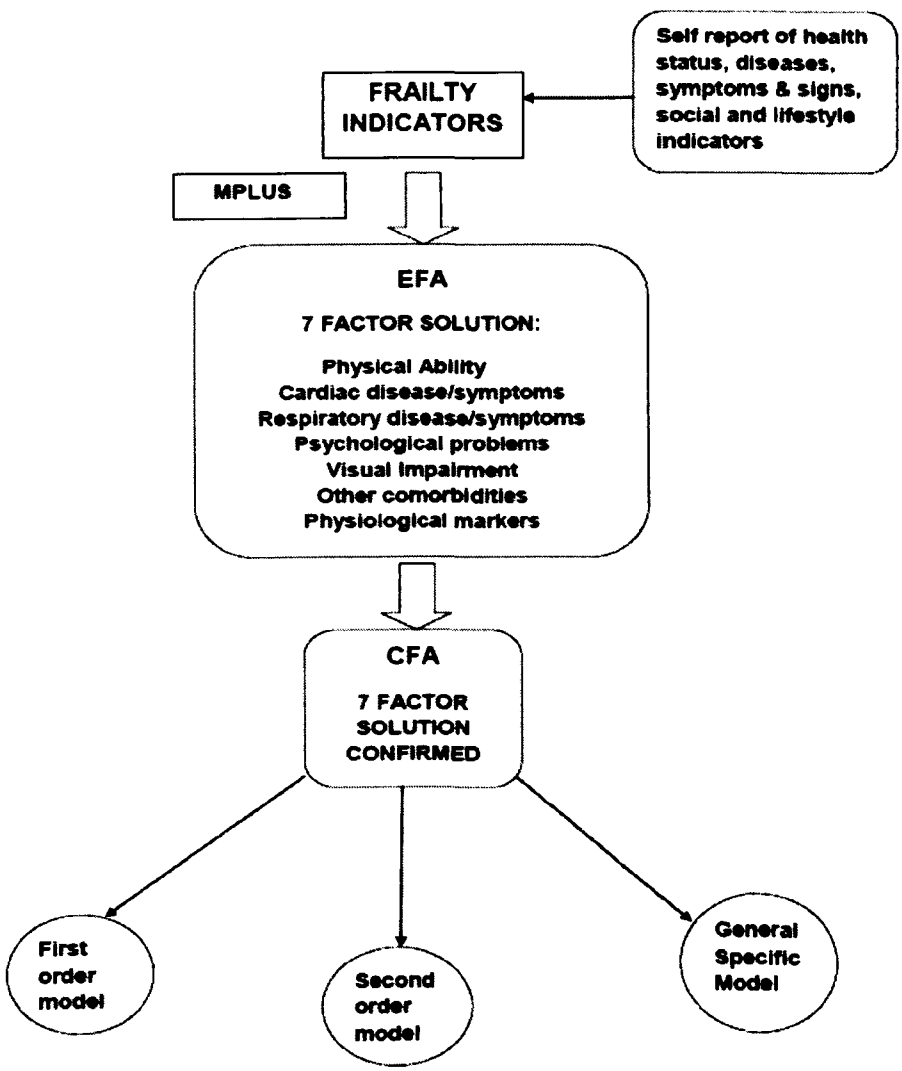
Methods

Statistical analysis: Factor analysis with Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA)

In order to better define frailty, factor analysis (FA) appropriate for binary data was conducted using the ***Mplus software (version 4.2).*** FA is a statistical technique used to analyze correlations among a wide range of observed variables to explain these variables, largely or entirely, in terms of their common underlying (latent) dimensions called *factors*, in this case, frailty[112]. EFA was used to explore the underlying factor structure of the frailty indicators and develop the construct/hypothesis of frailty. The resulting EFA model was subjected to CFA to further test this latent structure. We proceeded by testing the higher order dimensionality of the EFA driven 1st order solution by estimating a 2nd order and a general specific model. In EFA as well as the three CFA models (1st order, 2nd order and General Specific Models), Mplus initially estimated the factor loadings and item thresholds. Standardised factor loadings can be thought of as the correlation of the original/manifest variable (frailty indicator) with a latent factor and are useful in determining the importance of the original variable to the factor. Item threshold refers to the level of the latent factor (i.e. frailty) that needs to be attained for a response shift in the observed variables. Although the response scale for each frailty indicator is binary (1"present" or 0 "absent"), the underlying factor model assumes that each indicator varies on an underlying continuous scale and each person can be located on that continuum[118]. Persons located above a certain threshold on

that continuum will endorse that the frailty indicator was present. Each of these possible measurement models were analyzed to see which best fit the data as well as the concept of frailty. ***Figure 3.1*** gives an overview of the steps taken in factor analysis.

Figure 3.1: Overview of steps in factor analysis using BWHHS frailty indicators



Factor analysis was carried out on respondents with complete data on all 35 frailty indicators, which resulted in a study population of 1568 complete cases, as well as the total study population of 4286 women which included those with partial data (i.e. those with at least one frailty indicator missing). In addressing the problem of missing data in the frailty indicators used in the analysis, the model was estimated with the WLSMV (Weighted Least Squares, Mean and Variance adjusted) which applies pair wise missing data analysis using all individuals with observations for all possible pairs of variables in the data. Individuals with partial data are therefore retained in the analyses and their information was used for all further analyses. In our case, the pairs are made from frailty items.

A sensitivity analysis using an ***unpaired t-test*** was carried out to compare the mean difference between the complete case frailty score of 1568 women and the frailty scores of the total population of 4286 women with missing frailty indicators included (see ***Table 3.4***).

Table 3.4: Sensitivity analysis to compare the mean difference between frailty scores in complete dataset to frailty scores in dataset which includes missing variables

Frailty scores	Number of observations	Mean	Standard deviation	95%C.I.
Complete cases	1568	0.146	0.727	0.110 to 0.182
Cases including at least one missing indicators	4286	0.159	0.721	0.138 to 0.181
Mean difference*		0.013	0.023	-0.028 to 0.055

*Degrees of freedom=5852, p value 0.536

At a 5% level, the difference in means was not significant with a p value of 0.536, showing no difference in mean scores derived from both groups.

Goodness of fit tests

The *Scree plot* approach, the *Kaiser-Guttman* rule (for EFA only) and indices of fit such as the *Comparative Fit Index (CFI),* the *Tucker Lewis Index (TLI)* and the *Root Mean Square Error of Approximation (RMSEA)* (for both EFA and CFA) were used as a means of evaluating results of the FA. Both the *Scree plot* and *Kaiser-Guttman rule* was used to decide on the number of factors/dimensions to be retained for further analysis[119]. The *Scree plot* is a graph of each Eigen value, which represents the total variance of each factor,(Y-axis) against the factor with which it is associated(X-axis).The *Kaiser Guttman rule* retains only factors with Eigen value larger than 1[119].

The *CFI* refers to the discrepancy function adjusted for sample size. *TLI* was used to assess the incremental fit of a model compared to a null model. Both range from 0 to 1 with a larger value indicating better model fit. Acceptable model fit is indicated by a *CFI* and *TLI* value of 0.95 or greater. *RMSEA* is related to residual in the model. *RMSEA* values range from 0 to 1 where an acceptable model fit is indicated by an *RMSEA* value of 0.06 or less. The chi-squared goodness of fit test and these indices of fit were used to assess model fit as suggested by guidelines proposed by Hu and Bentler [120] . These three goodness of fit indices were emphasized since the chi-squared test was deemed highly sensitive to sample size, leading to rejection of well-fitting models.

Results

Exploratory factor analysis (EFA)

Seven factors were needed to adequately explain the common variance between the frailty indicators and were labelled as: *physical ability, cardiac disease or symptoms, respiratory disease or symptoms, physiological measures, psychological problems, co morbidity* and *visual impairment.* As stated earlier each of these identified latent factors were derived from subsets of indicators that correlated strongly with each other and weakly with other indicators in the dataset. They provided meaningful theoretical 'explanations' or 'interpretations' linking them to the overall construct of frailty. *'Physical ability'*

comprised of highly correlated indicators such as level of activity, ability to do household chores, go up and downstairs, walk out and about wash, dress or groom oneself. *'Cardiac and respiratory disease or symptoms'* included self report or doctor diagnosis of myocardial infarction, angina, asthma, chronic obstructive airways disease or emphysema and their associated symptoms of chest pain or discomfort, pain on uphill or level walking, shortness of breath, increase cough or frequent wheeze. The *'physiological measures'* included body mass index(BMI), waist hip ratio(WHR), pulse rate, blood pressure as well as evidence of orthostatic hypotension. Markers such as subjective feelings of anxiety or depression, self reports and diagnosis of memory problems and depression were meaningfully explained by *'psychological problems'*. Other indicators such as stroke, diabetes, hypertension, peptic ulcers, thyroid disease and cancer were also explained by *'co-morbidity'*. Lastly, 'visual impairment' explained the correlations between indicators of diagnosed cataract or glaucoma as well as a self report of visual problems.

Table 3.5: Summary of results from confirmatory factor analysis of the BWHHS and MRC Assessment study (complete and missing data)

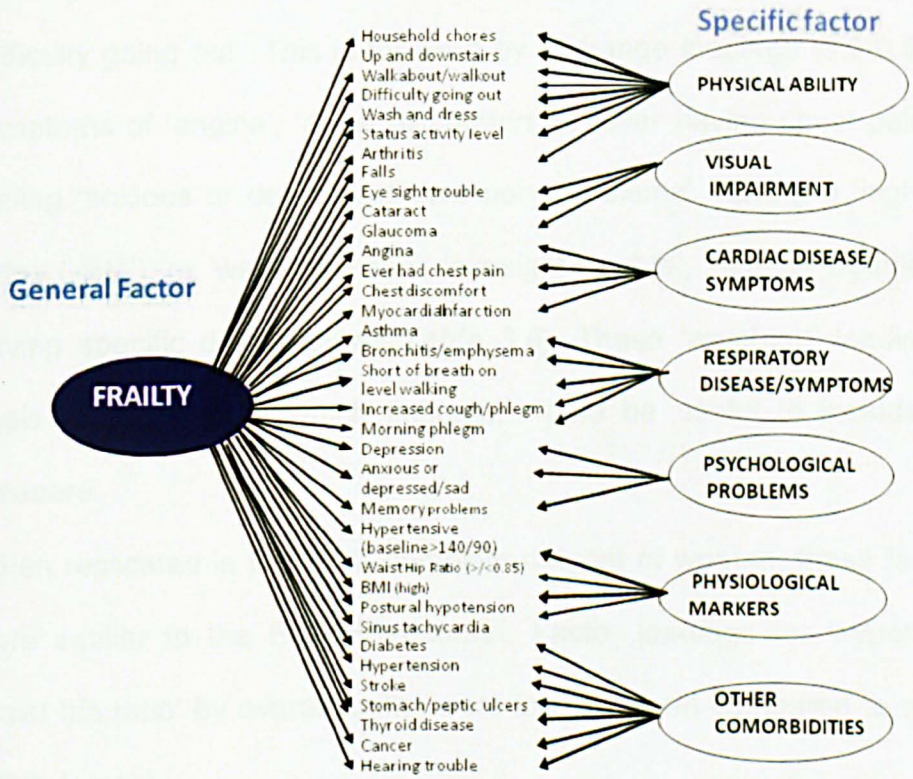
Indices of model fit	CFA 1st Order model				CFA 2nd Order model				General Specific model			
	BWHHS complete cases	BWHHS missing	MRC female complete cases	MRC female missing	BWHHS complete cases	BWHHS Missing	MRC female complete cases	MRC female missing	BWHHS complete cases	BWHHS missing	MRC female complete cases	MRC female missing
X2	6404.29	22275	42380	76468	6404	22275	42380	76468	6404	22275	42380	76468
Df	195	251	292	290	195	251	292	290	195	251	292	290
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CFI	0.938	0.932	0.962	0.968	0.931	0.925	0.954	0.960	**0.957**	**0.948**	**0.967**	**0.969**
TLI	0.949	0.950	0.970	0.976	0.944	0.946	0.965	0.970	**0.964**	**0.962**	**0.974**	**0.976**
RMSEA	0.032	0.032	0.025	0.027	0.034	0.033	0.027	0.029	**0.027**	**0.028**	**0.024**	**0.026**
			MRC male complete cases	MRC male missing			MRC male complete cases	MRC male missing			MRC male complete cases	MRC male missing
X2			23473	39003			1820	39003			23473	39003
Df			266	264			355	264			266	264
CFI			0.941	0.962			0.937	0.957			**0.954**	**0.970**
TLI			0.955	0.972			0.953	0.969			**0.964**	**0.978**
RMSEA			0.029	0.027			0.030	0.028			**0.026**	**0.024**

Cut off criteria for good fit- CFI&TLI >0.95, RMSEA <0.06- Hu and Bentler 1990

Confirmatory Factor Analysis (CFA)

We empirically compared three latent structures based on the EFA seven factor model: 1st order, 2nd order and General specific models. Model fit statistics for each of the models tested in both BWHHS and MRC datasets are shown in ***Table 3.5***. These results support the contention that the frailty model of choice for both BWHHS women and the MRC Assessment study (both men and women) was the ***General Specific model (See Figure 3.2)***.

Figure 3.2: General Specific Model



General refers to frailty, the general factor that is loaded (explained by) all the indicators. **Specific** refer to the 7 latent factors that account for the association between the frailty indicators and the specific dimensions/factors. The fit of the General Specific frailty model was better than each of the other two models ***(Figures 3.6 and 3.7 are described in the Discussion section)*** in both datasets. This was true for participants with complete data as well as those with missing data, with very little difference between them. In the BWHHS complete data, standardized factor loadings of the frailty indicators by the overall Frailty factor (i.e. correlations of the observed frailty indicators with Frailty) revealed highest loadings (0.60-0.77) on indicators such as being 'short of breath on level walking', the inability to do 'household chores', 'walking up and down stairs', 'walking about', 'wash and dress',' having a low 'status activity level' as well as 'difficulty going out'. This is followed by midrange loadings (0.3-0.55) of having symptoms of 'angina', 'chest discomfort' or 'ever having chest pain', 'arthritis',' feeling 'anxious or depressed', 'memory problems', having a 'high body mass index (BMI)' or 'waist hip ratio', 'eyesight trouble', 'hearing trouble' as well as having specific diseases(see ***Table 3.6***). These 'weighted' loadings form the basis of an idea for which indicator would be useful to include in a frailty measure.

When replicated in the MRC complete dataset of women, these factor loadings were similar to the BWHHS dataset. Factor loadings for 'hypertension' and 'waist hip ratio' by overall frailty, were lower in men compared to women in the MRC dataset.

Table 3.6: Standardized Factor loadings of the general/overall Frailty factor derived from the General Specific model in both the BWHHS and the MRC Assessment study.

Variable factor Loadings:	BWHHS complete cases	BWHHS Missing	MRC female Complete Cases	MRC Female missing	MRC Male Complete Cases	MRC Male missing
Household chores	0.736	0.759	0.632	0.722	0.718	0.765
Up and downstairs	0.725	0.748	0.739	0.800	0.791	0.808
Walkabout/walkout	0.685	0.673	0.745	0.821	0.865	0.878
Difficulty going out	0.601	0.635				
Wash and/or dress	0.612	0.594	0.592/0.521	0.683/0.620	0.657/0.604	0.712/0.685
Status activity level	0.616	0.585	0.655	0.731	0.746	0.785
Arthritis	0.421	0.434	0.324	0.322	0.176	0.206
Falls	0.261	0.390	0.342	0.389	0.387	0.444
Eye sight trouble	0.410	0.385	0.485	0.486	0.438	0.467
Cataract	0.325	0.305	0.229	0.201	0.180	0.186
Glaucoma	0.195	0.158	0.054	0.063	0.065	0.031
Angina	0.550	0.587				
Ever had chest pain	0.401	0.413	0.287	0.254	0.274	0.250
Chest discomfort	0.405	0.482	0.331	0.279	0.341	0.297
Myocardial Infarction	0.344	0.433	0.303	0.281	0.310	0.273
Asthma	0.263	0.347	0.196	0.154	0.224	0.201
Bronchitis/emphysema	0.260	0.320	0.336	0.284	0.369	0.311
Short of breath on level walking	0.770	0.815	0.676	0.624	0.699	0.683
Increased cough/phlegm	0.247	0.303	0.193	0.150	0.220	0.220
Morning phlegm	0.305	0.394	0.267	0.231	0.281	0.278
Depression	0.300	0.390	0.172	0.150	0.214	0.195
Anxious or depressed/sad	0.418	0.462	0.426	0.405	0.367	0.404
Memory problems	0.365	0.399	0.349	0.354	0.396	0.447

Continued

Variable factor Loadings:	BWHHS complete cases	BWHHS Missing	MRC female Complete Cases	MRC Female missing	MRC Male Complete Cases	MRC Male missing
Hypertensive (baseline>140/90)	0.036	-0.009	-0.054	-0.076	-0.110	-0.116
Waist Hip Ratio (>/<0.85)	0.362	0.262	0.228	0.278	0.034	0.040
BMI (high)	0.412	0.346	0.342	0.420	0.232	0.348
Postural hypotension	0.114	0.048	-0.020	-0.009	0.046	0.060
Sinus tachycardia	0.111	0.058	-0.030	-0.028	0.120	0.102
Diabetes	0.305	0.244	0.196	0.196	0.178	0.205
Hypertension	0.340	0.304	0.110	0.060	0.090	0.064
Stroke	0.412	0.403	0.372	0.411	0.402	0.432
Stomach/peptic ulcers	0.241	0.340	0.258	0.196	0.120	0.103
Thyroid disease	0.191	0.250	0.143	0.104	-0.090	0.095
Cancer	0.150	0.072	0.033	0.014	0.042	0.018
Hearing trouble	0.310	0.344	0.357	0.337	0.265	0.290

Table 3.7: Standardized factor loadings of the specific factors derived from the General Specific model

Specific Factors	BWHHS complete cases	BWHHS Missing	MRC female Complete Cases	MRC Female missing	MRC Male Complete Cases	MRC Male Missing
Physical Ability						
Household chores	0.533	0.524	0.624	0.561	0.500	0.477
Up and downstairs	0.557	0.532	0.483	0.414	0.399	0.378
Walkabout/walkout	0.622	0.627	0.562	0.459	0.366	0.343
Difficulty going out	0.622	0.581				
Wash and/or dress	0.635	0.627	0.641/0.632	0.577/0.602	0.657/0.604	0.605/0.540
Status activity level	0.217	0.263	0.470	0.411	0.746	0.274
Arthritis	0.372	0.356	0.106	0.043	0.176	0.115
Falls	0.104	0.097	0.179	0.138	0.387	0.183
Visual Impairment						
Eye sight trouble	0.792	0.792	0.488	0.467	0.470	0.448
Cataract	0.678	0.706	0.612	0.636	0.649	0.626
Glaucoma	0.668	0.673	0.523	0.515	0.566	0.567
Cardiac symptoms/disease						
Angina	0.619	0.602				
Ever had chest pain	0.674	0.674	0.835	0.829	0.838	0.866
Chest discomfort	0.411	0.387	0.466	0.476	0.344	0.393
Myocardial Infarction	0.885	0.797	0.680	0.702	0.737	0.733
Respiratory symptoms/disease						
Asthma	0.659	0.650	0.607	0.601	0.480	0.501
Bronchitis/emphysema	0.653	0.674	0.471	0.478	0.440	0.497
Short of breath on level walking	0.245	0.236	0.317	0.372	0.304	0.354
Increased cough/phlegm	0.582	0.546	0.491	0.533	0.550	0.546
Morning phlegm	0.621	0.596	0.509	0.538	0.540	0.525
Psychological problems						
Depression	0.583	0.524	0.156	0.228	0.365	0.335
Anxious or depressed/sad	0.773	0.800	2.174	1.501	0.721	0.792
Memory problems	0.208	0.207	0.107	0.174	0.367	0.346
Physiological markers						
Hypertensive (baseline>140/90)	0.754	0.258	1.853	0.084	1.282	1.063
Waist Hip Ratio (>/<0.85)	0.147	0.540	0.018	0.338	0.089	0.086
BMI (high)	0.149	0.464	0.045	0.722	0.039	0.068
Postural hypotension	0.339	0.111	0.120	-0.040	0.181	0.222
Sinus tachycardia	0.319	0.235	0.008	-0.060	0.058	0.016
Other co-morbidities						
Diabetes	0.353	0.382	0.305	0.267	0.253	0.188
Hypertension	0.567	0.467	0.542	0.647	0.507	0.591
Stroke	0.576	0.490	0.380	0.318	0.386	0.340
Stomach/peptic ulcers	-0.090	-0.077	-0.111	-0.073	-0.154	-0.092
Thyroid disease	-0.077	0.095	0.045	0.042	0.036	-0.059
Cancer	-0.144	-0.062	-0.011	0.009	-0.018	-0.005
Hearing trouble	-0.075	-0.208	-0.130	-0.095	-0.012	-0.044

In the General Specific model, the standardized factor loadings of frailty indicators on the seven specific latent factors (correlation of individual frailty indicators with each specific factor), are shown in ***Table 3.7.*** These loadings show how differently the frailty indicators correlate with frailty, compared to their specific factors. We derived individual frailty scores for all subjects in each dataset based on the selected model. The distribution of frailty in BWHHS women and both men and women of the MRC assessment study, by age group and sex are shown in ***Figures 3.3-3.5***. The BWHHS women (ages ranged from 60 to 79 years) in the older age group (over 75 years) had higher frailty scores i.e. were more frail compared to the younger age group (median scores 0.015 vs. 0.276). They also appeared to be more frail when compared to the MRC women, all of whom were over 75 years old (median scores 0.276 vs. 0.132). . In the MRC women, the median frailty scores increased with age and when stratified, were higher in those in the older age groups of 80-84 years and 85 years and above, with scores of 0.213 and 0.578 respectively. The MRC men, whose scores also increased with age, were less frail compared to the women (median scores -0.811 vs. 0.132) (see ***Figure 3.5***).

Figure3.3: Histogram showing the distribution of frailty scores in 1568 BWHHS women according to age.

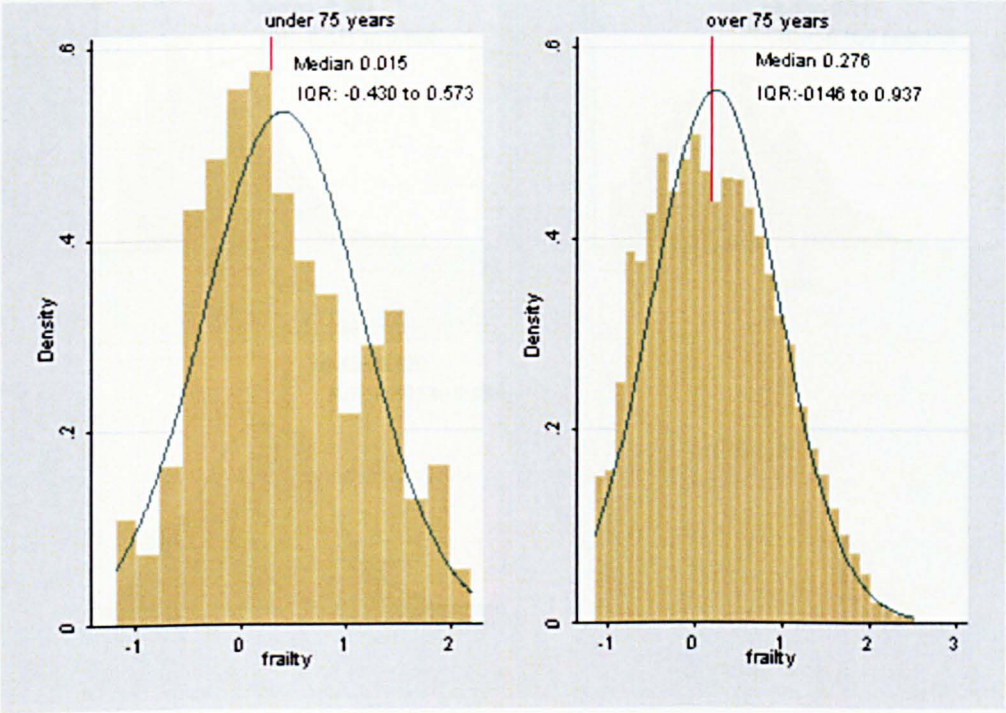


Figure 3.4: Histogram showing the distribution of frailty scores according to sex in the MRC Assessment study.

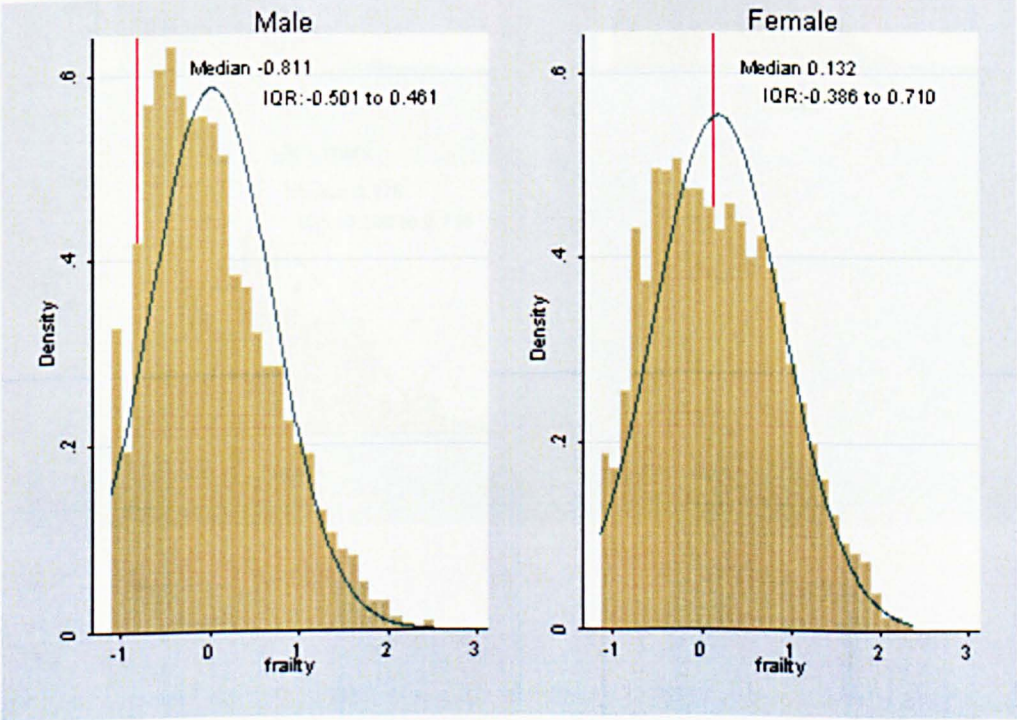
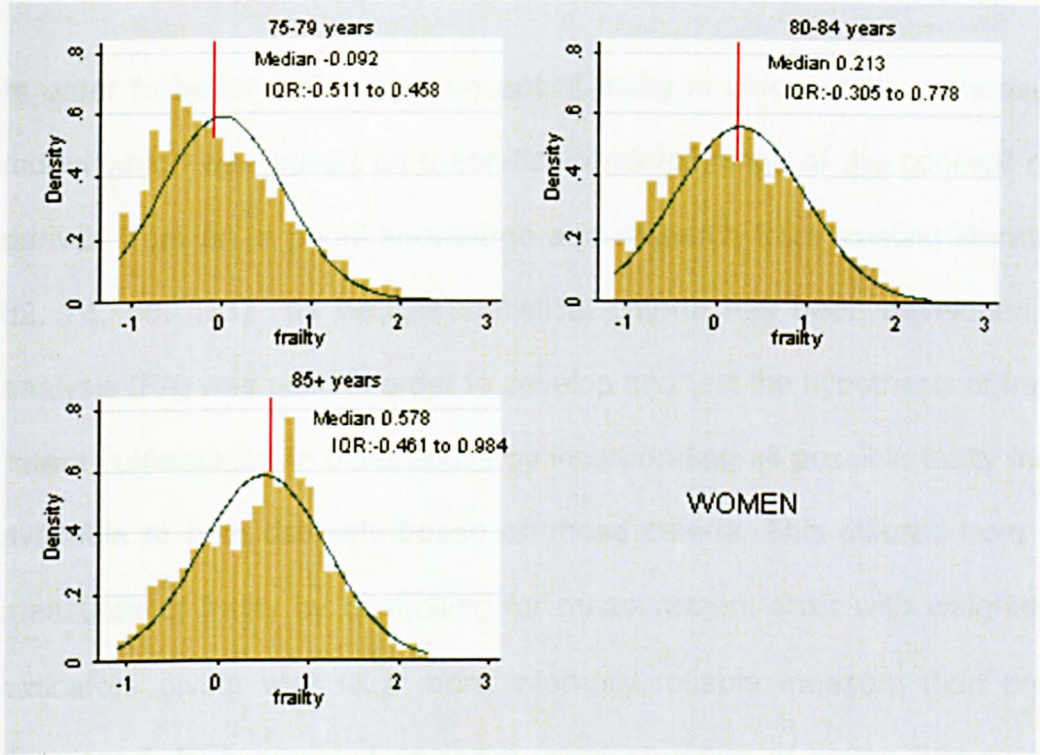
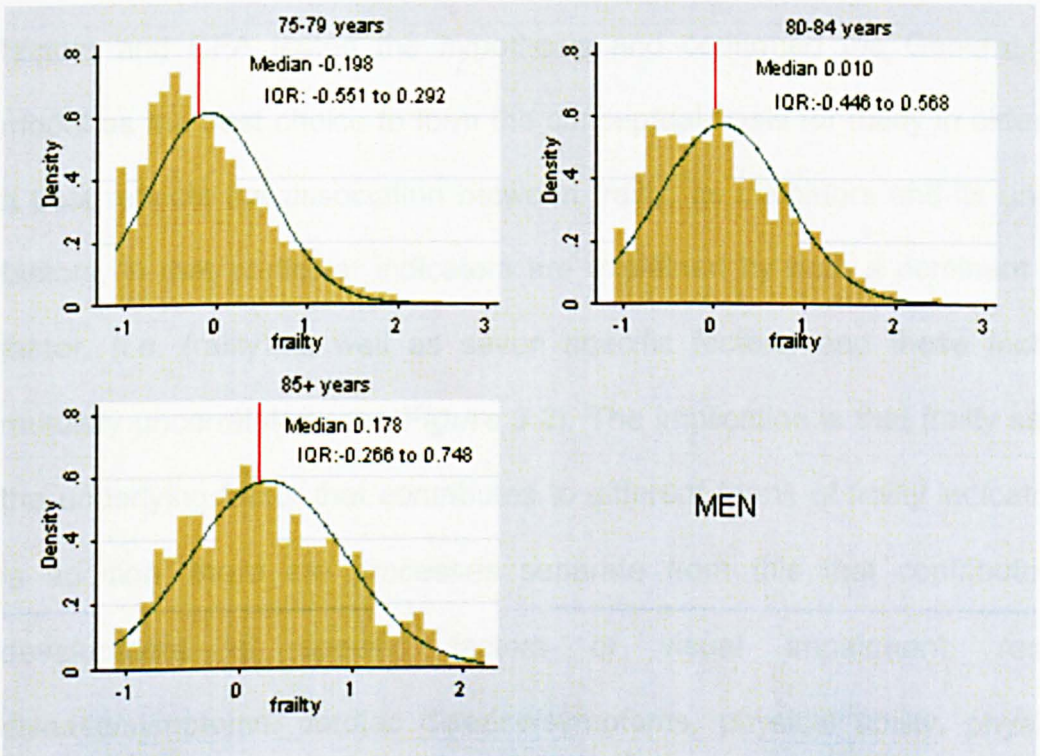


Figure 3.5: Histogram showing the distribution of frailty scores according to age in men and women of the MRC Assessment study



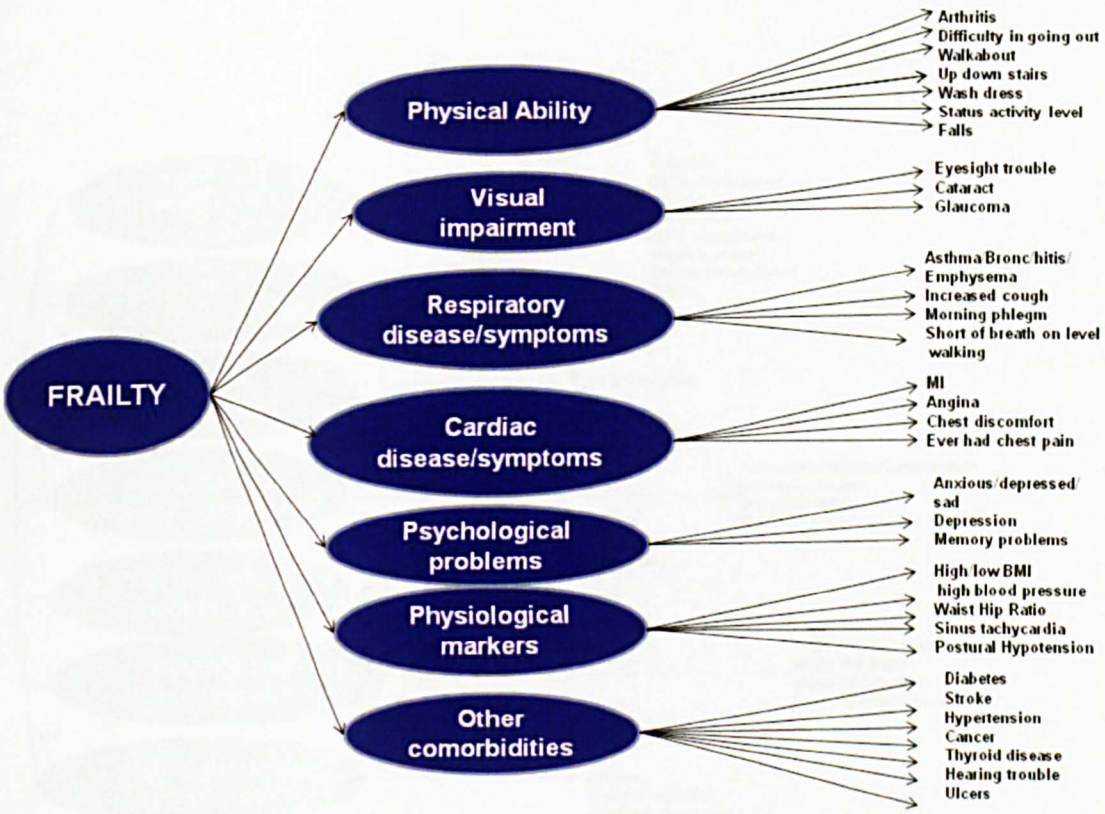


Discussion

In order to better define the concept of frailty in older adults, a measurement model which was based on theoretical underpinnings of the concept of frailty, derived from an 'a priori' knowledge and research from existing literature [35, 62, 74, 88, 121] as well as statistical criteria has been developed. Factor analysis (FA) was used in order to develop and test the hypothesis of frailty as a 'latent vulnerability' in older adults by incorporating all possible frailty indicators available to both datasets based on these criteria. This differed from existing measures of frailty by controlling for measurement error with weighted frailty indicators giving way to a more internally reliable measure than previously developed. EFA provided an initial latent structure of seven first order latent factors and CFA tested the hypothesis and confirmed the General Specific model as the best choice to form the conceptual basis for frailty in older adults. It best reflects the association between frailty, its indicators and its underlying factors, in that particular indicators are explained by both a dominant general factor, (i.e. frailty),as well as seven specific factors, and these factors are mutually uncorrelated (see ***Figure 3.2***). The implication is that frailty serves as the underlying factor that contributes to different forms of frailty indicators, and in addition, there are processes separate from this that contribute to the development of specific factors of visual impairment, respiratory disease/symptoms, cardiac disease/symptoms, physical ability, physiological markers, psychological problems and co-morbid disease, which vary independently of frailty. By contrast, in the 2nd order model, frailty was seen to drive/subsume all the factors/dimensions acting as a single broad, coherent

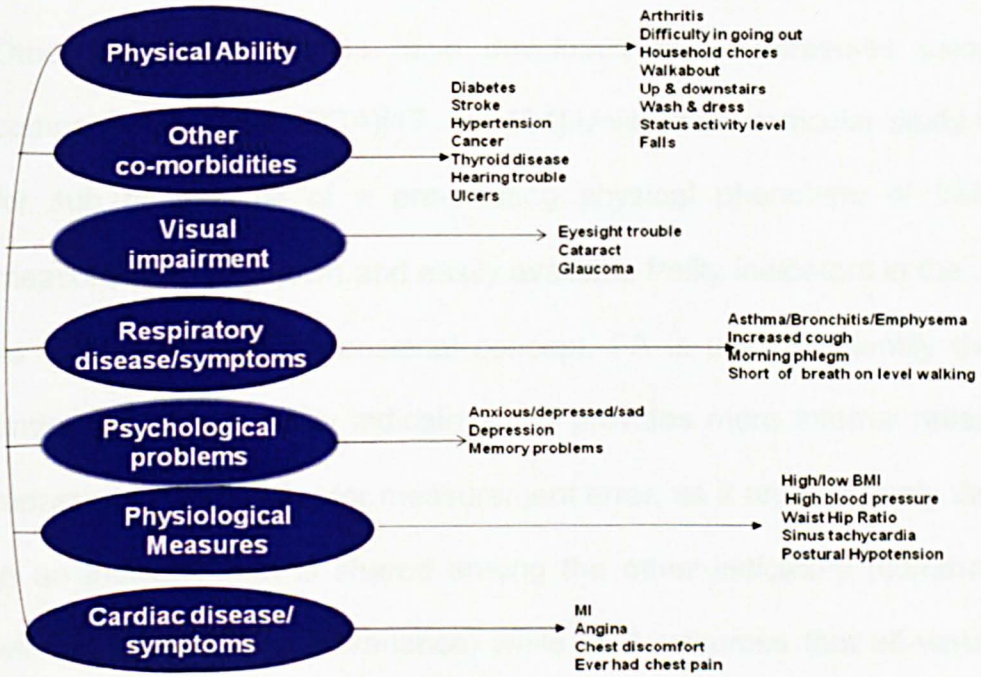
construct broken down into increasingly specific factors and indicators (see ***Figure 3.6*** below).

Figure 3.6: Second order model



In the 1st order model, frailty was represented by each of the seven specific factors which were correlated to each other (see ***Figure 3.7***).

Figure 3.7: First order model



On a conceptual level, these models (1st and 2nd order) do not fit in with the idea of frailty. Not all the specific factors need to be present for an individual to be considered frail, as implied by the second order model. For example, an elderly person with 'eyesight trouble' with 'difficulty with going out' may still be considered frail despite not having other co-morbidities, cardio-respiratory disease or symptoms. The problem with the 1st order model was that the factors need not necessarily be correlated to one another for frailty to occur (see ***Figures 3.2, 3.6 and 3.7*** to compare the models).

External to this measurement model were socioeconomic status (SES) indicators such as income, education, social class, marital status, lifestyle indicators as well as social contact. As frailty is likely to be socially patterned [74], SES was expected to have a causally influence on frailty [122]. Hence frailty can be thought of as a mixed (reflective and formative) construct, that is reflected in the binary frailty indicators, but also driven by SES status [123] among other external forces (e.g. built environment).

Other population studies have developed frailty measures using principal component analysis (PCA)[17, 61, 124].Unlike one particular study that looked for sub dimensions of a pre-existing physical phenotype of frailty[124],our measure used all known and easily available frailty indicators in the datasets so as to fulfil its multi-dimensional concept. FA is used to identify the structure underlying all the frailty indicators and provides more internal reliability to the measure by controlling for measurement error, as it analyzes only the variability in an indicator that is shared among the other indicators (common variance without error or unique variance) while PCA assumes that all variability in an indicator should be used in the analysis.

In both datasets, a majority of indicators represented by physical ability were ones that best explained frailty. This supports the theory that frailty is identified through characteristics directly related to physical function [74]. The analysis also highlighted the importance of 'shortness of breath on level walking' as a more important frailty indicator than diagnosed respiratory diseases. Similarly, reports of symptoms such as 'ever having chest pain /chest discomfort' had higher factor loadings than having had a myocardial infarction. These higher loadings of self reported symptoms compared to diagnosed conditions may reflect that the diagnosed diseases were already under control/treated in our

respondents. Although co-morbidities featured strongly in some existing measures[17, 40], our model focused specifically on diseases such as myocardial infarction, angina, stroke, diabetes, peptic ulcers and hypertension.

Strengths of this study include the construction of a measurement model of frailty in a large representative cohort of British women and replication in a further large cohort representative of the British community-dwelling older population of men and women, using variables that were direct inputs from the respondents, including both objective and subjective attributes. FA enabled the identification of latent dimensions of frailty that may not have been apparent from direct observation of the data. This also enabled us to develop a reliable measure that translates into a frailty score for use in future analyses.

Initial assessments of the distribution of frailty in both the BWHHS and MRC datasets showed that frailty increased with age in both men and women and was also higher in women than in men. The higher median frailty scores in the older BWHHS women aged 75-79 years may reflect the frailest in this study population as their scores were comparable to the scores of MRC women aged 80 years and above.

Limitations of this study lie in the fact that the frailty indicators used were derived from self reports of symptoms/ disease at baseline only; hence it is not a dynamic measure of frailty. We concentrated on only complete cases but found similar findings for those with missing data. Although indicators used were based on known indicators from existing measures, we were limited to those available in both datasets.

The following chapter will focus on testing the construct and external criterion validity of this new measurement model of frailty which will now be called the **British Frailty Index (BFI)**. Its performance in predicting survival,

hospitalisation and institutionalisation will be tested in **Chapter 5**. This new measure should lead to more valid and reliable answers to the ultimate question of whether frailty is indeed a useful measure in predicting adverse outcomes in older populations.

Summary:

- The British FI translates the concept of frailty as a latent vulnerability in older people through the use of factor analysis (FA), a robust analytical technique which uses latent variables as a means of data reduction to represent a wide range of attributes/variability among observed variables on a smaller number of dimensions or factors.
- Its advantage over previous frailty measures is that it corrects for measurement error and assigns relative weights in the association of each indicator with frailty.
- Seven subsets or factors explained the association between frailty indicators: visual impairment, respiratory disease/symptoms, cardiac disease/symptoms, physical ability, physiological markers, psychological problems and co-morbid disease.
- The reliability or internal consistency of the 'General Specific' model was shown by the goodness of fit of the confirmatory factor analysis. The validation of the model as a measurement of frailty was reaffirmed it was tested in a larger independent cohort of the MRC assessment study whose respondents were older of both sexes.

Chapter 4: Determinants of frailty

Background

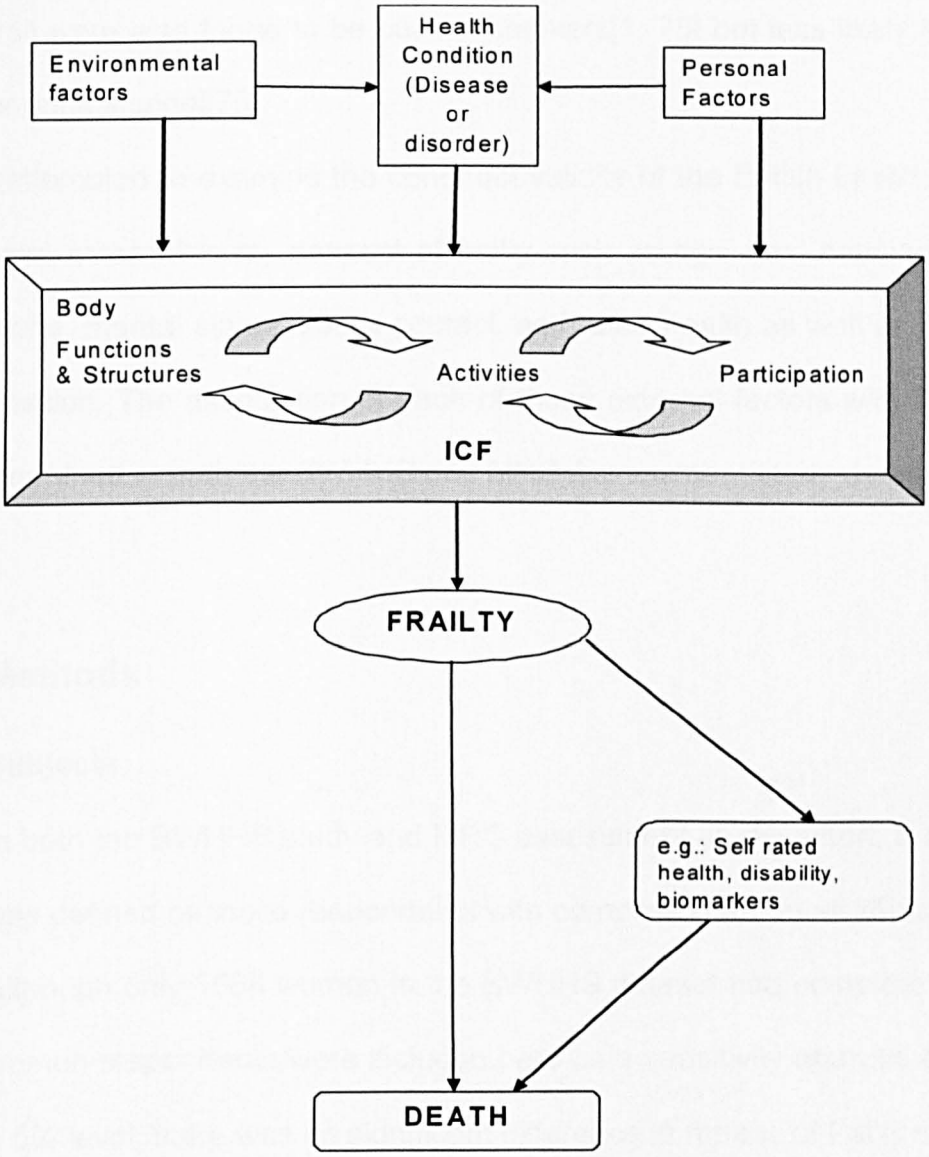
In the earlier chapters the heterogeneous nature of the frailty concept was reaffirmed by its historical background and evolution as well as the predictive validity of existing measures. With the British FI, I developed a measure which considers the inter-correlation of various frailty markers through the statistical method of factor analysis. Through factor analysis (FA), a robust measurement model of frailty was obtained and that included a latent frailty index that will be used in all further analyses.

In this chapter I examined the validity of the British FI in both the BWHHS older women population and in the MRC Assessment Study. Construct validity assesses whether the measure provides information on expected associations between frailty and criterion variables such as age, being more common in women than men, related to socioeconomic status, co-morbidity or self rated health [38]. Furthermore an assessment of evidence for criterion validity was made. This involved the correlation between the measure and a criterion variable (or variables) taken as representative of the frailty construct.

Frailty and its associated factors have been described widely in literature through other measures [1, 20, 78, 100]. A useful way of describing the experience of frailty would be by creating a theoretical causal path-diagram of frailty and its association with an adverse event. As mentioned in ***Chapter 1***, frailty can be described from an individual and societal perspective, within the context of the International Classification of Functioning, Disability and Health

(ICF) framework, a classification of health and its domains that describe body functions and structures, activities and participation[98]. When incorporated into this framework, frailty can be translated as the interaction between the health condition (disease) and contextual factors (environmental including physical, social and attitudinal environment and personal factors), as illustrated in ***Figure 4.1***. These interacting factors affect a person's bodily functions and their degree of activity and participation. These in turn determine his degree of frailty and indirectly, the risk of an adverse event which can be precipitated by certain stressors such as an acute infection or surgery. Personal factors on this causal pathway can include expected associations with frailty such as age, sex, marital status, living alone, smoking and alcohol intake. Environmental factors include those that constitute the physical environment such as type of accommodation (housing tenure); interaction of the individual to their social environment in terms of social contact or participation, as well as socioeconomic position status. A case study illustrating a clinical scenario using this pathway is presented in ***Chapter 7***.

Figure 4.1: Theoretical Causal path-diagram of frailty



The choice of covariates examined for its expected association with frailty did however depend on whether the variables were already included in the measure itself. Hence, the association of the British FI with basic activities of daily living or co-morbidity was not assessed because it had already been incorporated into the measure. Previous frailty measures have found significant associations with age[20, 100],female sex[20, 96],being unmarried[75] ,ethnic minority groups[20], poor self rated health[1, 100],low education[75, 77], low

income[1], poor cognitive function[41, 93], depression[20] and number of chronic diseases[20, 104],falls[1, 76], hip fractures [76]and disability[94]. The frail were also found to be current smokers[1, 75] but less likely to live alone[1] or drink alcohol[75].

I attempted to examine the construct validity of the British FI with factors which were external to my concept of frailty such as age, sex, housing tenure, living alone, marital status, social contact, self rated health as well as socioeconomic position. The association of each of these external factors with frailty was then examined in both the BWHHS and MRC Assessment study datasets.

Methods

Subjects

In both the BWHHS study and MRC assessment study cohort, a complete case was defined as those respondents with complete data on all 35 frailty indicators. Although only 1568 women in the BWHHS dataset had complete data, all 4286 women respondents were included here as a sensitivity analysis showed that at a 5% level, there was no significant difference in means of frailty scores, p value of 0.54) between the two groups. In the larger MRC Assessment study dataset only respondents with complete data (N=11195) were included in the analysis. They comprised of 6079 women and 4486 men.

Measurements

As detailed in ***Chapter 3***, the British FI was developed using factor analysis using the BWHHS study and this process was replicated in the MRC Assessment study. In both datasets, each respondent was assigned a frailty score developed from baseline observed variables –frailty indicators- using the selected General Specific model. This continuous frailty score was divided into quartiles and each ascending quartile classified as **'low or not frail', 'mild', 'moderate'** and **'severe'** frailty, so as to assess the degree of frailty when adjusted for sociodemographic and lifestyle variables. These variables were similarly collected in both datasets from self completed questionnaires and research nurse interviews at baseline (at entry into study) which dealt with social, demographic and lifestyle data. In the BWHHS dataset, a *multiple imputation* procedure was conducted on these variables using **Stata** version10 so as to enable inclusion of all 4286 respondents in this analysis. This was carried out because as the missing values were scattered throughout these variables, a substantial amount of power would be lost if the analysis were restricted to those with only complete data. Multiple imputations replace all the missing values with multiple versions (five in this case) of imputed ones. The BWHHS socio-demographic and lifestyle variables with missing data were imputed with the assumption that these were missing at random, where the 'missingness mechanism' does not depend on the unobserved data, i.e. there is no relationship between whether or not the covariate is missing and the value of the respondent's response variable[117]. This imputation procedure was not conducted with the sociodemographic and lifestyle variables in the MRC dataset as there were only a small numbers of respondents with missing data on each of these variables i.e. less than 2% missing data ranging from 0.1% to 1.8%.

These variables with the percentage of data missing in both datasets are presented in ***Table 4.1***.

Table 4.1: List of sociodemographic and lifestyle variables with percentage of missing data in the BWHHS and MRC Assessment study.

Sociodemographic and lifestyle variables	BWHHS		MRC Assessment Study	
	Number	Missing data (%)	Number	Missing data (%)
Age	4286	0	11195	0
Sex	-	-	11195	0
Current smoker	3960	326 (7.6)	11176	17 (0.2)
Alcohol intake	3908	378 (8.8)	11190	85 (0.8)
Living arrangement	4091	195 (4.6)	11115	80 (0.7)
Marital status	4106	180 (4.2)	11195	207 (1.8)
Housing tenure	4082	276 (4.8)	11138	57 (0.51)
Social contact	3064	1222(28.5)	111064	131 (1.2)
Socioeconomic position scores	3186	1100(25.7)	-	-
Self rated health	4052	234 (5.5)	11181	14 (0.1)

The sociodemographic and lifestyle variables included were age in years, sex (only for the MRC dataset which included men), living arrangements (living alone or with others), marital status (married/living with partner, single, divorced or separated or widowed). In the BWHHS dataset, good or poor social contact was derived from a combination of variables which assessed the frequency of contact the respondents had with their children, siblings, relatives or friends. In

the MRC dataset, this was defined as the frequency of contact the respondent had with any other people (daily, 2 to 3 times per week, less than twice a week or rarely). Housing tenure in the BWHHS dataset included whether the respondent lived in their own home, rented privately, rented from local authority or lived in other type of accommodation. In the MRC dataset, the 'other type of accommodation' was specified as council housing, sheltered accommodation, local authority or private residential home. In both datasets, 'self rated health' was rated as excellent, very good, good, fair and poor. Smoking habit in both datasets was similarly categorized as 'Never smoked', 1-9, 10-19, >20 cigarettes per day with the addition of 'ex-smokers' in the BWHHS dataset. In the BWHHS dataset, regular alcohol intake was categorized as 'yes' if intake was daily, most days or every weekend and 'no' if intake was once or twice a month, only on special occasions or not at all. In the MRC dataset, regular alcohol intake in the last year was categorized as 'yes' or 'no' but was further assessed by the amount of alcohol consumed, in those who drank more or less than either 10 single shots of spirits,10 glasses of wine or 10 half pints of beer a week.

Information on socioeconomic position was also only available in the BWHHS dataset. This was presented as a **life-course socioeconomic position (SEP) score** generated from 10 indicators [125]. These indicators included adult and childhood social class which were based on the register general's classification of occupation (a hierarchical classification: I, II, III non-manual, III manual, IV, V—with I (highest SEP) being professional occupations and V (lowest SEP) being manual unskilled occupations).Other indicators were pension arrangements, adult housing tenure, age at leaving full time education, the longest held occupation of the participant's father during her childhood,

childhood household amenities (bathroom, hot water, bedroom sharing, and car access), the longest held occupation of the participant and her spouse and car access. Childhood occupational social class of the women was based on their fathers' longest held occupation and adult (head of household) occupational social class was based on their husbands' longest held occupation, or their own for single women and for women whose occupation was of a higher social class than their husbands. Age at leaving full time education was classified into four categories: <15 years (lowest SEP), 15–17 years, 18–21 years, >21 years (highest SEP) [125]. Non binary indicators were recoded as follows: adult and childhood social class into non manual (I, II, III non-manual) and manual (III manual, IV, V); pension arrangements into state only or state plus other (employment or private pension); adult housing tenure into local authority (social housing) or other (owner occupied, private rental, living with a relative); and age at leaving full-time education into those leaving school at or younger than 15 years, or above that age. The score ranged from 0 (most advantaged position across the life course) to 10 (most disadvantaged position across the life course). However, as there were small numbers in the 0 category and in the 10 category, the 0 category was combined with the 1 category and the 10 category with the 9 category. Both weighted and unweighted scores were generated for adult and childhood socioeconomic position. Weighted scores gave greatest weight to adverse indicators that were least prevalent and as such may be thought of as being more severe indicators of adverse socioeconomic position. However, the analyses by unweighted score did not differ substantively from those using the weighted score and therefore the main analyses presented here the unweighted SEP scores was used.

Statistical analysis

A descriptive estimation was carried out using a *two way scatter plot* of the frailty score with each of the external factors such as age, sex, lifestyle factors such as smoking and alcohol, socioeconomic position, social contact, marital status, housing tenure, own age activity, living status as well as self rated health. As these independent variables were not normally distributed, median frailty scores with their respective inter-quartile range was calculated for each variable. The odds ratio with 95% confidence interval of each quartile of frailty from **'low or not frail', 'mild', 'moderate'** to **'severe'** frailty, by each sociodemographic and lifestyle variable was assessed using ***ordered logistic regression.*** This statistical technique used an ordered (from low to high dependent variable), in this instance, each ascending quartile of frailty corresponded to a higher level of frailty. These analyses were carried out in both datasets for comparison.

Results

Median and inter-quartile range (IQR) of frailty scores by the independent sociodemographic variables used for this analysis are shown in ***Table 4.2*** and ***Table 4.3*** for the BWHHS and MRC Assessment study respectively. In the BWHHS women, these median scores were shown to increase with age and in those who were current smokers. Women who lived alone had higher median frailty scores than those who did not (i.e. those who lived with their husbands, partners or relatives), as were those who were single compared to those who were married. Socioeconomic position scores calculated from the BWHHS dataset ranged from 1 to 9 (from advantaged to disadvantaged). Median frailty

scores by socioeconomic position scores for the BWHHS women increased almost linearly from the lower 'advantaged' group (i.e. lower SEP scores) to those who were more disadvantaged (i.e. higher SEP scores). Women who owned their own home had lower median scores compared those who rented privately or lived in local authority or other types of accommodation. Those who rated their health as poor had the highest median frailty scores compared to those who rated it as fair, good or excellent. There was very little difference in the median scores of those who reported good or poor social contact. Also, women who reported regular alcohol intake had lower median frailty scores compared to those who did not.

Similar results were found in both men and women of the MRC assessment study with the exception of the variable living alone, where those who lived alone had lower scores compared to those who did not. Also, frailty increased with age in this older cohort but women had higher median frailty scores when compared to men. Two way scatter plots showing median frailty scores by each independent variable provide further graphical description of these results. (see ***Figures 4.2- 4.12)***

Table 4.2: Median frailty scores and inter-quartile range according to independent sociodemographic and lifestyle variables in the BWHHS study population

Variables	Median	Inter-quartile range(IQR)
Age group:		
60-64	-0.07	-0.47-0.46
65-70	0.04	-0.04-0.60
71-74	0.13	-0.33-0.68
75-79	0.32	-0.18-0.85
Socioeconomic position scores:		
1	-0.15	-0.55-0.30
2	-0.15	-0.52-0.36
3	0.01	-0.40-0.52
4	0.06	-0.33-0.61
5	0.19	-0.31-0.74
6	0.25	-0.23-0.84
7	0.32	-0.24-0.99
8	0.46	-0.08-1.00
9	0.36	-0.01-0.91
Smoking, cigarettes per day:		
Never	-0.01	-0.44-0.53
Ex smoker	0.21	-0.27-0.77
1-9	-0.07	-0.34-0.61
10-19	0.19	-0.32-0.69
>20	0.50	0.03-1.05
Alcohol intake:		
No	0.18	-0.32-0.44
Yes	-0.05	-0.47-0.44
Lives alone:		
No	0.02	-0.42-0.56
Yes	0.24	-0.25-0.80
Marital status:		
Married	0.03	-0.42-0.56
Single	-0.08	-0.42-0.37
Divorced/separated	0.32	-0.11-0.85
Widowed	0.22	-0.27-0.82
Social Contact:		
Every day/week	0.08	-0.38-0.64
Every few months	0.07	-0.37-0.63
Every year	0.02	-0.38-0.67
Rarely/never	0.08	-0.38-0.67
Housing tenure:		
Own home	0.02	-0.42-0.55
Private rental	0.29	-0.22-0.85
Local authority rental	0.46	-0.11-1.037
Other	0.18	-0.31-0.77
Self rated health:		
Excellent	-0.51	-0.84--0.22
Good	-0.07	-0.44-0.34
Fair	0.76	0.32-1.14
Poor	1.37	0.88-1.80

Table 4.3: Median frailty scores and interquartile(IQR) range according to independent sociodemographic and lifestyle variables in the MRC assessment study population.

Variable	Median	Interquartile range(IQR)
Age in years:		
75-79	-0.139	-0.54-0.39
80-84	0.123	-0.36-0.71
>85	0.446	-0.11-0.92
Sex:		
Male	-0.081	-0.50-0.46
Female	0.132	-0.39-0.71
Current Smoker:		
No	0.03	-0.44-0.62
Yes	0.12	-0.42-0.66
Alcohol intake:		
No	0.26	-0.31-0.81
Yes	-0.01	-0.47-0.55
Lives alone:		
No	-0.03	-0.49-0.55
Yes	0.12	-0.37-0.68
Marital status:		
Married	-0.09	-0.52-0.46
Single	-0.02	-0.45-0.53
Divorced/Separated	0.06	-0.42-0.59
Widowed	0.19	-0.34-0.75
Social contact:		
Daily	-0.02	-0.49-0.57
2-3x/week	0.03	-0.43-0.60
<2x/week	0.21	-0.34-0.77
Rarely	0.28	-0.24-0.80
Housing tenure:		
Own home	-0.07	-0.50-0.48
Private rental	0.11	-0.38-0.67
Local Authority/Housing association	0.22	-0.32-0.79
Council/sheltered/Private residential	0.54	-0.04-0.99
Self rated health:		
Excellent	-0.25	-0.59-0.20
Very good/good	0.20	-0.28-0.70
Fair/poor	0.89	0.42-1.31

Figure 4.2: The association between frailty and age in the British Women's Heart and Health Study.

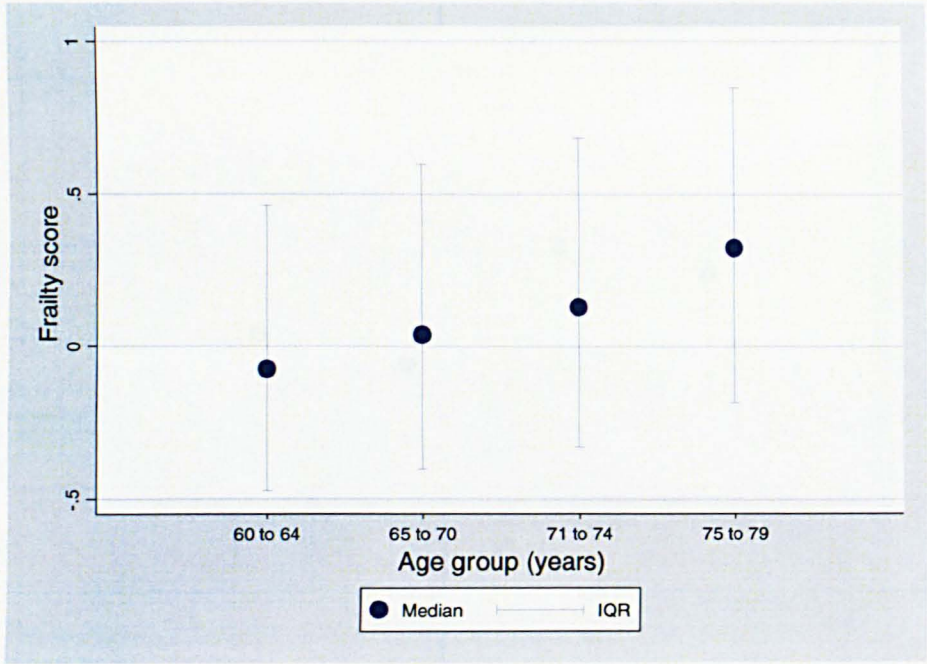
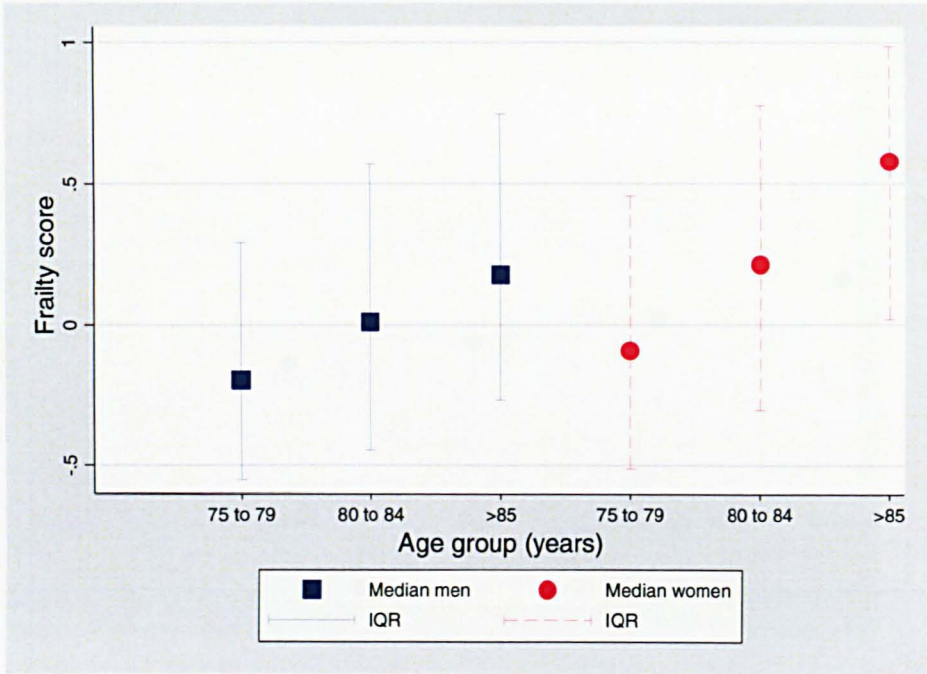


Figure 4.3: The association between frailty and age in men and women of the MRC Assessment study of older people.



Frailty and marital status

Figure4.4: The association between frailty and marital status in the BWHHS study

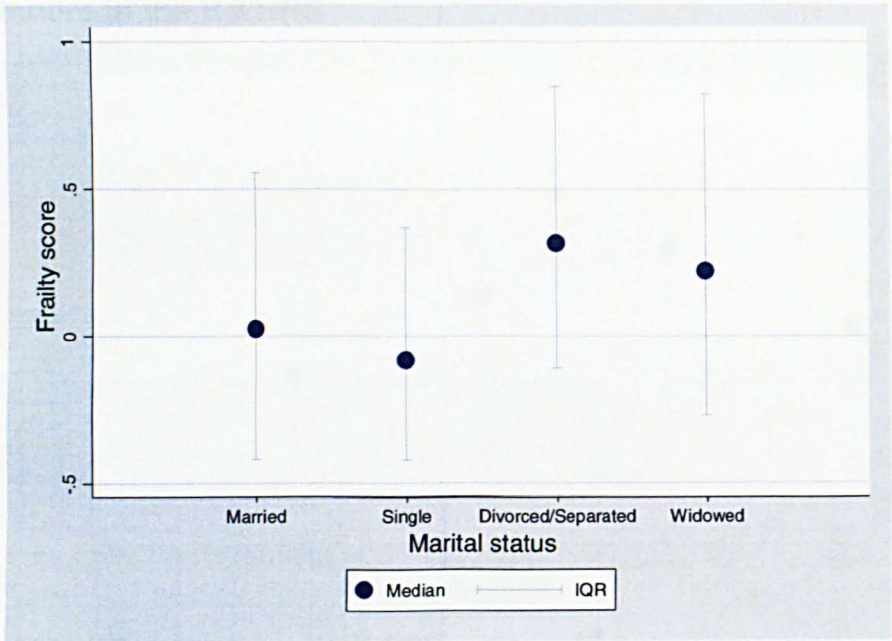
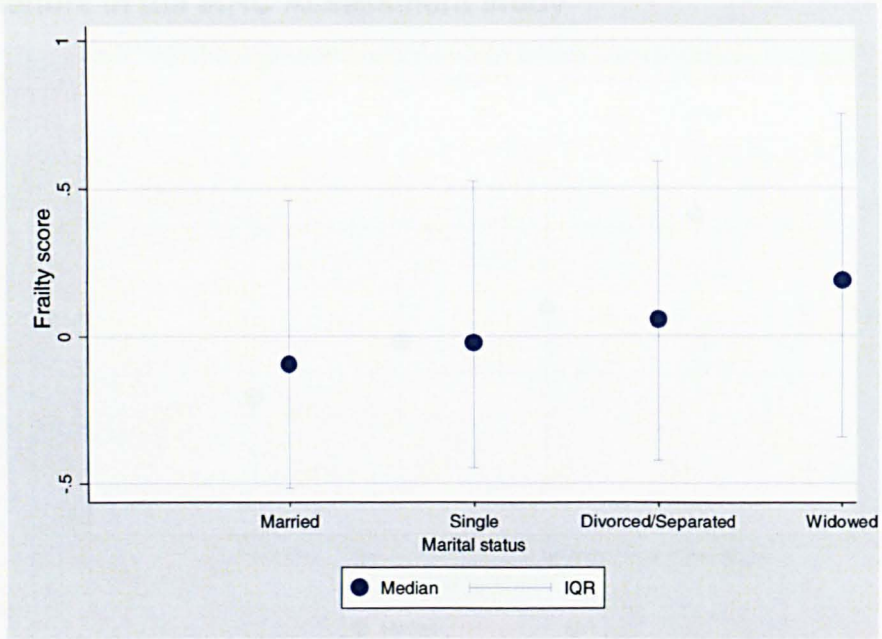


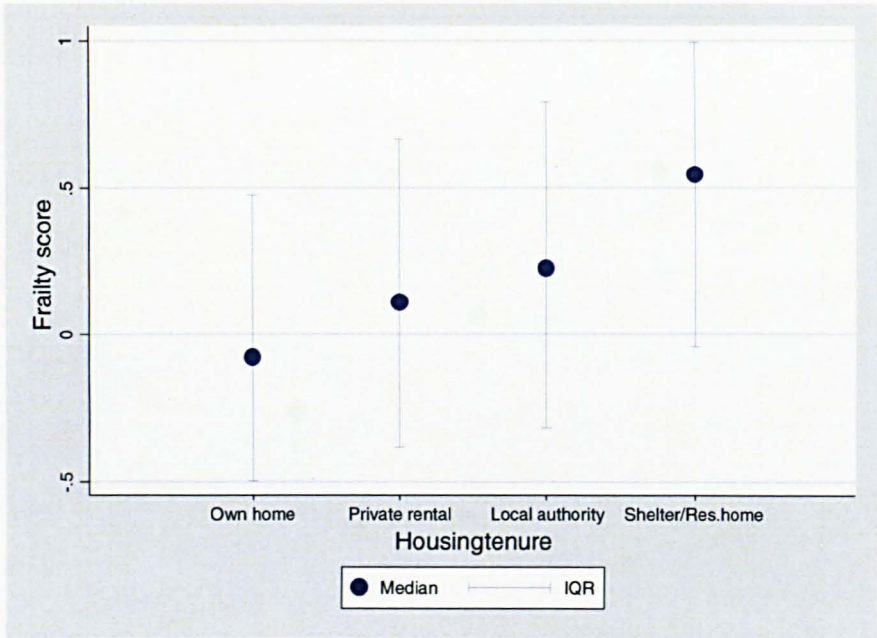
Figure 4.5: The association between frailty and marital status in the MRC assessment study



Frailty and housing tenure

Figure 4.6: The association between frailty and housing tenure in the BWHHS

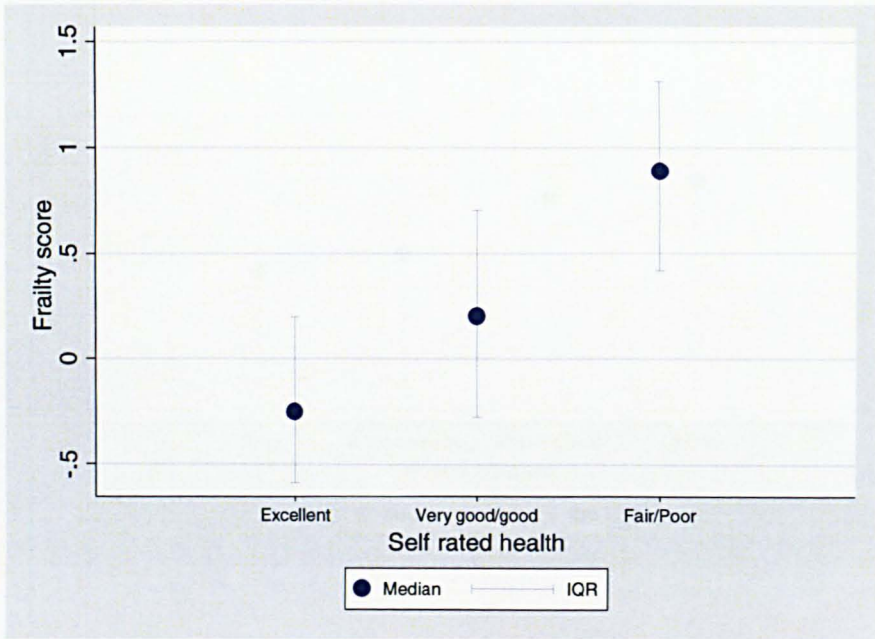
Figure 4.7: The association between frailty and housing tenure in the MRC Assessment study



Frailty and self rated health

Figure 4.8: The association between frailty and self rated health in the BWHHS

Figure 4.9: The association between frailty and self rated health in the MRC assessment study



Frailty and social contact

Figure 4.10: The association between frailty and social contact in the BWHHS

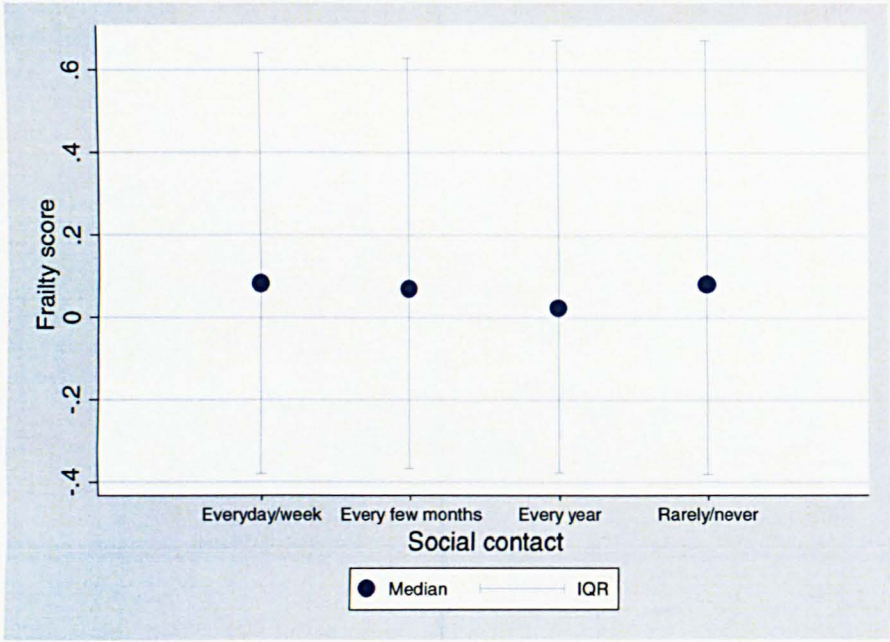


Figure 4.11 The association between frailty and social contact in the MRC assessment study

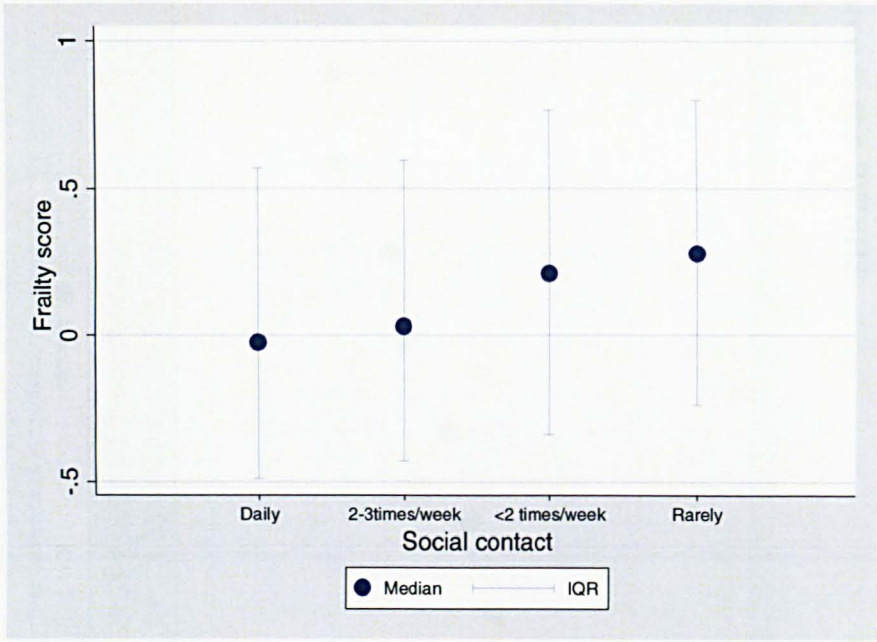
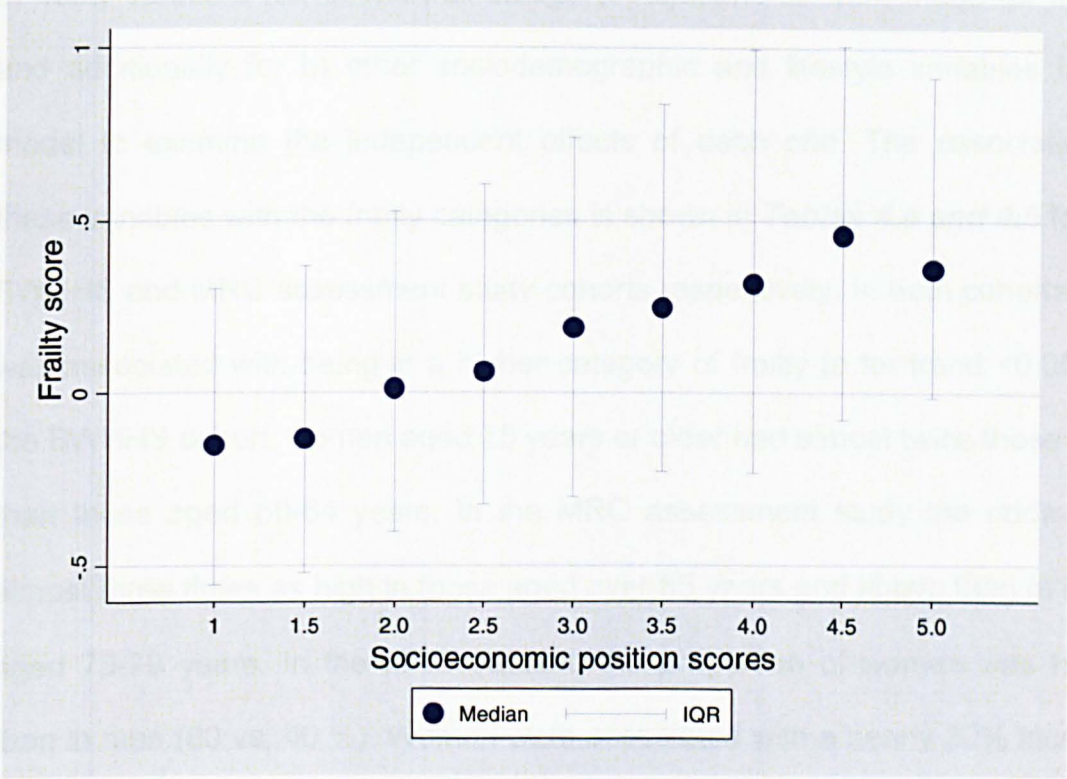


Figure 4.12: The association between frailty and socioeconomic position (SEP) scores in the BWHHS



The odds ratio calculated here was the effect of each independent socioeconomic and lifestyle variable on the odds of being in a higher category of frailty versus a low or not frail category. Adjustments were made for a) age and additionally for b) other sociodemographic and lifestyle variables in the model to examine the independent effects of each one. The association of these variables with the frailty categories is shown in ***Tables 4.4 and 4.5*** for the BWHHS and MRC assessment study cohorts respectively. In both cohorts, age was associated with being in a higher category of frailty (p for trend <0.001).In the BWHHS cohort, women aged 75 years or older had almost twice these odds than those aged 60-64 years. In the MRC assessment study the odds were almost three times as high in those aged over 85 years and above than in those aged 75-79 years. In the MRC dataset, the proportion of women was higher than in men (60 vs. 40 %). Women were associated with a nearly 30% increase in odds of being in a higher frailty category than men even after fully adjusting for all other sociodemographic and lifestyle variables.

These odds were also increased in those respondents who currently smoked (in addition to number of cigarettes smoked). The odds of being frail was highest among those who smoked > 20 cigarettes per day (fully adjusted OR 3.22,95%C.I.:2.20,4.72,p<0.01) and ex-smokers(fully adjusted OR 1.63,95%C.I.:1.46,1.82,p<0.001).In the MRC respondents, the odds of being in a higher frailty category increased significantly when assessed by the number of cigarettes smoked especially in those who smoked more than 20 cigarettes a day (fully adjusted OR 1.27, 95% C.I.:1.02,1.58,p<0.05).

BWHHS respondents who reported regular and increased amount of alcohol intake had significantly lower odds of frailty (fully adjusted OR 0.69, 95%

C.I.:0.61, 0.77,p<0.001. This association was similar but more significant in the MRC cohort (fully adjusted OR 0.72, 95% C.I.:0.65, 0.79,p<0.001).

For this part of the analysis, socioeconomic position (SEP) scores (only available in BWHHS dataset) were recoded as binary; 0 represented the less disadvantaged group with lower scores of one to four, whereas 1 represented the disadvantaged group with higher scores of five to nine. Women with higher SEP scores (more disadvantaged) had an increased odds of being in a higher frailty category than women who had lower SEP scores (more advantaged), (fully adjusted OR1.55, 95% C.I.:1.35, 1.77, p<0.001).

In the BWHHS respondents, living alone was associated with an increased odds of being in a higher category of frailty (fully adjusted OR1.22, 95% C.I.:1.02, 1.46, p<0.05). In the MRC cohort, the age adjusted odds were significantly increased when adjusting for age (OR 1.13, 95% C.I.:1.04, 1.21, p<0.01) but were attenuated when fully adjusted (OR 0.75, 95% C.I.:0.6, 0.83, p<0.001).

Among the BWHHS women, being single, significantly reduced the odds of being in a higher category of frailty (fully adjusted OR 0.59, 95% C.I.:0.46, 0.77, p<0.001) than those who were married. These odds were similarly reduced among MRC respondents who were single but this was not significant when fully adjusted, OR 0.94, 95% C.I.:0.78, 1.13, p=0.48. BWHHS and MRC respondents who were widowed had a higher age adjusted odds of being frail than those who were married. However, this remained significantly increased only among the MRC when fully adjusted (OR 1.45, 95%C.I.:1.31, 1.61,p<0.001)

The effect of having poor social contact compared to good was not associated with increasing levels of frailty in the BWHHS respondents. This association

however, was very significant in the respondents of the MRC assessment study (fully adjusted OR 1.80, 95%C.I.:1.00, 2.17, $p<0.01$).

Not living in or owning their own home also increased the odds of being in a higher frailty category in all respondents in both datasets These odds were especially high in the MRC respondents who lived in sheltered, local authority or private residential homes (fully adjusted OR 2.42,95%C.I.:2.11,2.78,$p<0.001$).

Lastly, self reports of fair or poor health compared to excellent health, greatly increased the odds of being in a higher category of frailty in the respondents of both datasets.

Table 4.4: Association of sociodemographic and lifestyle characteristics by frailty categories in the British Women's Heart and Health Study.

Variable	Frailty scores per quartile (%)					Age adjusted odds ratio 95%C.I.	Fully adjusted odds ratio 95% C.I.
	Low or not frail n=1072	Mild frailty n=1072	Moderate frailty n=1073	Severe frailty n=1069	Odds Ratio 95%C.I		
Age in years							
60-64	371(34.6)	315(29.4)	276(25.7)	218(20.4)	1.00	-	1.00
65-69	300(28.0)	292(27.2)	272(25.4)	270(25.3)	1.30(1.11,1.51)		1.22(1.03,1.45)
70-74	245(22.8)	286(26.7)	282(26.3)	298(27.8)	1.57(1.32,1.88)		1.45(1.20,1.77)
>75	156(14.6)	179(16.7)	243(22.6)	283(26.5)	2.14(1.83,2.49)		1.88(1.59,2.22)
Smoker,cigarettes per day							
Never smoked	686(64.0)	623(58.3)	575(53.6)	494(46.3)	1.00	1.00	1.00
Ex-smoker	281(26.2)	336(31.4)	363(33.9)	426(39.9)	1.61(1.45,1.79)	1.58(1.41,1.78)	1.63(1.46,1.82)
1-9	46(4.3)	52(4.9)	49(4.6)	47(4.4)	1.23(0.91,1.68)	1.25(0.91,1.71)	1.20(0.88,1.64)
10-19	46(4.3)	44(4.1)	56(5.2)	55(5.1)	1.44(1.08,1.93)	1.56(1.14,2.13)	1.49(1.11,2.01)
>20	13(1.2)	14(1.3)	29(2.7)	45(4.2)	3.10(2.15,4.46)	3.57(2.44,5.24	3.22(2.20,4.72)
Regular alcohol intake†							
No	615(57.4)	649(60.7)	710(66.2)	794(74.4)	1.00	1.00	1.00
Yes	457(42.6)	420(39.3)	362(33.8)	273(25.6)	0.61(0.54,0.68)	0.64(0.56,0.72)	0.69 (0.61,0.77)
Socioeconomic Position Score:							
Low (advantaged)	694(64.7)	680(63.6)	589(54.9)	449(42.1)	1.00	1.00	1.00
High(disadvantaged)	378(35.3)	389(36.4)	483(45.1)	618(57.9)	1.88(1.63,2.18)	1.81(1.57,2.10)	1.55(1.35,1.77)
Lives alone:							
No	797(74.3)	757(70.8)	718(67.0)	638(59.8)	1.00	1.00	1.00
Yes	275(26.7)	312(29.2)	354(33.0)	429(40.2)	1.55(1.38,1.74)	1.39(1.24,1.55)	1.22(1.02,1.46)
Marital Status:							
Married	717(66.9)	683(63.9)	656(61.2)	564(52.9)	1.00	1.00	1.00
Single	56(5.2)	63(5.9)	44(4.1)	30(2.8)	0.79(0.64,0.97)	0.75(0.60,0.92)	0.59(0.46,0.77)
Divorced/separated	47(4.4)	50(4.7)	79(7.4)	93(8.7)	1.92(1.53,2.41)	2.04(1.62,2.56)	1.28(1.01,1.62)
Widowed	252(23.5)	273(25.5)	293(27.3)	380(35.6)	1.53(1.35,1.73)	1.30(1.15,1.46)	0.88(0.75,1.04)
Social Contact:							
Good	730(68.1)	737(68.9)	753(70.2)	718(67.3)	1.00	1.00	1.00
Poor	342(31.9)	332(31.1)	319(29.8)	349(32.7)	1.01(0.91,1.12)	0.97(0.87,1.08)	1.04(0.92,1.18)
Housing tenure:							
Own home	921(85.9)	901(84.3)	869(81.1)	730(68.4)	1.00	1.00	1.00
Renting privately	104(9.7)	105(9.8)	141(13.1)	257(24.1)	1.74(1.37,2.15)	1.62(1.2,2.04)	1.35(1.10,1.66)
Renting local authority	29(2.7)	36(3.4)	42(3.9)	53(5.0)	2.33(1.95,2.79)	2.23(1.83,2.72)	1.59(1.29,1.96)
Other	18(1.7)	27(2.5)	20(1.9)	27(2.5)	1.37(0.91,2.07)	1.33(0.87,2.05)	1.25(0.78,2.00)
Present health:							
Excellent/Good	1016(94.8)	942(88.1)	753(70.2)	312(29.2)	1.00	1.00	1.00
Fair	55(5.1)	121(11.5)	305(28.4)	645(60.5)	10.8(9.0,12.9)	10.5(8.7,12.6)	9.65(8.12,11.46)
Poor	1(0.1)	4(0.4)	14(1.3)	110(10.3)	47.9(31.0,74.1)	45.7(29.5,70.9)	37.80(24.31,58.78)

***Fully adjusted p for trend <0.001 for all except variable 'social contact' p=0.6 and lives alone p<0.05, † Regular alcohol intake was also assessed by amount of alcohol consumed per wee**

Table 4.5: Baseline association of demographic and health characteristics with each quartile of frailty with percentages and odds ratio in the MRC assessment study of older people.

Variable	Frailty scores per quartile(%)				Odds Ratio 95%C.I.	Age adjusted odds ratio 95%C.I*	Fully adjusted odds ratio 95%C.I.
	Low or not frail n=3022	Mild frailty n=2697	Moderate frailty n=2740	Severe frailty n=2736			
Age in years:							
75-79	1923(63.6)	1495(55.4)	1277(46.6)	941(34.4)	1.00	-	1.00
80-84	814(26.9)	822(30.5)	903(33.0)	964(35.2)	1.78(1.63,1.93)		1.62(1.50,1.76)
>85	285(9.3)	380(14.1)	560(20.4)	831(30.4)	3.26(2.90,3.65)		2.76(2.46,3.09)
Sex:							
Male	1393(31.0)	1191(26.6)	1045(23.3)	857(19.1)	1.00	1.00	1.00
Female	1629(24.3)	1506(22.4)	1695(25.3)	1879(28.0)	1.52(1.42,1.63)	1.43(1.34,1.53)	1.27(1.06,1.53)
Smoking, cigarettes per day:							
None	2750(91.1)	2453(91.1)	2452(89.5)	2453(89.9)	1.00	1.00	1.00
1-9	101(3.4)	81(3.0)	107(3.9)	107(3.9)	1.17(0.98,1.40)	1.30(1.10,1.54)	1.27 (1.05,1.53)
10-19	91(3.0)	86(3.2)	95(3.5)	90(3.3)	1.08(0.92,1.28)	1.31(1.10,1.55)	1.25(1.05,1.48)
>20	75(2.5)	72(2.7)	84(3.1)	79(2.9)	1.14(0.91,1.42)	1.25(0.99,1.57)	1.27(1.02,1.58)
Regular alcohol intake†:							
No	524(17.5)	510(19.1)	647(23.7)	810(29.9)	1.00	1.00	1.00
Yes	2473(82.5)	2163(80.9)	2079(76.3)	1904(70.1)	0.61(0.56,0.68)	0.68(0.61,0.75)	0.72(0.65,0.79)†
Lives alone*:							
No	1784(59.3)	1466(54.7)	1371(50.3)	1330(49.2)	1.00	1.00	1.00
Yes	1223(40.7)	1213(45.3)	1356(49.7)	1372(50.8)	1.33(1.23,1.44)	1.13(1.04,1.21)	0.75(0.67,0.83)
Marital Status:							
Married	1548(52.1)	1224(46.4)	1076(39.9)	918(34.2)	1.00	1.00	1.00
Single	188(6.3)	180(6.8)	173(6.4)	135(5.0)	1.16(1.00,1.35)	0.95(0.82,1.10)	0.94(0.78,1.13)
Divorced/Separated	52(21.8)	45(1.7)	51(1.9)	46(1.7)	1.34(1.09,1.64)	1.32(1.05,1.67)	1.39(1.06,1.82)
Widowed	1181(39.8)	1190(45.1)	1394(51.7)	1587(59.1)	1.74(1.61,1.88)	1.38(1.28,1.48)	1.45(1.31,1.61)
Social Contact:							
Daily	1516(30.1)	1214(24.1)	1176(23.4)	1130(22.4)	1.00	1.00	1.00
2-3x/week	1084(26.4)	1031(25.0)	1043(25.4)	955(23.2)	1.13(1.03,1.23)	1.12(1.02,1.22)	1.14(1.04,1.25)
<2x/week	314(21.4)	322(21.9)	384(26.1)	450(30.6)	1.56(1.34,1.82)	1.48(1.28,1.71)	1.53(1.32,1.77)
Rarely	77(17.3)	103(23.1)	113(25.4)	152(34.2	1.84(1.55,2.19)	1.77(1.47,2.12)	1.80(1.00,2.17)
Housing tenure:							
Own home	2229(74.0)	1894(70.4)	1695(62.3)	1422(52.3)	1.00	1.00	1.00
Private rental	110(3.7)	108(4.0)	115(4.3)	122(4.5)	1.44(1.22,1.70)	1.34(1.13,1.59)	1.33(1.12,1.58)
Council/housing association rental	560(18.6)	560(20.8)	694(25.5)	809(29.7)	1.75(1.59,1.92)	1.78(1.62,1.95)	1.74(1.58,1.91)
Sheltered,local authority & private res.home	112(3.7)	127(4.7)	215(7.9)	36.6(13.5)	3.18(2.72,3.72)	2.51(2.15,2.92)	2.42(2.11,2.78)
Present health:							
Excellent	1021(33.8)	646(24.0)	397(14.5)	134(4.9)	1.00	1.00	1.00
Very good/Good	1930(63.9)	1910(70.9)	2002(73.2)	1595(58.4)	2.74(2.49,3.02)	2.88(2.64,3.15)	2.73(2.49,3.00)
Fair/Poor	69(2.3)	137(5.1)	336(12.3)	1004(36.7)	19.32(15.94,23.43)	22.23(18.41,26.84)	20.59(17.11,24.76)

***Fully adjusted p for trend <0.001 for all independent variables † Regular alcohol intake was also assessed by amount of alcohol consumed per week.**

Discussion

The external criterion validity of the British FI was assessed in two well represented British study populations. This measure was able to significantly demonstrate the effect of various socioeconomic and lifestyle variable on frailty, enabling comparisons to be made of this effect between the younger, female cohort of the BWHHS and both men and women of the larger and older MRC assessment study. In both cohorts, older age, smoking, not living in or owning one's own home, living alone and having poor self rated health independently increased the odds of being in a higher category of frailty. A socioeconomic position (SEP) score demonstrated that being disadvantaged (higher SEP score) was also strongly associated with higher levels of frailty in women of the BWHHS. This SEP score incorporated a more comprehensive range of socioeconomic factors, hence it strongly confirms similar associations between frailty and socioeconomic markers such as low education[1, 41] and income[20, 45],non white collar occupations [126]which had been assessed separately in other studies.

The association of all these variables used in this study were highly in keeping with the findings of other large population studies which used different frailty measures [74-76] [78, 105], thus confirming their important role with increasing levels of frailty as well as their role in the causal pathway of frailty. In both cohorts, respondents who reported having regular and increased alcohol intake had significantly reduced odds of being frail. This was similar to previous study findings which reported a negative association with alcohol intake and frailty [1, 75, 126], hence confirming that those who were frail tended to abstain from regular and increased alcohol intake than those who were not frail. The odds of

being in a higher frailty category were also reduced in respondents who were single when compared to those who were widowed divorced or separated (see ***Table 4.4 and 4.5***).

Additionally, in the MRC cohort, these odds were increased in women compared to men. Social contact was found to be more important with increasing age as it was shown that poor social contact did not increase the odds of being frail among the BWHHS cohort of women but were nearly doubled among both men and women of the older MRC respondents. This was in line with findings of other large population studies that showed an association between poor social contact[126] and social vulnerability [122] with frailty. However, these differences could be due to the difference in the way frailty was measured in these studies or could more likely indicate that the association with frailty was perhaps related to social participation of the frail individual with their environment rather than actual contact with relatives, friends or neighbours.

All these associations showed a significant trend with higher categories of frailty, even after adjusting for all the independent variables and thus provide evidence that a true relationship may exist between them. The identification of the association of these independent variables with increasing frailty would make them amenable to intervention. These include improving lifestyle modifications such as reduction of alcohol intake and stop smoking campaigns. These advertisements and prevention usually focus on younger people and could prevent the onset of frailty in later life but more targeted efforts could be improved in older people who were already at risk of frailty. At a community or primary care level, identification of frail older people who are socially isolated and living alone in poor housing could improve the allocation of social services to those truly in need and help budget the resources appropriately to the frail

who are known to be at increased risk of adverse outcomes. At the level of the community, social services with the help of primary care professionals could identify those who are socially and physically isolated and improve their social participation of older people by promoting activities at a community or day centres for older people. These activities could include workshops for the promotion of a healthy lifestyle that provide nutritional and dietetic support, improve existing skills, group exercise and other efforts that would help maintain their independence at home.

The association with poor self rated health was particularly significant in both datasets when using the British FI. This was in keeping with findings of several large study populations [1, 20, 76]. This relationship could be explained by the fact that poor self rated health itself was a strong predictor of co-morbidity as well as mortality. However a more reasonable explanation may be that poor health was on the causal pathway between frailty and mortality.

The BWHHS and the MRC assessment study of older people are large, population-based cohorts which are representative of British community dwelling older people. It has nurse-verified data on a whole range of sociodemographic and lifestyle data; hence these are reflected on a wide range of locations in the UK. Other strengths of this part of the thesis include use of only complete cases in both cohorts, with imputed independent variables in the BWHHS cohort as well as less than 2% missing data in the variables from the MRC cohort. The respondents in the BWHHS study consisted of only women who were younger (<80 years old) compared to the respondents of the MRC study. This enabled important comparisons to be made between a younger older population with an older and larger population of men and women. The cross sectional nature of the data used in this analysis would make causal

inference difficult, hence it is possible, but unlikely, that the associations observed are susceptible to reverse causality. Also, as the populations were largely Caucasian, there was no ethnic minority population used for comparison of the association of these independent variables with frailty.

This part of the analysis has not only showed important expected associations with frailty(construct validity) but has replicated the associations that were reported in previous studies in the expected directions, hence providing external criterion validity to this new measure of frailty. The results also suggest that by modifying the factors that were strongly associated with frailty, it may be possible to postpone the onset of frailty or ameliorate its further development in older people.

Summary:

- This newly developed British Frailty Index had expected associations with sociodemographic and lifestyle variables and demonstrated both construct and external criterion validity.
- Frailty is associated with increased age, female sex, smoking, living alone, poor social contact and not owning one's own home but not with being single or taking increased and regular alcohol intake.
- This study provided greater evidence for the association of frailty with socioeconomic position by using the BWHHS SEP score which incorporated various markers of socioeconomic position.

Chapter 5: Predictive validity of the British Frailty Index.

Introduction

One of the main reasons for identifying frail elderly people was to devise ways to reduce their burden of suffering through the early detection of frailty, its prevention and delay of frailty outcomes. However, until a 'gold standard' definition of frailty is agreed upon, we can only rely on predictive validity of a frailty measure to provide means of choosing between alternative measures[127]. In terms of the performance of a measure, its validity relates to its ability to predict an external- distal criterion at a future time.

The identification and measurement of frailty had always been dependent on its definition, which varied greatly; and in the way it was measured. Hence, it would be expected that different measures would yield different results, especially with regards to their predictive performance. However, regardless of how each frailty measure was constructed, most have shown the ability to predict adverse outcomes, namely death [20, 74, 100], hospitalization [20, 41], institutionalization [20, 40]and falls[75, 79]. This good predictive ability may be related to the fact that some of these measures included indicators that were already closely correlated with the adverse outcomes. For example, a measure that included indicators such as age, multiple co morbidities and poor self rated health which are highly correlated with death would certainly have a greater ability to predict death than one that did not.

Since it is regarded as a latent vulnerability in older people[2],frailty was not something which could be observed or measured directly.The British Frailty Index, a purely measurement driven model was based on this theoretical premise and provided internal reliability in that it measured frailty itself and not other external criteria such as death. It did so by considering inter correlations of indicators that were associated with frailty as a latent factor and excluding those that were not.

In this chapter, death (all-cause mortality) was chosen as the external criterion because of its simplicity as an outcome measure. Furthermore, as frailty is on the trajectory between age and death, it can therefore be associated with mortality from all causes of death.

The main aim of this chapter was to assess the long term survival of respondents using the British Frailty Index (BFI). As this measure was developed from indicators measured at baseline (start of study) an analysis of survival over the whole follow up period was conducted to assess its predictive ability in both the BWHHS and MRC assessment study cohorts. However to understand the time series distribution in the various causes of death associated with frailty, a sub-analysis of cause specific mortality was undertaken. I also examined whether frailty was associated with an increased risk of first time hospitalization or institutionalization with data that was available in the MRC assessment study.

Data and Methods

Study Population

A detailed description of both datasets is available in Chapter 3. Briefly, all 4286 respondents (60% response rate) of the BWHHS who entered the study between April 1999 and March 2001 were included in this analysis. This was based on a sensitivity analysis using an unpaired t-test to account for missing data which did not importantly change any of the results. At this baseline period, the women recruited were aged between 60 to 79 years with a mean age of 68.9 years. All these women were followed up from the date of their entry into the study until the 10th of August 2008. This date referred to the censored date which indicates the last time their status was known (e.g. the last time they were known to be alive).

In the MRC assessment study, the analyses were carried out on 11195 out of 14639 respondents as they had complete data on indicators used to derive their respective frailty scores. Both the men and women aged between 75 years and 108 years with a mean age of 80.8 years. The men and women had a mean age of 80.4 years and 81.1 years respectively.

The British Frailty Index (BFI)

Frailty was represented as a continuous score, as this was estimated by the selected measurement model. An assessment was made of the distribution of scores in each dataset. These scores were then divided into quartiles, the first to fourth quartiles reflecting the lowest to highest levels of frailty. Each ascending quartile was labelled as ***'not frail/ low, mild, moderate and severe frailty.***

Outcomes

The principal outcome measures for hypothesis testing were **mortality, hospital** and **institutional admissions**. In both datasets, mortality follow-up was achieved by registering all eligible patients with Office of National Statistics (ONS) for notification of death, date and cause of death. In the BWHHS, 633 out of 4286 respondents have died (14.8%). In the mortality analysis, all the BWHHS women were followed up from the date of their entry into the study until the censored date of 10th of August 2008, giving a median follow up period of 8.2 years (range 4 months to 9.3 years).This date referred to the censored date which indicates the last time their status was known (e.g. the last time they were known to be alive).

Since their entry into the study until the 4th of October 2007, 7469 out of 11195 respondents of the MRC Assessment study have died (66.7%). Of the 6709 women, 4197 had died (62.6%). Of the 4486 men, 3272 had died (72.9%). In the mortality analysis, all MRC respondents were followed up for a median time of 7.9 years (range 22 days to 12.6 years). Specific cause of death referred to cause of death related to a particular system. These deaths occurred in the cardiovascular system, circulatory, respiratory, gastrointestinal, renal, genitourinary, musculoskeletal, nervous system, in addition to mental health, infection or diabetes related deaths as well odd and unknown causes of death. The main causes of death focused in this analysis were cardiovascular, cancer, respiratory and circulatory causes. The other causes were combined in view of the small number of deaths in each subgroup.

Information on hospitalization and institutionalization was only available for analysis in the MRC assessment study. Data on hospital admissions were collected for each respondent for a 2-year period from the time of the study

entry by using information from hospital discharge letters in the patients' GP records. Information collected included specialty, dates of admission and discharge, diagnoses, specialty of consultant. The discharge letter was considered to be a reliable source since this was the routine method of providing information to general practitioners from hospital services[115]. This analysis used 'time to first hospital admission' as the outcome measure. For this analysis, the MRC respondents were followed up for a median time of 2 years (range 22 days to 2 years)

Institutional admissions were collected on an ongoing basis for each patient from the date of the baseline assessment until a censor date (30th September 2000). In the analysis using admission into an institution as the outcome measure, all MRC respondents were followed up for a median time of 3.9 years (range 1.6 to 5.7 years).

Statistical analysis

A multivariate Cox proportional hazards model was employed to assess the independent contribution of the British FI to predicting adverse events such as all cause mortality, cause specific mortality, hospitalization and institutionalization. In both datasets 'time to event' was calculated from the respondent's date of entry into study to a 'censored' date. This date represented the respondent's date of death, first admission to hospital and date of entry into an institution. 'Censored' individuals referred to all subjects who had not experienced the event at the last date their status was known. They instead contribute to the number of respondents 'at risk' of the event up until this point. The ***proportional hazards assumption (PHA)*** was assessed in both datasets based on ***Schoenfeld*** residuals prior to the analysis. The assumption was that

the hazard ratio (the probability or risk of an event) for each respondent with or without the event, remained constant, i.e. did not change over time.

To further determine the association between frailty and its adverse outcomes, potential confounders were introduced into the Cox regression model such as age, sex(for the MRC study), marital status, housing tenure, living alone or otherwise, smoking, alcohol intake and socioeconomic position(SEP) scores (BWHHS only).These covariates were identified to be associated to both frailty and its adverse outcomes. They were identified on the basis of 'a priori' hypothesis, its association with the frailty (see Chapter 4) and its role as a risk factor for the outcome (e.g. death). Furthermore, confounders must not be a factor on the causal pathway between frailty and its adverse outcome. Crude, partially adjusted (age and/or sex) and fully adjusted models were fitted for these outcomes. A test for interaction was performed to assess whether there was a difference in the effect of frailty at different ages and by sex. Any evidence of interaction in this association was subjected to stratification of the Cox models by age and sex. The analysis was adjusted for the sampling design of the surveys resulting in robust standard errors clustering on town (BWHHS) and general practice (MRC).

Results

To assess the independent predictive validity of the BFI, I evaluated its association with three important adverse health outcomes; mortality (all cause and cause specific), first hospital admission and institutionalization. This was ascertained using Cox proportional hazards models based on these adverse events occurring throughout the length of follow-up in each dataset.

All cause mortality

In the BWHHS cohort of women whose median follow up period was 7.9 years, the cumulative incidence of mortality was 14.8%. This increased from 8.5% in the lowest quartile of frailty scores (low/not frail) to 24.9% in the highest quartile (severe frailty). In the MRC assessment study in which the respondents had a median follow up period of 8.2 years, the cumulative incidence of mortality was 66.7% and ranged from 53% in the lowest quartile up to 83% in the highest quartile of frailty. This incidence also increased similarly with age in both cohorts. ***Figures 5.1 and 5.2*** show the distribution of frailty among all respondents in both datasets who were still alive and those that had died, conducted at the end of the analysis time. These graphs demonstrated considerable overlap between the scores in those that were still alive or were dead at this time. This enabled cut-off points of varying degrees of frailty to be established with respect to all cause mortality; whereby those who were severely frail were dead by the end of the analysis.

Figure 5.1: Distribution of frailty scores among 4286 women of the BWHHS who were alive or dead at the end of the analysis.

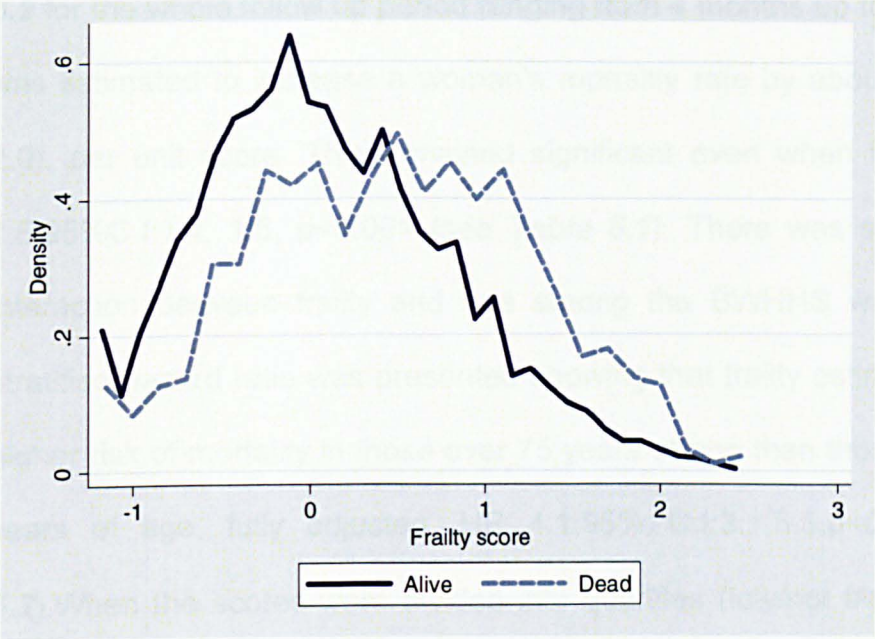
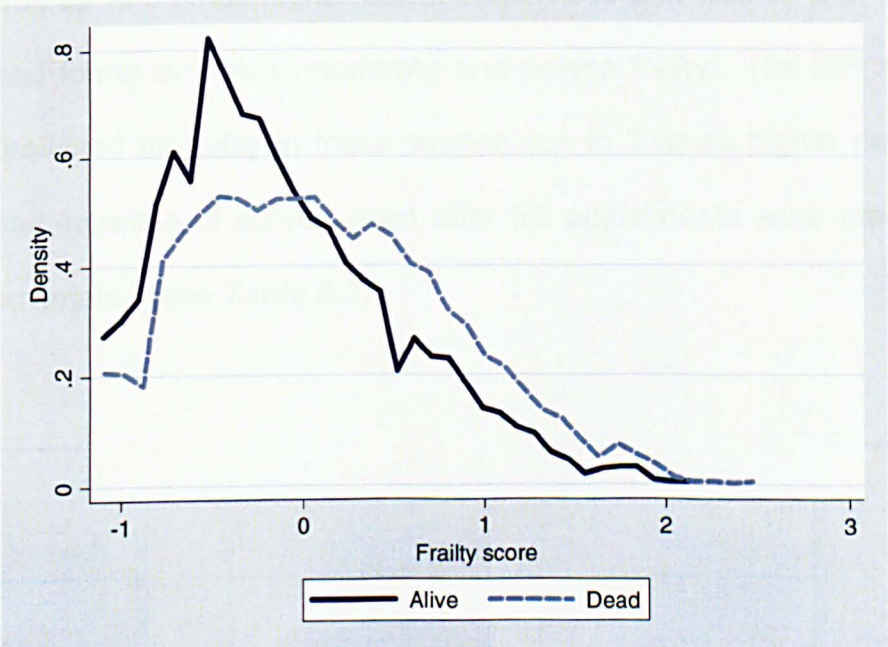


Figure 5.2: Distribution of frailty scores among 11195 men and women of the MRC assessment study who were alive or dead at the end of the analysis.



As there was no violation of the proportional hazards assumption in the BWHHS dataset, the hazard ratio for all cause mortality was displayed in ***Tables 5.1 and 5.2*** for the whole follow up period ranging from 4 months up to 9.3 years. Frailty was estimated to increase a woman's mortality rate by about 1.8(95%C.I.:1.7, 2.0), per unit score. This remained significant even when fully adjusted, HR 1.5:95%C.I:1.4, 1.6, p<0.001 (see ***Table 5.1***). There was strong evidence of interaction between frailty and age among the BWHHS women, so an age stratified hazard ratio was presented showing that frailty estimated a four times higher risk of mortality in those over 75 years of age than those aged 60 to 64 years of age, fully adjusted, HR 4.1,95% C.I:3.1,5.5,p<0.001 (see ***Table 5.2***).When the scores were divided into quartiles (low/not frail, mild, moderate and severe frailty), the HR was calculated for those who were in the second to fourth quartiles at baseline (mild, moderate and severe), each relative to those with the lowest quartile of frailty (not frail/low frailty) The crude HR for mortality was up to 3 times higher per unit frailty score in women with scores in the third and fourth quartiles (moderate and severe frailty). The BFI still independently predicted mortality in these women (up to 2 times higher risk of mortality per unit increase of score), even after full adjustments were made for associated covariates (see ***Table 5.3***).

Table 5.1: Hazard ratios for mortality per unit increase in frailty scores in 4286 BWHHS women

Frailty	Total(N)	Number of deaths	HR	95% C.I
Crude	4286	633(14.8%)	1.8	1.7-2.0
Age adjusted	4286	633(14.8%)	1.7	1.6-1.8
Fully adjusted*	4280	631(14.7%)	1.5	1.4-1.6
p-value **			<0.001	<0.001

*fully adjusted for age, socioeconomic position scores (SEP), smoking, alcohol intake, marital status, living alone and housing tenure.
**p value is for crude, age and fully adjusted HR.

Table 5.2: Age stratified association between frailty and all cause mortality in the BWHHS study

Age group	Number (%)	Crude	Fully adjusted
60-64	1180(27.5)	1.0	
65-70	1134(26.5)	1.6(1.2,2.2)	1.7(1.3,2.3)
71-74	1111(25.9)	2.5(1.8,3.5)	2.6(1.8,3.80
75-79	861(20.1)	3.8(2.9,5.1)	4.1(3.1,5.5)
Total	4286(100)		
p(trend)		<0.001	<0.001

† Fully adjusted refers to adjustments made for socioeconomic position scores (SEP), smoking, alcohol intake, marital status, living alone, and housing tenure.

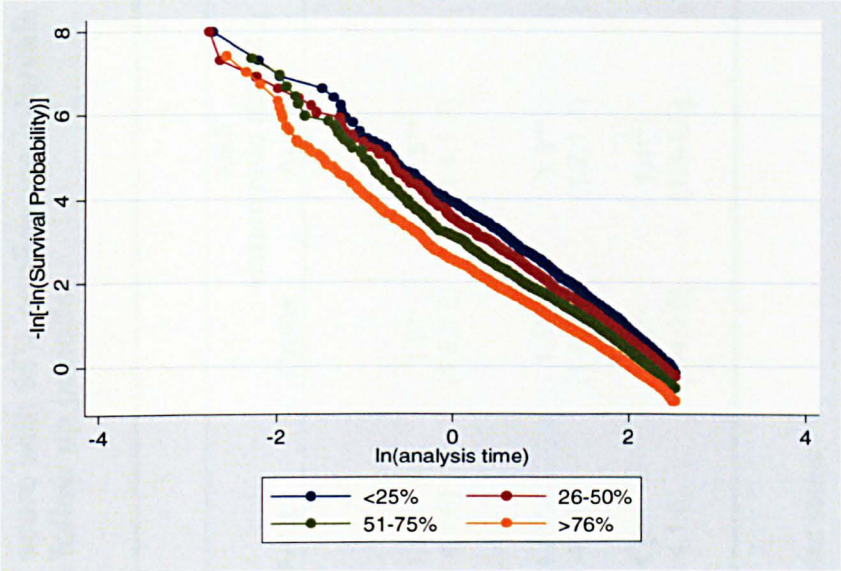
Table 5.3: Hazard ratios(95%C.I.) for mortality according to frailty category in 4286 BWHHS women

Hazard ratio	**Frailty category(scores per quartile)**			
	Low/Not frail (N=1072)	**Mild (N=1072)**	**Moderate (N=1073)**	**Severe (N=1069)**
Crude	**1.0**	1.4*(1.0,1.9)	1.6**(1.2,2.2)	3.2**(2.5,3.9)
Age adjusted	**1.0**	1.3(1.0,1.8)	1.5*(1.1,2.0)	2.7**(2.2,3.2)
Fully-adjusted†	**1.0**	1.3(0.9,1.8)	1.4*(1.1,1.8)	2.3**(1.9,2.8)
p trend		<0.001	<0.001	<0.001

*p<0.05
**p<0.001
† Fully adjusted refers to adjustments made for age, socioeconomic position scores (SEP), smoking, alcohol intake, marital status, living alone, and housing tenure.

The survival experience of groups within the MRC assessment study was also compared with the hazard ratio using the Cox proportional hazards model. However, for the whole duration of analysis time (i.e. time of entry into study to exit date of 4th October 2007), the assumption of non-proportional hazards was violated. This violation is presented graphically in ***Figure 5.3*** where groups with different quartiles of the frailty score (adjusted for age and sex) were compared over the whole analysis time (log transformed). This graph suggests that the hazard ratio for each ascending quartile (mild moderate or severe frailty) relative to the 1st quartile of the frailty score (low/not frail) decreases with time, i.e. the lines converge over time. However, the plots should be parallel if the proportional hazards assumption were true. To fulfill the assumption of proportional hazards, the analysis time was split or divided into three shorter time periods: 0 to 2.5 years, 2.5 to 5.5 years and 5.5 to 12.6 years (end of follow up time). This resulted in three Cox regression models which are jointly presented in ***Table 5.4***.

Figure 5.3: Log-log plot of frailty survival curves per quartile, adjusted by age and sex.



In unadjusted analysis of all three Cox models, frailty independently predicted all cause mortality in both men and women of the MRC assessment study with hazard ratios ranging from 1.5 to 2.2,p<0.001. After adjusting for covariates, frailty remained a significant predictor of all cause mortality with hazard ratios ranging from 1.3 to 1.8, p<0.001 (see ***Table 5.4***). However, frailty doubled the mortality rate per unit score in the first 2.5 years of follow-up in both sexes, but this rate was attenuated in later periods of follow up as shown in ***Figure 5.4***. When the scores were divided into quartiles, frailty remained the strongest predictor of all cause mortality in the highest quartiles of frailty (moderate and severe frailty), even after fully adjusting for all covariates (see ***Table 5.5***).

There was weak evidence of interaction between frailty and different age groups as well as sex later in the analysis (after 5.5 years of follow up), p=0.08. Hence the third Cox model was stratified by age and sex as shown in ***Table 5.6***. Frailty remained a significant predictor of all cause mortality in both men and women up to the age of 85 years (p<0.001). In those aged over 85 years, this was only significant in men (p<0.05).

Table 5.4: Frailty and all-cause mortality: hazard ratios per unit increase in frailty score with 95% confidence intervals for men, women and total population in the MRC Assessment study population over three follow up periods.

	Follow up time (years)								
	0-2.5 Hazard ratio (95% C.I)			2.5-5.5 Hazard ratio (95% C.I)			>5.5 Hazard ratio (95% C.I)		
	Crude	Age	Full‡	Crude	Age	Full‡	Crude	Age	Full‡
Men	2.1** (1.9-2.4)	2.0** (1.8-2.2)	1.9** (1.7,2.1)	1.6** (1.5-1.8)	1.5** (1.4-1.7)	1.5** (1.4,1.6)	1.7** (1.5,1.8)	1.5** (1.4,1.7)	1.5** (1.4,1.7)
Women	2.2** (2.0-2.4)	1.9** (1.7-2.1)	1.8** (1.6,2.0)	1.8** (1.7-2.0)	1.6** (1.5-1.7)	1.5** (1.4,1.6)	1.5** (1.4,1.6)	1.3** (1.2,1.4)	1.3** (1.2,1.4)
Total	2.0** (1.9,2.2)	1.9**† (1.8,2.1)	1.8** (1.7,2.0)	1.7** (1.6,1.8)	1.6**† (1.5,1.6)	1.5** (1.4,1.6)	1.5** (1.4,1.6)	1.4**† (1.3-1.5)	1.4** (1.3,1.5)

** p<0.001
†adjusted by age and sex
‡fully adjusted by age, sex, smoking, alcohol intake, social contact, housing tenure, living alone and marital status,

Table 5.5: Hazard ratios per unit increase in frailty score in ascending quartiles of frailty in 11195 men and women of the MRC Assessment study (example of Cox model 1)

All cause mortality					
Men					
Frailty scores Quartile	**Total N**	**Number of deaths (%)**	**HR (95% C.I.)**	**Age adjusted HR (95%C.I.)**	**Fully adjusted HR (95% C.I.)**
1st	1393	838(25.6)	1.00	1.00	1.00
2nd	1191	822(25.1)	1.5(1.2,1.9) **	1.4(1.1,1.8)*	1.4(1.1,1.7)*
3rd	1045	835(25.5)	2.6(2.1,3.2) **	2.3(1.8,2.8) **	2.1(1.6,2.6) **
4th	857	777(23.8)	4.5(3.6,5.6) **	3.8(3.0,4.7) **	3.2(2.5,4.0) **
p trend			<0.001	<0.001	<0.001
Women					
1st	1629	764(18.2)	1.00	1.00	1.00
2nd	1506	823(19.6)	1.9(1.5,2.4) **	1.8(1.4,2.2) **	1.6(1.3,2.1) **
3rd	1695	1141(27.2)	2.8(2.2,3.7) **	2.4(1.8,3.1) **	2.3(1.8,3.0) **
4th	1879	1469(27.2)	5.0(4.0,6.2) **	3.7(2.9,4.7) **	3.3(2.6,4.4) **
p trend			<0.001	<0.001	<0.001
Total population†					
1st	3022	1602(21.4)	1.00	1.00	1.00
2nd	2697	1645(22.0)	1.6(1.4,1.9)**	1.6(1.3,1.8) **	1.5(1.2,1.7) **
3rd	2740	1976(26.5)	2.5(2.1,2.9) **	2.3(2.0,2.7) **	2.2(1.8,2.6) **
4th	2736	2246(30.1)	4.1(3.6,4.8) **	3.7(3.3,4.2) **	3.3(2.9,3.8) **
Total	11195	7469(100)			
p trend			<0.001	<0.001	<0.001

* p<0.05
**p<0.001
†total population age (and sex) adjusted HR
‡Fully adjusted refers to adjustments made for age, sex, alcohol, smoking, housing tenure, social contact, living alone and marital status.

Figure 5.4: Hazard ratio for mortality per unit increase in frailty scores within each time band in the MRC Assessment study

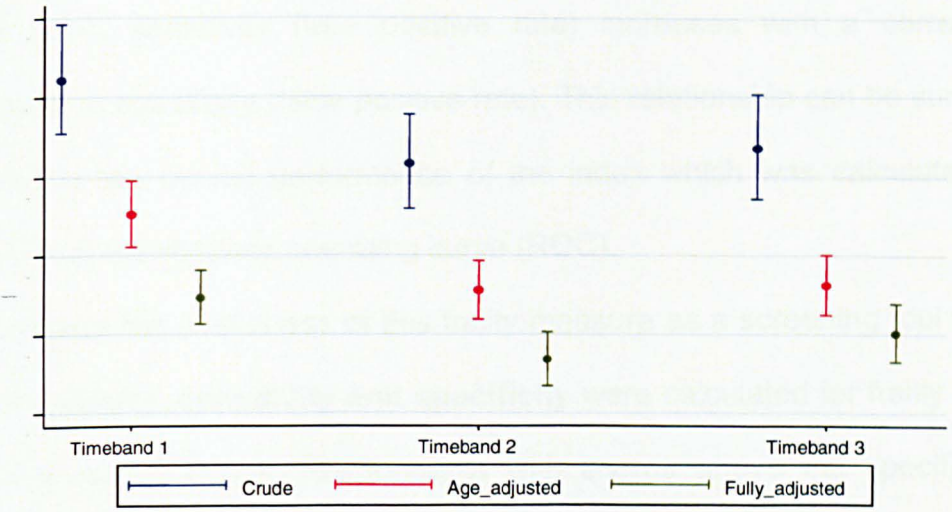


Table 5.6: Frailty and all cause mortality: Hazard ratios per unit increase in frailty score stratified by age and sex in 11195 men and women of the MRC assessment study, from 5.5 years to end of follow up period.

		All cause mortality					
Frailty	**Age(years)**	**Men**		**Women**		**Total**	
		HR	95%C.I	HR	95%C.I	HR	95% C.I
Crude	75-79	1.6**	1.5-1.8	1.4**	1.3-1.5	1.4**	1.3-1.5
	80-84	1.6**	1.4-1.8	1.5**	1.3-1.7	1.5**	1.3-1.6
	85+	1.4*	1.1-1.7	1.2*	1.0-1.4	1.2*	1.0-1.3
Partial adjusted	75-79	-	-	-	-	1.4**†	1.3-1.5
	80-84	-	-	-	-	1.5**†	1.4-1.6
	85+	-	-	-	-	1.2**†	1.1-1.3
Fully‡ adjusted	75-79	1.5**	1.4-1.7	1.3**	1.2-1.4	1.4**†	1.3-1.5
	80-84	1.5**	1.3-1.8	1.4**	1.2-1.6	1.4**†	1.3-1.6
	85+	1.4*	1.1-1.8	1.1	1.0-1.4	1.2**†	1.1-1.3

*p<0.05 **p<0.001
† adjusted for age and sex
‡Fully adjusted refers to adjustments made for sex, alcohol, smoking, housing tenure, social contact, living alone and marital status.

Sensitivity and specificity

As with any continuous scale of measurement, the different cut-off points in the British FI result in differing levels of specificity and sensitivity. When the cut-off point rises, sensitivity (true positive rate) increases with a corresponding decrease in specificity (false positive rate). This relationship can be summarized by testing the overall performance of the index which was calculated as the area under the receiver operating curve (ROC).

To evaluate the usefulness of this frailty measure as a screening tool to predict future mortality, **sensitivity and specificity** were calculated for frailty scores at different cut-off points. Respondents with scores above the specified cutoff point, were deemed to be frail, and below it, not frail. This showed that at lower cutoff points the measure was more sensitive but at higher cutoff points the measure was more specific.The area under the ROC curve was 0.64 ***(Figure 5.5)*** in the BWHHS population and 0.65, 0.63, 0.62 in Cox model 1, 2 and 3 of the MRC assessment study population ***(Figure 5.6)*** respectively, showing a moderate ability of the British FI in predicting all cause mortality.

Figure 5.5: Receiver Operating Curves assessing the ability of the British FI in predicting death in the BWHHS study population of 4286 women.

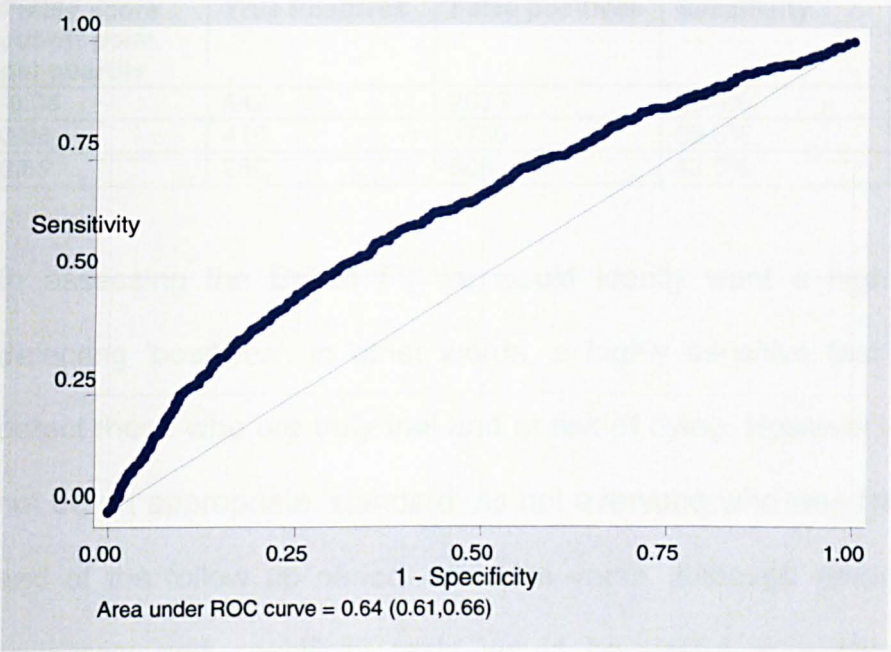


Figure 5.6: Receiver Operating Curves assessing the ability of the British FI in predicting death in the MRC assessment study.

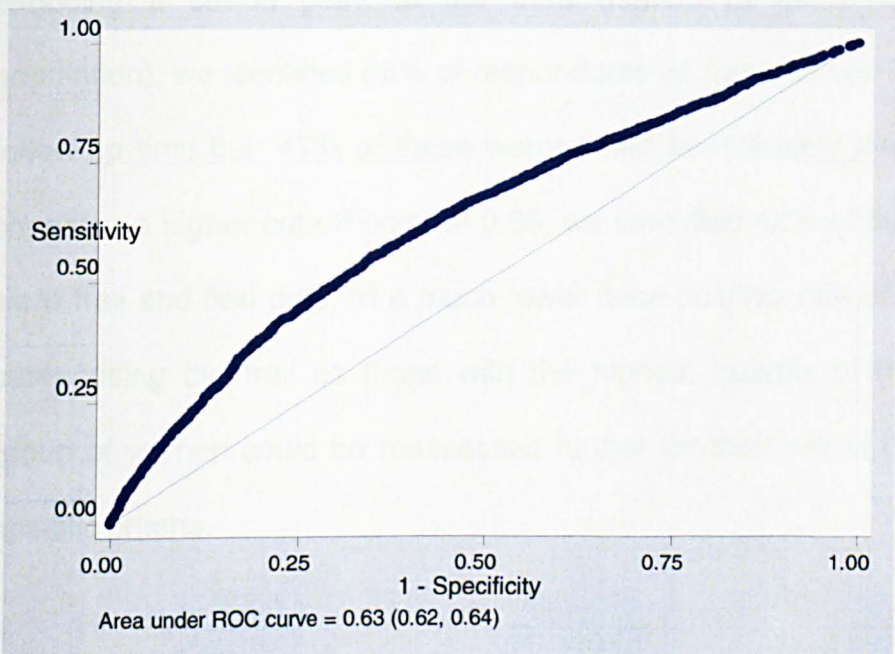


Table 5.7: Frailty score cut-off points in the 4286 women from the BWHHS study population

Frailty score cut-off point per quartile	True Positives	False positives	Sensitivity	1-Specificity (FPR)
-0.38	542	2673	85.6%	73.2%
0.08	415	1730	65.6%	47.3%
0.65	266	806	42.0%	22.1%

In assessing the British FI, we would ideally want a high success rate of detecting 'positives', in other words, a highly sensitive test that was able to detect those who are truly frail and at risk of dying. However, death status may not be an appropriate 'standard' as not everyone who was frail had died at the end of the follow up period, and vice versa. Although predicting death using sensitivity and specificity tests would be useful in a clinical setting as a screening tool, assessing the measure's ability to predict death using this test may not be entirely appropriate diagnostically. For example(see ***Table 5.7***), by choosing a cut-off point at the third quartile of frailty (0.08 in BWHHS population), we identified 66% of respondents as frail and had died at the end of follow up time but 47% of these women had been falsely identified. However, choosing a higher cut-off point of 0.65; we identified 42% of the population who were frail and had died, at a much lower false positive rate of 22%. Hence, re-categorising the frail as those with the highest quartile of frailty scores, this group of women could be reassessed further for their risk of death using more specific criteria.

Cause specific mortality

Further analysis into the association between frailty and specific causes of death was conducted on the MRC assessment study dataset. The proportional hazard assumption was fulfilled in all three Cox models for the periods specified in previous mortality analysis. ***Table 5.8*** shows the frequency of deaths from causes related to a specific system. The most prevalent cause of death in this study population was due to **cardiovascular disease (27.8%), cancer (13.3%)** and **respiratory disease (10.7%).**

Table 5.8: Frequency of deaths related to specific causes of 11195 respondents of the MRC study population with complete data on frailty.

Deaths	Population (N)	Percentage (%)
No deaths	3726	33.3
Cardiovascular disease(CVD)	3111	27.8
Cancer	1495	13.3
Respiratory disease	1193	10.7
Circulatory (not CVD)	213	1.9
Digestive	321	2.9
Other*	1136	10.1
Total	11195	100

*Other deaths due to diabetes, infection/parasitic, renal, nervous, mental, genitor-urinary (not renal), musculoskeletal system, unknown and odd causes of death.

Table 5.9: Frailty and cause specific mortality, hazard ratio per unit increase in frailty score in 11195 men and women of the MRC assessment study, in three different time bands.

Cause Of Deaths	Follow up time (years)								
	0-2.5			2.5-5.5			>5.5		
	Hazard ratio (95% C.I)			Hazard ratio (95% C.I)			Hazard ratio (95% C.I)		
	Crude	Partial	Full	Crude	Partial	Full	Crude	Partial	Full
Cardiovascular disease	2.1** (1.9,2.2)	2.2** (2.0,2.3)	1.8** (1.7,2.0)	1.8** (1.7,2.0)	1.9** (1.8,2.0)	1.7** (1.6,1.8)	1.6** (1.5,1.7)	1.7** (1.6,1.8)	1.5** (1.4,1.7)
Cancer	1.5** (1.4,1.7)	1.6** (1.4,1.8)	1.5** (1.3,1.7)	1.0 (0.9,1.2)	1.1* (1.0,1.3)	1.0 (0.9,1.1)	1.1* (0.9,1.3)	1.2* (1.1,1.4)	1.1 (1.0,1.3)
Respiratory	2.8** (2.5,3.1)	3.0** (2.7,3.4)	2.3** (2.0,2.7)	2.1** (1.9,2.3)	2.2** (1.9,2.5)	1.8** (1.6,2.1)	1.7** (1.5,1.8)	1.8** (1.6,1.9)	1.5** (1.4,1.7)
Circulatory	2.2** (1.8,2.7)	2.3** (1.8,2.8)	2.1** (1.7,2.6)	1.4* (1.1,1.8)	1.4* (1.1,1.8)	1.3* (1.0,1.6)	1.4** (1.2,1.7)	1.5** (1.2,1.7)	1.4** (1.1,1.7)
Others†	2.6** (2.2,3.1)	2.3** (1.9,2.8)	2.2** (1.7,2.8)	1.9** (1.6,2.2)	1.5** (1.3,1.8)	1.5** (1.3,1.7)	1.4** (1.3,1.6)	1.2** (1.1,1.4)	1.2** (1.1,1.4)

* p value<0.05
**p value<0.001
†Other deaths not related to specific systems
Fully adjusted refer to adjustments made for age, sex, alcohol, smoking, housing tenure, living alone, and marital status social contact and self rated health.

In the first two years of follow up, frailty doubled the mortality rate per unit increase of score in deaths from cardiovascular disease, circulatory and respiratory disease, even after fully adjusting for all covariates. This risk was attenuated with increasing lengths of follow up (see ***Table 5.9***).

First hospital admission

Frailty was found to be an independent predictor of the risk of first time hospitalization in the MRC assessment study population, with 1.5 times increase in risk after fully adjusting for all covariates as shown in ***Table 5.10.*** There was evidence of interaction between frailty and sex ($p<0.05$) but not with age and hence the data was stratified by sex. This showed that frailty predicted a slightly higher risk of the first hospital admission in men compared to women (HR 1.6 versus HR 1.5). When the scores were divided into quartiles, relative to the lowest quartile, frailty doubled the risk of a first hospital admission in the highest quartile, even after adjusting fully for all covariates (see ***Table 5.10***).

Table 5.10: Frailty and first hospital admission, hazard ratio per unit increase in frailty score in 11195 men and women of the MRC assessment study.

	First Hospital admission					
Frailty	**Men**		**Women**		**Total**	
	HR	**95%C.I**	**HR**	**95%C.I**	**HR**	**95% C.I**
Crude	1.7**	1.5-1.8	1.6**	1.5-1.7	1.6**	1.5-1.6
Age adjusted	1.6**	1.5-1.7	1.5**	1.4-1.6	1.6**†	1.5-1.6
Fully adjusted	1.6**	1.5-1.7	1.5**	1.4-1.6	1.5**	1.4-1.6

* p value<0.05
**p value<0.001
†adjusted by age and sex
‡Fully adjusted refer to adjustments made for age, sex, alcohol, smoking, housing tenure, living alone, and marital status social contact and self rated health.

Table 5.11: Frailty and first hospital admission, hazard ratio per unit increase in frailty score by frailty category in 11195 men and women of the MRC assessment study.

Hazard ratio	Frailty scores per quartile			
	Low/Not frail	Mild	Moderate	Severe
Crude	1.0	1.3**(1.2,1.5)	1.8**(1.6,1.9)	2.3**(2.1,2.5)
Partially adjusted†	1.0	1.3**(1.2,1.5)	1.7**(1.6,1.9)	2.3**(2.0,2.5)
Fully-adjusted‡	1.0	1.3**(1.1,1.4)	1.7**(1.5,1.9)	2.2**(2.0,2.4)
p trend		<0.001	<0.001	<0.001

* p value<0.05
**p value <0.001
†adjusted by age and sex
‡Fully adjusted refer to adjustments made for age, sex, alcohol, smoking, housing tenure, living alone, marital status, social contact and self rated health.

Institutional admission

Frailty was found to be an independent predictor of institutionalization in both men and women of the MRC assessment study. As shown in ***Table 5.12***, frailty doubled the rate of institutionalization in both men and women in this population with a slight attenuation in the rate after fully adjusting for all the covariates and was higher in men than women. In ***Table 5.13***, frailty increased the rate of institutional admission by nearly three times in those with the highest quartile of score (severe frailty) even after fully adjusting for all the covariates.

Table 5.12: Frailty and risk of institutionalization: hazard ratios with 95% confidence intervals for men and women in the MRC Assessment study population

Frailty	Institutionalization					
	Men		Women		Total	
	HR	95%C.I	HR	95%C.I	HR	95%C.I
Crude	2.2**	1.9-2.5	1.9**	1.6-2.2	2.0**	1.8-2.2
Age adjusted	1.9**	1.6-2.3	1.6**	1.3-1.8	1.7**†	1.5-1.9
Fully adjusted‡	1.7**	1.4-2.0	1.5**	1.2-1.7	1.5**	1.3-1.7

**p value<0.001
†adjusted by age and sex
‡Fully adjusted refers to adjustments made for age, sex, alcohol, smoking, housing tenure, living alone, marital status, social contact and self rated health.

Table 5.13: Frailty and institutional admission, hazard ratio per unit increase in frailty score by frailty category in 11195 men and women of the MRC assessment study.

Hazard ratio	Frailty scores per quartile			
	Low/Not frail	Mild	Moderate	Severe
Crude	1.0	1.7**(1.3,2.1)	2.1**(1.7,2.5)	4.2**(3.3,5.3)
Partially adjusted†	1.0	1.5*(1.2,1.9)	1.7**(1.4,2.0)	2.9**(2.3,3.7)
Fully-adjusted‡	1.0	1.4*(1.1,1.8)	1.5**(1.3,1.8)	2.5**(1.9,3.2)
p trend		<0.001	<0.001	<0.001

* p<0.05
**p value <0.001
† adjusted by age and sex
‡Fully adjusted refers to adjustments made for age, sex, alcohol, smoking, housing tenure, living alone, marital status and social contact.

Discussion

The predictive validity for adverse outcomes of the British FI was assessed in this chapter. Using this measure, frailty was shown to be an independent predictor of all cause mortality in these two cohorts of community dwelling older people after adjustments were made for age, sex, socioeconomic position, living alone, marital status, social contact and housing tenure. In similar large study populations [20, 41, 74, 100] there were great variations in the potential confounders adjusted for with little attention focused on how they might explain the association between frailty and its adverse outcome. Efforts to rigorously control for potential confounding may also reduce this association to non significance and result in over adjustments due to co-linearity of the covariate with the explanatory variable (frailty). In this study, this was seen with the 'self rated health' and 'own age activity' covariate which was excluded from the analysis. The variations in number and type of potential confounders may often reflect the type of frailty measure used for example; a more physiological measure such as Fried's frailty phenotype (adjusted with sixteen covariates) were additionally adjusted for objective measures of subclinical disease such as brachial and tibial systolic blood pressure, abnormal left ventricular ejection fraction, major ECG abnormalities[20].

Although age was included in the Cox model in both cohorts, there was strong evidence of interaction by age in the association between frailty and mortality. Hence age stratified hazard ratios were presented where the effect of frailty on all cause mortality differs according to different age categories, with an increase in frailty estimated mortality in higher age groups seen in both cohorts. A distinct finding of this analysis was that frailty was a stronger predictor of all- cause

mortality at earlier periods of follow-up (within the first 2.5 years from baseline) in the larger and older MRC assessment study population. As those with a severe degree of frailty were already dead earlier in the follow up period, this analysis identified the more robust in the population but also and more importantly, those who were frail but still surviving in the community. It is the frail survivors (with mild to moderate frailty) who could be potential targets in the longer term for preventive or therapeutic strategies aimed at reducing their risk for further adverse outcomes. There were no significant differences in frailty related mortality between the sexes at earlier ages (75-79, 80-84 years) but frailty predicted a higher mortality rate in men over the age of 85 years which was an expected result as men do have a higher mortality than women at extremes of age.

Further analysis on this dataset showed that frailty was a strong independent predictor of cardiovascular, circulatory and respiratory related deaths. Frailty was also an independent predictor of death from cancer in the MRC respondents but only in the first two and a half years of follow up. This suggests that this could be related to survival bias associated with the type of cancer (whether the cancer was slow growing or rapidly progressive could affect time to death).

Another important finding was that frailty was a strong independent predictor of first time hospitalization and institutional admissions in the MRC cohort, confirming the findings of other large population studies [1, 20, 40]. Frailty also predicted a higher rate of institutionalization in men even after fully adjusting for all the covariates.

All these findings were most significant at the third and fourth quartiles of frailty scores where respondents were classified as moderate or severely frail. The

decision of which cut-off point to use when determining who was frail or not at baseline would highly depend on what this measure was used for. As a screening tool it could be used to correctly identify those at highest risk of adverse outcome, but at a compromise on its specificity and result in a high false positive rate. As this measure was highly sensitive in capturing those who were frail but still alive, this measure has the potential to target the severely frail survivors in the population (at the highest quartile of score) and enable more sensible decisions to be made on which type of service (preventive, rehabilitative or even palliative) was to be extended to this highly vulnerable group of elderly people. This would help reduce the burden of suffering that they endure as well as help reduce the cost on the health service. As mentioned earlier, longer term goals of prevention, therapy or intervention could target those with mild to moderate degree of frailty to reduce their future risk of adverse outcomes.

A limitation of this analysis was that socioeconomic position was only measured and adjusted for in the BWHHS cohort using the SEP score. Also both cohorts consisted of a large Caucasian majority, therefore the effect of frailty in predicting adverse outcomes could not be inferred to those belonging to an ethic minority group. Another limitation is that only the risk for a first or single hospitalization was examined in this study. As frailty strongly predicted risk of first hospitalization, future work with this new frailty measure should perhaps focus on repeated hospital admissions which are a common problem among elderly people and drive a large part of the burden and costs associated with frailty.

Lastly, future work will involve refinement of this measure by reducing the number of frailty indicators, selecting those indicators with greater weights and

rescaling the score so that it is more user friendly, especially for use in a primary care setting.

In conclusion, this study provides good insight into the predictive validity of the British Frailty Index and supports its relationship with adverse outcomes that occur early as well as those occurring over long follow up periods. Hence, it should provide a convenient and cost-effective measure for guiding public health efforts in the community dwelling older people.

Summary

- Frailty is a strong independent predictor of all cause mortality in both the BWHHS and MRC assessment study cohorts, especially in higher age groups.
- The British FI is the first measure to independently predict cause-specific mortalities from cardiovascular, respiratory and circulatory causes among community dwelling older people in the U.K.
- Frailty is also a strong independent predictor of time to first hospitalization and institutionalization on both men and women.
- The British FI has potential use in targeting the severely frail survivors in the population (at the highest quartile of score) to enable more sensible decisions to be made on which type of service (preventive, rehabilitative or even palliative) was to be extended to this highly vulnerable group of older people.

Chapter 6: Comparison between the British frailty index with a well known index and other single markers of frailty.

Introduction

In the previous chapters, I have examined the construct, external criterion and predictive validity of the British Frailty Index (FI). The question posed in this chapter was whether this newly developed measure was better at predicting all cause mortality than another well validated measure, in addition to single markers of frailty.

The measure chosen for comparison with the British FI was the Canadian Study of Health and Aging (**CSHA) frailty index**, which was initially developed for elderly Canadians. Apart from being closely related to a more multi dimensional concept of frailty, the CSHA index is one of the most widely published frailty measures, having been evaluated in many study populations [42, 78, 102, 105]. In constructing this index, *Rockwood et al* aimed for a measure that could evaluate impairments in many body systems, accommodate change, was graded and conceptually simple. By combining items in a single index, frailty was explicitly based on the idea that 'the more things individuals had wrong with them, the higher the likelihood that they would be frail'.[107] This likelihood of frailty was associated with a greater risk of adverse outcomes. With regard to the specific nature of the variables that were included in the frailty index, Rockwood et al reported that when a

sufficiently large number of variables were considered (whether 40, 70 or even 90), the variables could be selected as different combinations yielded comparable predictions of the risk of adverse outcomes[40]. The individual variables in the CSHA were 'unweighted' as the frailty index treated all the problems equally. Other studies have reproduced a high correlation between an equal weights deficit count and mortality which indicates this approach to frailty measurement is valid [40, 80, 105]. However, the British FI, derived using factor analysis, adjusts for measurement error and assigns relative weights to each frailty indicator in association with frailty. This provides a more refined model which identifies the specific contribution of variables to best explain the underlying construct of frailty and distinguish those who are frail from those who are not.

Despite the many different measures used to identify frailty and factors associated with its concept, there is general agreement amongst frailty researchers that a core feature of frailty is an increased vulnerability to stressors due to impairment of multiple inter-related physiological systems[73]. This negative interplay involves several key systems, especially the muscular, neuroendocrine, and immune systems to create a downward spiral that we eventually recognize as frailty [29]. On this basis, several correlates or markers of frailty have been proposed in order to identify frailty more precisely[28]. Although currently, no single marker could fully assess the complexity of frailty, there is growing evidence that certain contributing factors could facilitate a person's entry into the frailty state, or a define a pre-frailty state. These include factors that have been implicated in the

pathophysiology of frailty such as chronic inflammation, which may be due to regulatory failure of the immune system during the aging process[28, 29].The inflammatory markers most studied with respect to frailty, aging and survival have been interleukin-6 (IL-6)[31, 32, 128], tumour necrosis factor alpha (TNF-α)[129] and C-reactive protein (CRP)[33, 130]. These markers are not the only mediators of the adverse outcomes associated with frailty. In addition to CRP, markers of coagulation such as fibrinogen and D-dimer are also implicated with frailty in view of their role in the generation of atherosclerosis and prediction of cardiovascular outcomes [31, 131]. Other markers studied in relation to frailty include metabolic markers such serum albumin[129], haemoglobin [132], white cell count[32, 133], cholesterol [84, 134] and glucose[31]. Physical markers such as sarcopenia (degenerative muscle loss) which has been indirectly associated with leptin levels in the blood through modulations of growth hormone secretion, provide another frailty criteria which is included in the widely known phenotype of physical frailty by Fried et al [20]. However, further studies have suggested a link between frailty and obesity in older people , specifically in relation to body mass index(BMI) and central obesity[121, 135].Orthostatic hypotension thought to be a normal accompaniment of aging, reflects baroreceptor dysfunction and decreased responsiveness to sympathetic stimulation in older people[136]. This may also be related to physical frailty, which is conceptualized as a reduction in physiological reserve capacity.

Other possible correlates of frailty include self rated health, a subjective evaluation by an individual of their overall health status, which is also an important predictor of mortality among community living elderly people[16].

With this background in mind, there were two **aims** in this chapter. The first was to assess how the small, weighted British FI compared to a larger, unweighted additive type of measure (CSHA frailty index) in predicting adverse health outcomes, namely all cause mortality, institutionalization and hospitalization. To provide a more balanced comparison, the predictive validity of an abridged CSHA FI with an equal number and type of variables to the British FI was also compared. The second aim was to assess the correlation of the British FI with single markers of frailty and compare its predictive ability with these single markers using data from the BWHHS cohort.

Methods

Study population

The study populations used for this analysis was as detailed in Chapter 5. Briefly, all 4286 women, aged between 60 to 79 years in the BWHHS dataset were included in the first part of the analysis. There were 633 deaths until censored date of 10th August 2008 giving a median follow up period of 8.2 years (range 4 months to 9.3 years). In the MRC assessment study, the mortality analysis was carried out on respondents with complete data. Since entry into the study until the 4th of October 2007, 7469 out of 11195 respondents of the MRC Assessment study have died (66.7%). Of the 6709 women, 4197 had died (62.6%). Of the 4486 men, 3272 had died (72.9%). In the mortality analysis, all MRC respondents were followed up for a median time of 7.9 years (range 22 days to 12.6 years. When 'time to first hospital admission' was used as the outcome measure, the MRC respondents were followed up for a median time of 2 years (range 22 days to 2 years).This shorter follow up period for hospitalization data was because these data were not collected for the full duration of follow up. For similar reasons, in the analysis using admission into an institution as the outcome measure, all MRC respondents were followed up for a median time of 3.9 years (range 1.6 to 5.7 years).

The second part of the analysis which compared the British FI with single measures of frailty was confined to 3331 women who had complete data on all the blood markers of frailty including physical measurements of blood pressure, height, weight, waist and hip and nurses' estimation of life

expectancy. All these were collected at baseline examination and interview by a trained nurse.

Replication of CSHA measure using the BWHHS and MRC assessment cohorts

The CSHA Frailty Index (FI) score was calculated as the proportion (from a given set) of deficits present in a given individual, and indicating the likelihood that frailty was present. The ranges of deficits were counted from variables collected from self reports or clinically designated symptoms, signs, disease and disabilities that were readily available in survey or clinical data. The variables for each FI were recoded as binary with value '1' when the deficit was present and '0' when absent. For example, if a total of 20 deficits were considered, and the individual had 3, then the frailty index value is 3/20=0.15.

FI=X/Y=Sum of deficits/total number of variables

Using the equation above, I replicated two versions of the CSHA FI using the method above using unweighted variables derived from the BWHHS and MRC assessment study datasets. The difference between the two versions was that the first version was larger (51 and 44 variables in the BWHHS and MRC study dataset respectively) whereas the second was calculated from the same type and number of variables as the British FI (36 and 35 variables which were identified via factor analysis in the BWHHS and MRC study dataset respectively). Details of the variables included in each CSHA FI are given in the ***Appendix.***

Single markers used in this analysis

At the start of the study, the respondents were assessed by research nurses, who apart from completing the survey, were responsible for taking blood samples and measurements of height, weight, waist and hip measurements. Blood was drawn from the respondents who attended the interview following an overnight fast using standardized protocols. Based on the expectation that a 65 year old woman would live on average, another 20 years, the nurses were asked to provide an estimation of life expectancy in years that the respondent might expect.

The single markers identified were those available mainly to the BWHHS dataset. These included blood markers (inflammatory and metabolic) such as IL-6, CRP, D-dimer, white cell count, haemoglobin, albumin, glucose and total cholesterol. Unfortunately, TNF-α and leptin levels were excluded as they were only measured on small sub-sets of respondents (n=500, for case-control studies) and therefore demonstrated very limited statistical power to this part of the analysis. Other single measures examined include BMI, which was calculated by dividing the respondent's weight (kg) by height squared (m).Waist hip ratio (WHR) was calculated as the ratio of measured waist circumference (side measurements at the waist identified as midpoint between the iliac crest below and the lower edge of the ribs above) to hip circumference measured around the hips at maximum point of circumference. Orthostatic hypotension (OH) was calculated from the respondents' blood pressure levels which were measured at the time of the interview, with two sitting measurements followed by two standing measurements (all at 1-min intervals). OH was defined as a drop of

≥10mmHg in diastolic blood pressure and/or a drop of ≥20mmHg in systolic blood pressure on standing (based on the differences between the first sitting and fourth standing measurements, within 3min of standing)[137]. The respondents' perception of their health status (i.e. self rated health ranging from excellent to poor) was also included in this analysis. Data was presented as a mean ±SD for the variables used here so as to standardize the increase in hazard ratio per 1 standard deviation of the continuous variables measured.

Data analysis

Cox proportional hazards regression analysis was used to compare the difference between hazard ratios for adverse outcomes when using the British FI and the CSHA frailty index. Hazard ratios for all cause mortality were compared in both the BWHHS and MRC assessment study datasets and risk of first hospital admission and institutionalization was assessed using data which was only available in the MRC assessment study.

The correlations between frailty (using the British FI) and each of the single measures of frailty were calculated using Pearson's correlation. To evaluate the relationship between each single measure with frailty level, Pearson κ^2 tests were used for categorical variables and analysis of variance F tests were used for continuous variables. Each level of frailty represents increasing quartiles of the respondent's score ranging from 'no/low frailty' to 'mild', 'moderate' and 'severe' frailty. The comparison of hazard ratios for all cause mortality between the British FI and single measures of frailty was made using the BWHHS dataset. In both datasets, the covariates introduced

into the Cox regression model were age, sex(for the MRC study), marital status, housing tenure, living alone or otherwise, social contact(good or poor),smoking, alcohol intake and socioeconomic position (SEP) scores (BWHHS only). Crude, partially adjusted (age and/or sex) and fully adjusted models were fitted for these outcomes. Additionally, as a summary index of the performance of each measure, the area under the receiver operating curve (ROC) was calculated, where the greater the area, the greater the test performance. This curve was generated from different cut-off points calculated along a continuous scale of measurement, resulting in a graph which plots sensitivity (y axis) versus 1-specificity (x axis).

Results

Descriptive statistics are shown in ***Table 6.1*** below comparing the British FI and the CSHA FI using both the BWHHS and MRC assessment study cohorts. As these measures were not normally distributed in both these cohorts, the frailty scores were presented median and inter-quartile range (IQR).

Table 6.1: Median scores with inter-quartile range of the British FI and CSHA FI in both the BWHHS and MRC assessment study cohorts.

Frailty	BWHHS			MRC Assessment study		
	Number	Median	IQR	Number	Median	IQR
British FI	4286	.077	(-0.38,0.65	11195	0.04	(-0.44, 0.63)
CSHA FI*	4286	0.16	(0.10,0.25)	11195	0.23	(0.15,0.44)
CSHA FI**	4286	0.17	(0.11,0.28)	11195	0.18	(0.12,0.28)

* CSHA FI using 51 or 44 variables in the BWHHS and MRC assessment study respectively
** CSHA FI using 36 or 35 variables in the BWHHS and MRC assessment study respectively

Figures 6.1 and 6.2 demonstrate the spread of frailty scores as measured using the British FI, the CSHA FI as well as the abridged version of the CSHA FI. These figures show that in both cohorts, the British FI has greater variance, giving a more refined distribution of frailty and serves as a better population metric compared to the CSHA FI.

Figure 6.1: Graph box showing median and inter quartile ranges of the British FI and the CSHA FI calculated in 4286 BWHHS cohort.

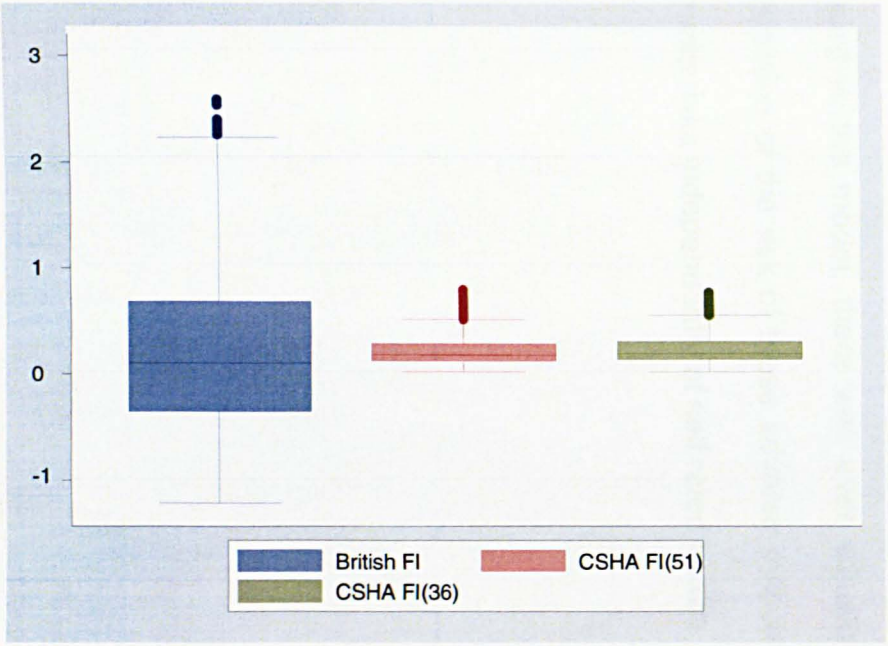
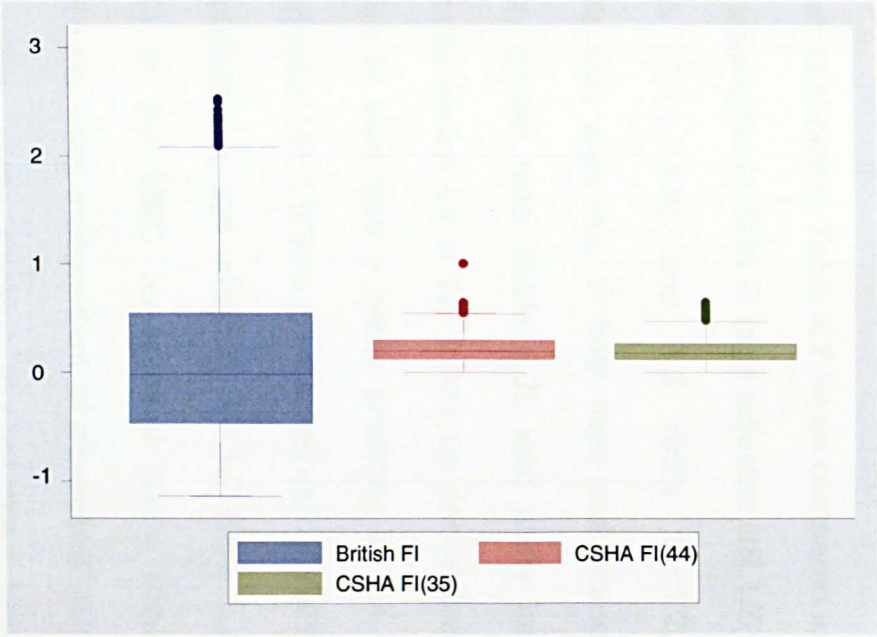


Figure 6.2: Graph box showing median and inter quartile ranges of the British FI and the CSHA FI calculated in 11195 men and women of the MRC assessment study cohort.



The British FI was a better predictor of all cause mortality in the women of the BWHHS cohort as shown in ***Table 6.2***, when compared to both the larger and the reduced unweighted CSHA FI (age adjusted HR 1.7(95% C.I:1.6,1.7)versus 1.4(95% C.I:1.3,1.4) and 1.3 (95% C.I:1.2,1.4), $p<0.001$ respectively). This was also true in both men and women of the MRC assessment study cohort (see ***Table 6.3***), with frailty being a stronger predictor of mortality earlier on in the follow up period (between 0 to 2.5 years). The British FI was also a better predictor of the risk of hospital admission; age adjusted HR 1.5(95% C.I:1.4,1.6) vs. 1.3 (95% C.I:1.2,1.4) as well as institutionalization (age adjusted HR 1.7 (95% C.I:1.5,1.9)vs. 1.4 (95% C.I:1.2,1.5) in the MRC assessment study cohort (see ***Table 6.4***).These predictions were independent of covariates such as age, sex, socioeconomic position scores, smoking, alcohol intake, living alone, marital status, housing tenure and social contact. When the covariate 'self rated health' was included in the model, there was over adjustment which did result in underestimation of the risk of these adverse outcomes. However, frailty estimated these risks independently of self rated health.

Table 6.2: Comparison of hazard ratios for mortality per unit increase in frailty scores in 4286 BWHHS women using three different measures

Frailty	Total(N)	British FI	CSHA FI(51)	CSHA FI (36)
Crude	4286	1.8(1.7-2.0)	1.4(1.4,1.5)	1.4(1.3,1.4)
Age adjusted	4286	1.7(1.6-1.8)	1.4(1.3,1.4)	1.3(1.2,1.4)
Fully adjusted*	4280	1.4(1.3-1.5)	1.3(1.2,1.4)	1.2(1.1,1.3)
p-value **		<0.001	<0.001	<0.001
Area under ROC curve		0.64(0.6,0.7)	0.67(0.6,0.7)	0.65(0.6,0.7)

*fully adjusted for age, socioeconomic status (SES), smoking, alcohol intake, marital status, living alone and housing tenure.

**p value is for crude, age and fully adjusted hazard ratio (HR).

Table 6.3: Comparison of hazard ratios for all cause mortality per unit increase in frailty scores in the MRC Assessment study using three different measures of frailty

Outcome	Follow up time (years)								
	0-2.5			2.5-5.5			>5.5		
	Hazard ratio (95% C.I)			Hazard ratio (95% C.I)			Hazard ratio (95% C.I)		
	Crude	Age	Full*	Crude	Age	Full*	Crude	Age	Full*
British FI									
All cause mortality	2.0** (1.9,2.2)	1.9** (1.8,2.1)	1.8** (1.7,1.9)	1.7** (1.6,1.8)	1.6** (1.5,1.6)	1.5** (1.4,1.5)	1.5** (1.4,1.6)	1.4** (1.3,1.5)	1.4** (1.3,1.5)
CSHA FI (44 variables)									
All cause mortality	1.6** (1.5,1.7)	1.5** (1.4,1.6)	1.5** (1.4,1.6)	1.4** (1.4,1.5)	1.3** (1.3,1.4)	1.3** (1.2,1.4)	1.3** (1.3,1.4)	1.2** (1.2,1.3)	1.3** (1.2,1.3)
CSHA FI (35 variables)									
All cause mortality	1.5** (1.4,1.5)	1.4** (1.3,1.4)	1.4** (1.3,1.4)	1.3** (1.3,1.4)	1.3** (1.3,1.4)	1.2** (1.2,1.3)	1.3** (1.2,1.3)	1.2** (1.1,1.2)	1.2** (1.2,1.3)

*fully adjusted for age, sex, smoking, alcohol intake, marital status, living alone, social contact and housing tenure

**p value<0.001

Table 6.4: Comparison of hazard ratios for hospitalization and institutionalization per unit increase in frailty scores in the MRC Assessment study using three different measures of frailty

Outcome	Hazard ratio (95% C.I) Crude	Age	Full*
British FI			
First hospital admission†	1.6**(1.5-1.6)	1.5**(1.4,1.6)	1.5**(1.4,1.6)
Institutionalization‡	2.0**(1.8,2.2)	1.7**(1.5,1.9)	1.6**(1.4,1.8)
CSHA FI (44 variables)			
First hospital admission†	1.4**(1.3,1.4)	1.3**(1.2,1.4)	1.3**(1.2,1.4)
Institutionalization‡	1.5**(1.4,1.6)	1.4**(1.2,1.5)	1.3**(1.2,1.4)
CSHA FI (35 variables)			
First hospital admission†	1.3**(1.2,1.3)	1.3**(1.2,1.3)	1.3**(1.2,1.3)
Institutionalization‡	1.5**(1.4,1.6)	1.3**(1.2,1.4)	1.3**(1.2,1.4)

*fully adjusted for age, sex, smoking, alcohol intake, marital status, living alone, social contact and housing tenure.

**p value<0.001

† refers to time to first hospital admission in the first two years of follow up.

‡ refers to time to institutionalization over a median time of 3.9 years of follow up

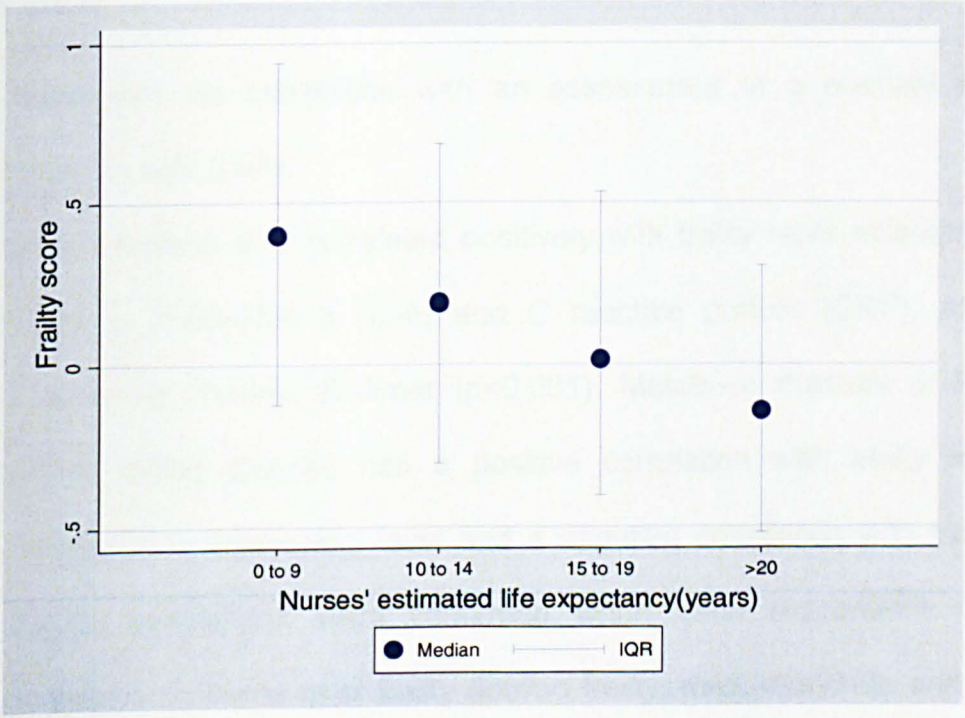
Table 6.5: Correlations between frailty as defined by the British FI and single markers of frailty in the BWHHS dataset*

	Frailty	IL-6	CRP	D-Dimer	Albumin	Glucose	Cholesterol	Hb	WCC	BMI	WHR	OH	Est. life exp.	Self Rated Health
Frailty	1													
IL-6	**0.14(<0.0001)**	1												
CRP	**0.16(<0.0001)**	0.37	1											
D-Dimer	**0.1 (<0.0001)**	0.18	0.18	1										
Albumin	**-0.11(<0.0001)**	-0.15	-0.22	-0.13	1									
Glucose	**0.16(<0.0001)**	0.05	0.1	-0.01	-0.04	1								
Cholesterol	**-0.08(<0.0001)**	-0.08	-0.05	-0.04	0.2	-0.05	1							
Haemoglobin(Hb)	**-0.03(<0.05)**	-0.05	-0.08	-0.09	0.19	0.06	0.08	1						
White cell count(WCC)	**0.05(<0.05)**	0.08	0.09	0.03	0.01	0.03	0.02	0.03	1					
Body Mass Index(BMI)	**0.32(<0.0001)**	0.08	0.16	0.06	-0.14	0.15	-0.02	0.08	0.02	1				
Waist hip ratio(WHR)	**0.26(<0.0001)**	0.06	0.15	0.02	-0.04	0.18	0.03	0.1	0.05	0.37	1			
Orthostatic hypotension(OH)	**0.01(0.58)**	0	0	0	0.02	0.02	0.01	0.01	0	-0.03	1			
Estimated life expectancy	**-0.26(<0.0001)**	-0.07	-0.09	-0.09	-0.09	-0.1	0	0	-0.06	-0.13	-0.13	-0.05	1	
Self rated health(SRH)	**0.28(<0.0001)**	0.06	0.06	0.05	-0.05	0.09	0	-0.02	0.01	0.09	0.05	0.01	-0.1	1

* Correlations were conducted on 3331 women with non missing data on the variables above using Pearson's correlation.

The strength of relationships between frailty and single measures of frailty are shown in ***Table 6.5***. The strongest relationship with frailty as measured using the British Frailty Index, were with BMI, self-rated health status, waist hip ratio as well as the nurses' estimation of life expectancy. BMI, self rated health and waist hip ratio were positively correlated with frailty ranging from 0.26 to 0.38 ($p<0.001$). The nurses' estimation of life expectancy however, correlated negatively with frailty($r= -0.26, p<0.001$), meaning that those with higher estimated years of life expectancy had lower frailty scores and were therefore less likely to be frail (see ***Figure 6.3***).

Figure 6.3: The association between frailty and nurses' estimate of life expectancy in the BWHHS study



When comparing the frequencies of estimated life expectancy by frailty categories, there were more than twice as many respondents with a lower

estimated life expectancy(0 to 9 years) in the severe frailty category compared to the not frail/low frailty category (34.7% versus 13.5%). Correspondingly, there were twice as many respondents with a high estimated life expectancy (> 20 years) in those who were not frail compared to those with severe frailty (39.7 versus 17.5) (see ***Table 6.6*** below).

Table 6.6: Nurses' estimated life expectancy by frailty category.

Nurses estimated life expectancy (years)	Low/Not frail (%)	Mild frailty (%)	Moderate frailty (%)	Severe frailty (%)	Total (%)
0-9	117(13.5)	139(16.3)	188(22.1)	242(34.7)	686(20.6)
10-14	223(25.7)	244(28.7)	280(32.9)	248(32.6)	995(29.9)
15-19	183(21.1)	185(21.7)	164(19.3)	139(18.2)	671(20.1)
20 or more	344(39.7)	283(33.2)	219(25.7)	133(17.5)	979(29.4)
Total	867(100)	851(100)	851(100)	762(100)	3331(100)

There was no correlation with an assessment of a postural drop in blood pressure with frailty.

Blood markers that correlated positively with frailty were inflammatory markers such as interleukin 6 (IL-6) and C reactive protein (CRP), as well as the coagulation marker, D-dimer ($p<0.001$). Metabolic markers of frailty such as fasting blood glucose had a positive correlation with frailty whereas blood albumin and cholesterol level had a negative correlation with frailty ($p<0.001$). These correlations were confirmed when each respondent was assessed according to the level of frailty (low/no frailty, mild, moderate and severe frailty) as shown in ***Table 6.7***. Levels of markers such as IL-6, CRP, D-dimer and fasting glucose were significantly higher in those classified as severely frail. This group also had significantly lower levels of total cholesterol, albumin and haemoglobin. Respondents classified as being severely frail were associated

with lower estimated years of life expectancy, poor perception of their health status (self rated health) and a higher BMI and waist hip ratio compared to those who were not frail or had low levels of frailty.

The results of the Cox regression analysis in ***Table 6.8*** showed that 'self rated health', frailty as measured by the British FI, and waist hip ratio were independent predictors of all cause mortality in the BWHHS respondents. Higher levels of IL-6, CRP and D-dimer were associated with a higher risk of all cause mortality ($p<0.001$). However, higher estimated life expectancy in years, higher albumin and a higher total cholesterol level were associated with a significantly lower risk of all cause mortality ($p<0.001$).

The analysis using area under the ROC curve was used to compare the ability of each measure to predict all cause mortality. Both the larger and reduced version of the CHS index had a higher calculated area than the British measure: 0.67(95%C.I:0.65, 0.69) /0.65(95%C.I:0.62, 0.67) vs. 0.64(95%C.I:0.61, 0.66) (see ***Table 6.2***), showing a moderate predictive ability. With the exception of markers such as self rated health and IL-6, the area under the ROC curve for the British FI was higher than most of the single markers which had values of <0.6 (see ***Table 6.8***).

Table 6.7: Single measures of frailty by frailty status in 3331 BWHHS respondents

Single Frailty Measures†	Low/Not frail (n=867)	Mild (n=851)	Moderate (n=851)	Severe (n=762)	p value
IL-6,pg/ml	2.59	2.78	3.48	4.21	<0.001
CRP, mg/l	2.44	2.81	3.46	4.85	<0.001
D-Dimer, ng/ml	116.91	127.46	139.94	161.66	<0.001
Albumin, mg/l	44.22	44.20	43.87	43.64	<0.001
Glucose, mmol/l	5.80	5.89	6.19	6.34	<0.001
Cholesterol, mmol/l	6.71	6.59	6.58	6.48	0.001
Haemoglobin, g/dl	13.54	13.51	13.53	13.45	<0.05
White Blood Cell, $10_3/mm_3$	7.23	7.03	7.25	7.23	<0.001
Body Mass Index, kg/m_2	25.78	26.76	27.75	29.67	<0.001
Waist Hip Ratio (WHR)	0.79	0.81	0.83	0.84	<0.001
Orthostatic hypotension(%)	24.30	26.36	25.49	23.86	0.50*
Estimated life expectancy,yr	15.80	14.82	13.55	11.88	0.001
Self rated health (%)	1.47	1.47	14.71	82.35	<0.001*

*p value was derived from Pearson's chi square test for categorical variables; the other p values were derived using Scheffês test.

†Values of the single measures is the standardized mean within each category of frailty.

Table 6.8: Estimated age and fully adjusted hazard ratios for all cause mortality associated with an increase of one SD and the area under the ROC curve using the BWHHS frailty measure and other single markers of frailty*

Measure	Hazard ratio (95%C.I.) Age adjusted	Hazard ratio (95%C.I.) Fully adjusted	p value	Area under the ROC curve
BWHHS frailty measure	1.44(1.33,1.56)	1.38(1.28,1.48)	<0.001	0.64
IL-6,pg/ml	1.20(1.12,1.28)	1.17(1.09,1.25)	<0.001	0.63
CRP, mg/l	1.16(1.11,1.21)	1.14(1.09,1.18)	<0.001	0.58
D-Dimer, ng/ml	1.17(1.09,1.26)	1.17(1.08,1.27)	<0.001	0.60
Albumin, mg/l	0.80(0.72,0.89)	0.83(0.74,0.92)	<0.001	0.43
Glucose, mmol/l	1.10(1.05,1.16)	1.11(1.06,1.16)	<0.001	0.54
Cholesterol, mmol/l	0.82(0.74,0.91)	0.83(0.76,0.92)	<0.001	0.45
Haemoglobin, g/dl	0.94(0.86,1.03)	0.91(0.86,1.02)	<0.05	0.47
White Blood Cell, $10^3/mm^3$	1.04(1.00,1.07)	1.03(1.00,1.06)	<0.05	0.61
Body Mass Index, kg/m^2	0.95(0.83,1.09)	0.92(0.81,1.03)	<0.5	0.47
Waist Hip Ratio (WHR)	1.24(1.15,1.33)	1.20(1.11,1.29)	<0.001	0.57
Orthostatic hypotension	1.06(0.99,1.14)	1.08(1.00,1.15)	<0.5	N/A†
Estimated life expectancy, years	0.72(0.61,0.84)	0.76(0.66,0.90)	<0.001	0.35
Self rated health	1.97(1.67,2.31)	1.86(1.57,2.19)	<0.001	0.63

*data are mean ± SD unless otherwise specified **fully adjusted for age, socioeconomic status (SES), smoking, alcohol intake, marital status, living alone and housing tenure. †N/A(not applicable) as orthostatic hypotension is a binary variable and not suitable for ROC analysis.

Discussion

Comparisons have previously been made between two widely known and widely used frailty measures; the **CSHA frailty index** which was first validated in the Canadian Study of Health and Aging (CSHA) and **Fried's phenotype** measure of frailty. This was in relation to their predictive ability for adverse outcomes and as well as their correlations with specific markers of frailty [129, 138, 139].In this chapter, I compared the British frailty index (FI) with the well validated CSHA frailty index using two British cohorts of older people and showed that the British FI had greater variance in the distribution of scores compared to the CSHA FI (see ***Figure 6.1*** and ***6.2***). Hence, the British FI would serve as a better population metric than the CSHA FI as it enables those people with varying degrees of frailty from low to mild, moderate and severe to be better distinguished over a wider range of scores. The British FI was a better predictor of all cause mortality than CSHA FI in both cohorts independent of similar potential confounders. It was also a better estimate of the respondents' increased risk of hospital admission per unit of frailty score than both versions of the CSHA index. However, the outcome of hospitalization in this study only involved the time to first hospital admission for each respondent during the whole follow up period of the MRC assessment study. In view of the results, this would suggest that further analyses into those with multiple admissions, would indeed be of value in classifying the frailest among this population of community dwelling older people. Institutionalized older people are often labelled as frail and hence, the risk of institutionalization has become a recognized frailty adverse outcome[40]. Using the British FI, frailty also estimated a better increased and independent risk of institutionalization, per unit score than the

CSHA index. These findings serve to emphasize the advantage of the British Frailty Index over the CSHA index; in that it is a reduced measure which corrects for measurement error and assigns relative weights in the association of each indicator with frailty (**see Chapter 3**).In developing this measure, the weighted latent variables that best explained frailty were captured, excluding those that did not. This resulted in a measure that attempts to measure frailty itself as opposed to being an indicator of an older person's global health status. As the two different measures of frailty are based on different theoretical constructs, they would certainly capture different groups of older people. Hence the results above suggest that the British FI would serve as a better predictor of adverse outcomes in community dwelling older people than an unweighted and additive type of index.

Despite showing stronger associations with adverse outcomes, in the analysis of the area under the ROC curve, both the British FI and the replicated CSHA index showed a similarly moderate ability (0.64 and 0.65) to predict death (see ***Table 6.1***). For example, in comparing how well each index separates those who develop the outcome from those who do not, the difference was only 1%. However, area under the ROC curve may not address fully the question of whether one index is superior to the other in terms of clinical usefulness. Ease of making measurements, interpretation of output and additional clinical information provided by graphical displays of risk and the calculation of the numbers needed to screen (NNS) may be more helpful for the clinician in determining whether a new marker or measure is useful[140].

I was also interested to examine the strength of the relationship between frailty and specific single frailty markers which related to the biological underpinnings of frailty[30]. The results were in keeping with other community dwelling older

population studies [31, 32, 84, 121] in that with increasing frailty, levels of IL-6, CRP, D-dimer and fasting glucose increased significantly ($p<0.001$).The frailest in the BWHHS population were also significantly associated with lower albumin, haemoglobin and cholesterol levels. As mentioned in ***Chapter 3***, seven latent factors best explained frailty using the British FI, which among others, included signs and symptoms of cardio-respiratory disease as well as chronic disease such as diabetes and hypertension. Therefore the association of frailty with the markers used in this analysis is certainly to be expected as these markers are also raised in these diseases or states in older people [128, 130]. For example, the association of frailty with increased inflammation (IL-6 and CRP) and coagulation could possibly be influenced by any underlying cardiovascular disease and diabetes in this older study population.

Although frailty has been conceptualized as a wasting syndrome with weight loss as a key component, the physical measurements of BMI and WHR were also highest in the severely frail in the BWHHS population. This finding supports a recent study which found that subjects with the lowest frailty index and the lowest prevalence of Fried's rules based measure were those with a high BMI of 25-29.9. They also found that in each BMI category, and using either measure of frailty, those with a high waist circumference were significantly more frail [121]. In this analysis, although frailty was positively correlated to BMI and WHR, only WHR was an independent predictor of all cause mortality per increase in 1 SD of waist hip ratio (HR 1.19, 95% C.I.:1.11, 1.28, $p<0.001$). In view of the rise in obesity in older populations, lifestyle modifications incorporating a healthy diet and regular exercise should be an important agenda in the prevention of frailty and its adverse outcomes. However these efforts

should not merely target the usual overweight/obese older adults but those who exhibit signs of central obesity, regardless of BMI category.

Most significantly correlated to frailty was self rated health, with poor self rated health being highest in those respondents in the severe frailty group. This strong association with frailty was not surprising seeing that this marker is not only a strong independent predictor of mortality but also of successful aging and an independent predictor of the use of health services among older people[141]. Although self rated health lies on the causal pathway between frailty and mortality, when it was adjusted for in the model, the British FI still predicted mortality and other outcomes independent of self rated health. This indicates that the British FI was not simply measuring more general aspects of the health status.

The analysis also introduced a novel marker of frailty provided by the BWHHS cohort. This was 'estimated life expectancy' where the research nurses were asked to provide an estimation of life expectancy that the respondent might expect. It was interesting to note that women with a higher estimated number of years of life expectancy were less frail and correspondingly, women with a much lower estimate of life expectancy had higher levels of frailty. This was in keeping with a lower risk of death (HR 0.76, 95% C.I:0.66, 0.90, $p<0.001$) among the BWHHS women who were estimated to have a higher life expectancy.

The association of frailty with the specific blood and physical markers shown here do support the theories that frailty is characterized by dysregulations in multiple physiologic systems and increases an older person's vulnerability for serious adverse outcomes [16, 20]. The low correlations of these markers with frailty also support the theory that frailty is a complex phenomenon that cannot

merely be assessed or measured using a single or simple tool. It is suggested here that these markers constitute one of many interrelated precursors of a pathway that leads to a pre- frailty state. Recognition of the centrality of the interrelatedness of these markers to frailty is a key to providing guidelines for its prevention and therapy among community dwelling older people.

There are some limitations to this part of the analysis. Firstly, frailty was only calculated from variables taken at baseline (at start of the study). Prospective calculation of frailty and collection of the specific markers would enable a more comprehensive analysis that would help further understanding as to how they would change over time.

Secondly, in the part of the analysis, the BWHHS cohort was confined to respondents with only complete data on all blood and physical markers of interest, introducing a possible bias in the results of the study. The missing data was due to the fact that some respondents (who may represent a portion of the severely frail in the BWHHS study), had replied to the questionnaires via post as not all were able to attend the interview and have their blood taken.

The study findings provide further evidence of the association of a weighted and measurement error adjusted frailty score with important adverse outcomes. The British FI can be rescaled, reduced and refined into a short questionnaire which would include only questions pertaining to variables with higher weights. In this shorter form it would be amenable for use in a primary care as a quick, easy and none invasive measure for screening frail older people at risk in the community

Summary:

- The more internally reliable British FI (weighted and adjusted for measurement error) is a better predictor of all cause mortality than the CSHA FI in two well representative older British population cohorts.
- The British FI is also a better predictor of risk of institutionalization and hospitalization than the CSHA frailty index in both older men and women of the MRC assessment study.

- The British FI has greater variance which produces a more refined distribution of frailty and serves as a better population metric compared to the CSHA FI.

- In keeping with similar study findings, frailty, as defined by the British FI, is significantly correlated with specific physiological markers which are highly associated with all cause mortality and implicated in the pathophysiology of frailty.
- The British FI confirms the concept of frailty as a complex multi-dimensional one and is a better predictor of all cause mortality than single markers of frailty.

Chapter 7: Overall discussion and conclusions

What are the contributions made to identifying frailty from concept to measure?

It has been five decades since the term 'frail' was first coined to describe the vulnerable state and needs of older people in British hospitals[8]. Although the reasons behind the identification and measurement of frailty have generally remained the same, its complexity remains a limiting factor in reaching a consensus definition. Geriatricians who have long appreciated the complex and heterogeneous nature of health problems in the older person still have problems in translating the clinical profile of frail elderly people into a quantifiable clinical assessment tool. This complexity is one of the reasons why it has been so difficult to assess frailty with a single indicator or simple clinical tool. Furthermore, the various opinions thus far have led to a 'fractured' message being conveyed as to what frailty truly is. This situation arises as a result of different researchers providing different reasoning behind their definitions. These conflicting ideas have resulted in the development of numerous measures which were designed for different settings, purposes and priorities. It is therefore not surprising that it has been a challenge to reach a consensus definition and develop a common frailty assessment tool that could be utilized not just by clinicians in primary care or tertiary centres but by research gerontologists as well as public health practitioners. The failure in reaching this consensus is a major barrier for developing more effective and efficient primary and secondary preventive measures[26].

Despite the uncertainty around the idea of frailty, there has been progress made in its identification in older people, from its concepts to its measurement.

Various concepts and measures have attempted to map out important associations with the aging process[2], its pathophysiology [16, 129] and associations with co-morbidity [62, 88] and disability[16, 20], sociodemographic and lifestyle factors[51, 126]. The prognostic value of measuring frailty has been evident in its relationship with adverse outcomes such as hospitalization, institutionalization and death [1, 20, 40, 41, 94] . This has led to a general agreement that the core feature of frailty is 'an increased vulnerability to stressors due to impairments in multiple, interrelated systems that lead to a decline in homeostatic reserve and resiliency[16, 68].The level of commitment made to the detection, prevention and treatment of frailty in older people is seen as an important step closer towards reducing the increased burden of cost and care to the providers of healthcare services, social services, the economy and to the society in which the individuals themselves and their carers live in.

Findings from this study: similarities and differences with other measures.

The question posed prior to conducting a systematic search of all possible definitions of frailty in older adults was whether there was a clear pattern between the early to current concepts of frailty and the operational definitions that have resulted from them. As frailty remains undefined, the systematic literature review was extensive as it incorporated a wide range of terms so as to capture articles that had attempted to define or measure frailty. Although 'frailty' or 'frail' was the major descriptive term used, this review revealed that other terms such as 'vulnerable'[43, 44], 'functionally impaired', 'functional limitations' or 'functional disability'[22, 45, 46] were often used to describe or identify the

same frail older population at risk of adverse events. This explained the overlap between frailty and disability and efforts made to distinguish between them[88]. This thesis argues that the incorporation of indicators of functional impairment into a frailty assessment tool is appropriate seeing that there are varying degrees of functional impairments in the frail older person. This is evident in the various measures of physical function used in existing frailty measures [20, 47, 83]. To exclude these indicators would be denying their importance in the assessment of frailty in people belonging to much older age groups.

The systematic literature reviews and meta-analysis in ***Chapter 2*** confirmed that there was little coherence in the many frailty studies conducted over the whole search period from the 1960s to this current time. The original concept of frailty as a multi-dimensional syndrome had been transposed to a focus on physical/physiological function and biomarkers of frailty reflecting the move away from the original idea of holistic geriatric medicine practice and a patient-centred approach. This may have been in response to more technological approaches and a need to be more objective in applying the science of measurement. It could also be due to the physicians' desire for more tangible and objectively confirmed evidence of patients' needs, which were more likely to be treatable by medical means.

In the last two decades, there have been more validation studies focused on two main types of frailty measures; the *frailty index* which is a measure of deficit accumulation[107] and the *rules based phenotype of frailty[20].* To date there has been no formal meta-analysis of prognostic studies of various frailty measures. All the studies which met the search selection criteria demonstrated significant associations between their respective measures and all-cause

mortality. In the meta-analysis conducted here (see ***Chapter 2***), 18 prognostic studies which used different frailty measures in large study populations confirmed the lack of coherence between studies by demonstrating extensive heterogeneity in the prediction of all-cause mortality even after considering factors such as age, sex, type of measure used, number of covariates adjusted for and duration of follow up.

The development of the various frailty measures found in the literature had involved the additive combination of indicators or separate measures to form either a rules based or an unweighted index of deficit accumulation. Although these types of measures demonstrated validity especially in relation to prediction of adverse outcomes, there remained a major issue of measurement error associated with frailty measures that combined several directly observed variables together. I also questioned whether these measures were truly measuring frailty alone or were measuring a combination of other entities such as co-morbidity or disability. Furthermore, from a clinical perspective, the identification of frailty in an older person may not be directly obvious and its complexity may require further investigation of other 'latent' or not directly observed factors. For example, an elderly diabetic patient who may appear relatively well and mobile could have an underlying degree of cognitive impairment or hypertension from macro-vascular complications of diabetes or visual impairments due to diabetic retinopathy. These factors could render him more vulnerable to certain stressors (such as an acute infection or surgery) that lead to the occurrence of adverse events. In this example, the clinical presentation may be subtle, often asymptomatic and only evident over time when excess vulnerability to stressors reduces the older person's ability to maintain or regain their homeostasis[2]. Bearing these factors in mind, the

development of a measure through the combination of directly observed variables or frailty indicators may not fit well with the concept of frailty as a 'latent vulnerability' in older people.

Hence in ***Chapter 3***, I developed a measurement model of frailty using the statistical method of factor analysis. Exploratory factor analysis was used to develop the hypothesis on frailty from a wide range of frailty indicators which were identified through 'a priori' hypotheses and previous literature. This method derived subsets of indicators that correlated strongly with each other and weakly with other indicators in the dataset, providing meaningful theoretical 'explanations' or 'interpretations' linking them to the overall construct of frailty. These indicators were corrected for measurement error and assigned relative weights in their association with frailty. Seven subsets or factors explained the association between frailty indicators: visual impairment, respiratory disease/symptoms, cardiac disease/symptoms, physical ability, physiological markers, psychological problems and co-morbid disease. This hypothesis was tested by confirmatory factor analysis which confirmed the *General specific model* as the best choice to form the conceptual basis for frailty in older adult. The implication with this model is that frailty serves as the underlying factor that contributes to different forms of frailty indicators, and in addition, there are processes separate from this that contribute to the development of the seven specific factors, which vary independently of frailty. In the clinical example given above of the elderly diabetic patient, his degree of frailty is contributed by frailty indicators belonging to factors such as 'visual impairment', 'psychological problems' and 'co-morbidities' which by themselves are mutually uncorrelated.

Although the identification of these seven factors was in keeping with other measures based on similar domains [40, 43, 62], the development of a tool

(using indicators which are both weighted and corrected for measurement error) lends added credibility to it being a more reliable measurement of frailty. The reliability or internal consistency of the 'General Specific' model was shown by the goodness of fit of the confirmatory factor analysis. The validation of the model as a measurement of frailty was reaffirmed when the same model was tested in a larger independent cohort of the MRC assessment study whose respondents was older and comprised both sexes. Furthermore, the higher weighted frailty indicators higher weights associated with them may provide more precise information as to which cluster of frailty indicators are important in identifying frailty in older people.

This newly developed British frailty index had expected associations with sociodemographic and lifestyle variables and demonstrated both construct and external criterion validity (see ***Chapter 4***). These confirmed the findings of similar large study populations [74-76, 78, 105] especially in the association of frailty with increased age, female sex, smoking, living alone, poor social contact and not owning one's own home. This study provided greater evidence for the association of frailty with socioeconomic position by using the BWHHS SEP score, a comprehensive assessment of socioeconomic position which incorporated various markers of socioeconomic position[125]. It strongly confirms similar associations between frailty and socioeconomic markers such as low education[1, 41] and income[20, 45],non white collar occupations [126]which had been assessed separately in other studies.

Low socioeconomic position was associated with being in a higher frailty category among the BWHHS women.

This new measure demonstrated predictive validity in the association of frailty with all-cause mortality (see ***Chapter 5***) in both study cohorts. However, in the initial assessment of the distribution of frailty among all respondents at the end of each analysis period, there was great overlap between respondents who were dead or were still alive at that time (see ***Figures 5.1 and 5.2 in Chapter 5***). This enabled cut-off points of varying degrees of frailty to be established with respect to all cause mortality. A distinct finding in the MRC study respondents who were older and followed up for a longer period of over 12 years was that frailty(measured at start of the study) was a stronger predictor of all- cause mortality at earlier periods of follow-up (within the first 2.5 years from baseline). Those with a severe degree of frailty were already dead earlier in the follow up period, leaving the more robust, mild and moderately frail who were still surviving in the community. Those who were severely frail and predicted to have a higher risk of mortality earlier in their follow up may be at a stage where they would benefit from more palliative or rehabilitative services rather than preventative or curative services. It is the frail survivors (with mild to moderate frailty) who could be potential targets in the longer term for preventive or therapeutic strategies aimed at reducing their risk for further adverse outcomes. These cut offs in relation to time to event would be especially useful in aiding the clinical decision making process. This would allow for more informed and cost effective allocation of scarce but valuable resources for older people.

The British frailty index is also the first frailty measure that has been used to independently predict *cause-specific* mortality among community dwelling older people after adjusting for possible confounding with age, sex, SEP score, smoking, alcohol intake, social contact, living alone, housing tenure and marital

status. This index was an independent predictor of cardiovascular and respiratory deaths in all three time periods of follow up in both the men and women of the MRC Assessment study. Frailty was also an independent predictor of death from cancer in the MRC respondents but only in the first two and a half years of follow up. This effect may be due to the reason mentioned earlier that the frailest in the population especially those suffering from rapidly progressive cancer tend to die early in the follow up period.

Another important finding was that the British frailty index was a strong independent predictor of 'time to first hospitalization and institutionalization in both older men and women. The risk of both events was especially high among those categorized as severely frail at the start of the study. This also confirmed the findings of other large population studies [1, 20, 40]. Identification of those at higher risk of hospitalization and institutionalisation could help allocation of appropriate community resources according to their degree of frailty which might then prevent these adverse outcomes. This includes interventions by social services, palliative care or home or specialist nursing services that provide patient and carer support so as to prevent unnecessary admissions into hospital or an institution.

The British frailty index estimated a higher risk of all these adverse events compared to the well known and much validated CSHA additive index of deficit accumulation, regardless of whether a larger number or smaller number of indicators were used to form the CSHA index. In keeping with similar study findings [31, 32, 84, 121], the association of frailty with the specific blood and physical markers shown here do support the theories that frailty is characterized by dysregulations in multiple physiologic systems and increases an older person's vulnerability for serious adverse outcomes [16, 20]. The low although

significant correlations of these markers with frailty support the theory that frailty is a complex phenomenon that cannot merely be assessed or measured using a single or simple tool. Hence, the British FI confirms the concept of frailty as complex and multi-dimensional functioning as a better predictor of all cause mortality compared to single markers of frailty (see **Chapter 6**).

Strengths and Limitations of the study

Both strengths and limitations have previously been addressed in relation to the topic of each specific chapter but are generally discussed here.

Strengths

To date, the British frailty index is the first measure of frailty developed in a large population study in the United Kingdom. The BWHHS and MRC assessment study participants were drawn from 23 and 53 general practices respectively from across England, Wales and Scotland and therefore are fairly representative of the British community dwelling older population. In the BWHHS, the 60% response rate is moderate but consistent with other baseline data collection in large epidemiological surveys[142]. The findings were reaffirmed upon validation of the method of measurement in the independent MRC assessment study cohort of older (75 years and above) community dwelling men and women. The frailty indicators included in the factor analysis were limited to include ones that were only available to both datasets. However, as factor analysis captures unobserved heterogeneity in the latent variables, if we were to include other relevant frailty indicators to the model, the relative

ordering of individuals would still remain unaltered, and the frailty indicators would still fall under the same seven factors.

To address the problem of missing data in the BWHHS covariates that were adjusted for in the Cox regression model, a multiple imputation procedure provided unbiased estimates of the parameters and their standard errors in the model. This was not necessary for the MRC assessment covariates adjusted for, as they had less than 2% missing data.

This multidimensional measure identified seven key factors associated with frailty which by themselves are amenable to modification through their prevention, treatment or intervention. In comparison to the CSHA FI, the British FI has greater variance, giving a more refined distribution of frailty and thus serves as a better population metric (see ***Figure 6.1 and 6.2 in Chapter 6***).

This new measure also demonstrated internal construct, external criterion and predictive validity in these two large cohorts. Furthermore, it provides important information about the survival prediction of older people over long follow up periods which makes it a good prognostic tool that would aid in the planning and allocation of health care services for them.

Limitations

As nearly all our participants are older Caucasians, our results may not necessarily be generalisable to younger adults or other ethnic groups. The BWHHS study respondents were those who were able to attend the interview and medical examination at baseline suggests that they were relatively less frail compared to non-responders. Therefore, this study cohort may underestimate the degree of frailty among the population it derived its sample from.

Frailty was only calculated from variables taken at baseline (at start of the study). Prospective calculation of frailty and collection of the specific markers would enable a more comprehensive analysis that would help further understanding as to how they would change over time. A comparison of a static version of frailty (measured at a single point in time) with a dynamic version(which changes over time) could demonstrate whether older persons who retain the capacity to improve still have considerable reserves and are not frail/less frail[73].

Another limitation is that only the risk for a first or single hospitalization was examined in this study. As frailty strongly predicted risk of first hospitalization, future work with this new frailty measure should perhaps focus on repeated hospital admissions which are a common problem among older people and drive a large part of the burden and costs associated with frailty.

A theoretical causal pathway of frailty

The main part of my analysis dealt with the association between frailty and death. ***Figure 7.1*** illustrates the causal pathway in the relationship between frailty and its adverse outcomes, by incorporating the International Classification of Functioning, Disability and Health (ICF) framework (see ***Chapter 1***) as a guide to this pathway[98]. We can describe frailty within the context of this framework by the interaction between the health condition (disease) and contextual factors (environmental including physical, social and attitudinal environment and personal factors). These interacting factors affect a person's bodily functions and their degree of activity and participation. All these in turn contribute to the experience of frailty in older people, which depending on certain stressors, may lead to the occurrence of adverse events such as death.

Case scenario

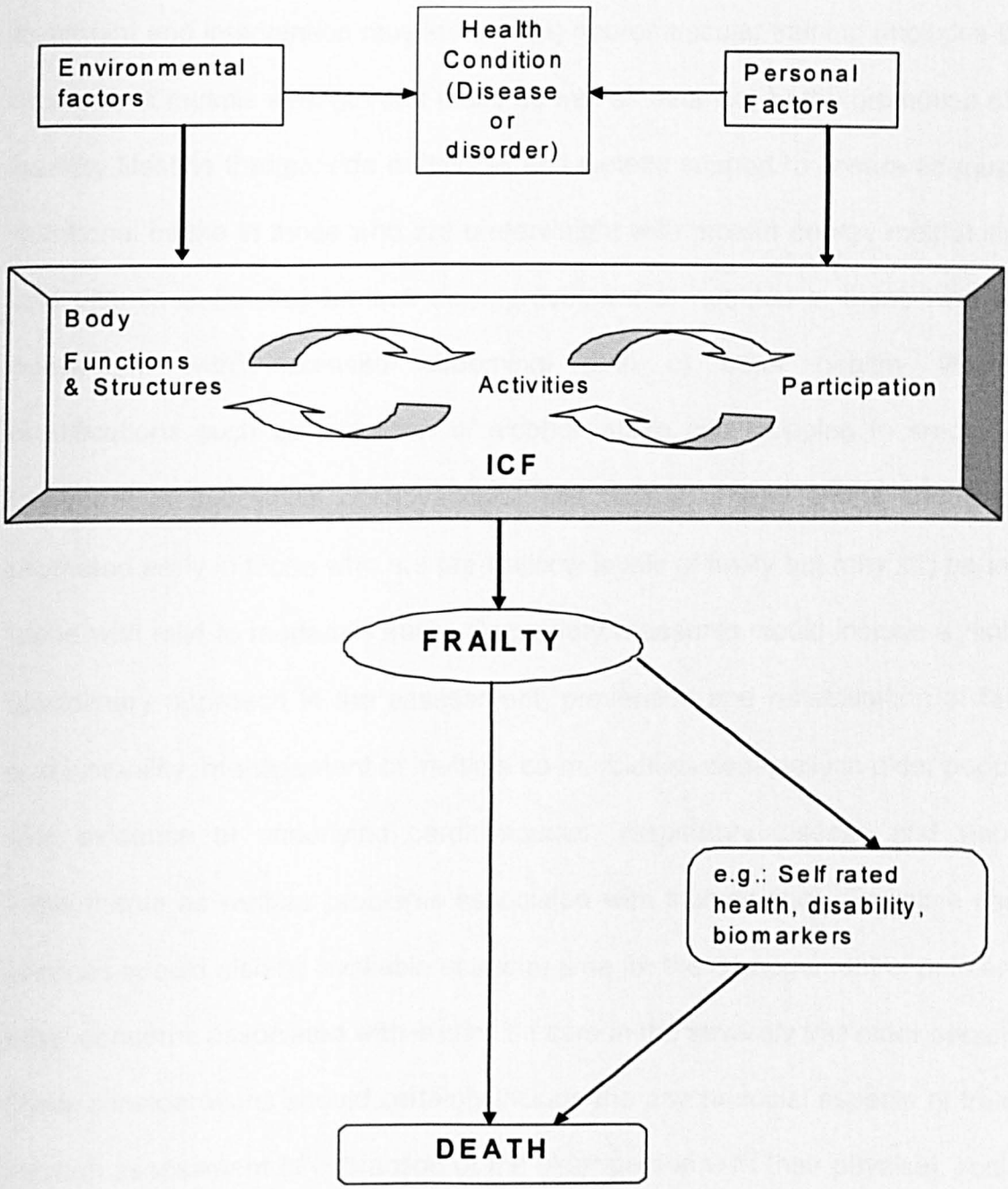
I illustrate the causal pathway for frailty with a case study of a 70 year old widowed gentlemen suffering from congestive cardiac failure. This health condition resulted in his symptoms of short of breath on exertion and swelling of his legs. He was limited in certain activities of daily living and had to take time with his personal care as well as going up and down the stairs. He lived alone in a third floor flat in a building with no elevators and this limited his social outings with friends and family. A recent fall had reduced his confidence after which he mostly confined his outings to visits to the general practitioner. At a recent visit for a bout of cough and fever he was diagnosed with a bronchopneumonia and was admitted to hospital. His condition did not improve; he passed away after two weeks in hospital.

This scenario demonstrates how the interaction of various factors can lead to frailty and how a stressor (in this case bronchopneumonia) can affect a frail individual's risk of an adverse event. As illustrated in ***Figure 7.1***, the individual's experience of frailty is described as an interaction between his heart condition and his environmental and personal factors which in turn affects his function and participation in certain activities. These factors determine his degree of frailty and indirectly, his risk of an adverse event. Personal factors on this causal pathway include age, sex, marital status, living alone, smoking, and alcohol intake. Environmental factors include those that constitute the physical environment such as type of accommodation (housing tenure); interaction of the individual to their social environment in terms of social contact or participation, as well as socioeconomic position status.

Another factor on the causal pathway is 'self rated health' which is an indicator of the global health status. The level of frailty experienced by the individual can

result in either a good or poor self rated health. Disability which is classified as 'activity limitation'[98] is also on this pathway indicating why there exists great overlaps between frailty and disability. The inclusion of specific biomarkers on this pathway provides more biological plausibility to the association of frailty and its adverse outcomes.

Figure 7.1: Theoretical Causal path-diagram of frailty



Implications of frailty to clinical practice, research and policy.

The British FI has attempted to return the measurement of frailty back to a more holistic geriatric approach. It has done so through the reliable identification of seven specific domains which present frailty as a multi-dimensional and complex phenomenon. The identification of the seven factors that best explained the concept of frailty provides many possibilities for its specific prevention, treatment and intervention.

Following the development of the British FI, primary prevention of frailty, its treatment and intervention may include : a) neuromuscular training (includes the increase of muscle strength and mass as well as balance) b) the promotion of a healthy lifestyle that provide nutritional and dietetic support to ensure adequate nutritional intake in those who are underweight with protein energy malnutrition and vitamin deficiency as well as improvement of nutrition in those who are overweight with increased abdominal girth c) other healthy lifestyle modifications such as reduction of alcohol intake and stopping to smoke d) treatment of subclinical cardiovascular risk factors. These efforts should be promoted early in those who are pre-frail/low levels of frailty but may still benefit those with mild to moderate frailty. Secondary measures would include a multi-disciplinary approach in the assessment, prevention and rehabilitation of falls and instability, management of multiple co-morbidities especially in older people with evidence of underlying cardiovascular, respiratory disease and visual impairments as well as problems associated with incontinence. Palliative care services should also be available at a later time for the management of pain and other concerns associated with end of life care in the severely frail older person. Other considerations should certainly include the psychosocial aspects of frailty through assessment of interaction of the older person with their physical, social

and attitudinal environment. This is through early assessment and treatment of cognitive impairments, anxiety or depression especially in older people who are socially isolated; as well as the assessment of the physical environment in those who are physically isolated and living in poor housing. Social services with the help of primary care professionals and independent bodies such as 'Age Concern' could identify older people who are socially and physically isolated and improve their social participation by promoting activities at home or at a community or day centres for older people. These activities could include improving existing skills, group exercise and other efforts that would help maintain their independence at home.

The implication of frailty on research involves the identification of its underlying causes and the discovery of ways to prevent it. Ultimately, this would enable the treatment of primary causes of frailty which is still currently under investigation. Efforts in this direction have been in understanding the pathophysiological foundations of frailty through identification of specific biomarkers associated with it. The association of frailty with cardiovascular risk has been shown with inflammatory markers such as IL-6, TNF-alpha and CRP as well as coagulation markers such as D-dimer and fibrinogen [128, 130]. This finding has been consistent across the different frailty measures including the British frailty index. Certainly this thesis provides evidence in support of this by the strong association of frailty with cardiovascular signs and symptoms and the prognostic value of the British frailty index in predicting cardiovascular mortality in both older men and women. The identification of biomarkers associated with frailty brings about the question of whether they would be appropriate as a suitable tool for its assessment. The complexity and multi-dimensional nature of

the frailty concept demonstrated in this thesis suggests that this idea is still in very much need of investigation and debate.

As this measure was highly sensitive in capturing those who were frail but still alive, it has the potential to identify the severely frail from the mild/moderately frail in the population; enabling more informed, sensible and cost effective clinical decision making. This index would serve as a guide in the allocation of appropriate healthcare services to the patients in the appropriate frailty category. These may include primary prevention of frailty as mentioned earlier, with targeted treatment of risk factors in those who are not frail (pre-frail); further treatment and intervention for those with mild or moderate frailty; and home nursing, rehabilitation or even palliative care for the severely frail at the highest risk for adverse events. These efforts are in response to the public health implications of frailty as a significant and modifiable economic burden on health care services. The British Frailty Index could potentially serve as an important public health indicator and in view of its prognostic value, it can serve as an indicator monitoring the results of health interventions. Randomized trials of such strategies would be required to determine their cost-effectiveness.

Areas for future work

There are ways in which work presented in this thesis could be further extended. These include the following recommendations:

The life course approach

The life course approach to the epidemiology of chronic conditions is built on the premise that various biological, behavioural, social and environmental factors throughout (early, adult and late) life can independently, cumulatively and interactively influence health and disease in old age[143]. The interest in the life course determinants of ageing stems from the general idea that its process occurs from the beginning of life, driven by the rate of accumulation of molecular and cellular damage[144]. This idea is supported by growing evidence from life course and historical cohorts showing that adult health, function and risk of age related chronic diseases have their origins in early life experience, sharing common risk factors and causative mechanisms[144]. The focus on the life course determinants of aging has led to its application in the study of frailty. This is due to the fact that frailty has been seen as a consequence of accelerated ageing and therefore lies on the causal pathway between ageing and death. Linking life-course factors to frailty will increase our understanding of its origins, its lifetime determinants and enable the study of the evolution of frailty through a person's life course. Life-course determinants of frailty would involve biological factors such as biomarkers (including genetic markers), psychological, social as well as environmental factors. For example, or the development of type 2 diabetes depends partly on environmental influences and behaviour in early life[73]. Another example of risk factors or

markers across the life course include evidence such as the association of decreased grip strength in mid life with an increased risk of functional decline and disability 25 years later[145].

Research on frailty has been aimed at identifying 'clusters of vulnerability, weaknesses, instabilities and limitations with shared causes' [27]. The British FI, derived from subsets of indicators that correlated strongly with each other and weakly with other indicators in the dataset, identified seven latent factors or 'clusters' of indicators which best explained the concept of frailty. Empirical testing of these seven latent factors could provide insight into the concept of frailty from a life course perspective. A life course approach could examine the relative importance of these individual factors/components of frailty and assess whether they present or cluster together at different stages in life, more often than would be expected if they were independent. These latent factors could also be examined for shared common causes and their outcomes later in life.

Identification of the causes of frailty early in life would suggest that its prevention in later life would need to occur early. Based on current evidence, the occurrence of frailty in later life can be delayed by interventions such as neuromuscular strength training which is associated with improved physical performance in older people [146-148]. Targeting training interventions at strategic times for example at retirement which may coincide with the pre-frail stages would be worth evaluating. Early life determinants of frailty have important implications for the policy makers in terms of planning effective prevention or treatment strategies for populations.

Future studies specific to frailty

Further to the life course approach to frailty mentioned above, a more complete understanding of the important domains of frailty might be better served by conducting a prospective cohort study which is designed to answer specific questions on frailty. However, this would of course involve a considerable amount of time and it is questionable whether expending resources on setting up new studies would be feasible. The existing World Health Organisation Study on Global Ageing and Adult Health (SAGE)[149] set up by the Multi-Country Studies unit will provide extensive data to examine the associations of a wide range of variables on relevant outcomes. Ensuring a strong focus on frailty in the SAGE studies would be helpful.

Refinement of the British FI

The British FI could be refined by reducing the number of frailty indicators needed to explain frailty under its seven latent factors by retaining those with higher weights relative to the others. The resulting shorter index could then be converted to a short questionnaire which could be easily applied for use in a primary care or hospital setting in the detection of frailty in community dwelling older people. It would be particularly important to develop and evaluate simple and non invasive versions of the British FI for use in developing countries where the rate of population ageing is occurring at a more rapid pace than in the developed world and the cost of measuring frailty using more sophisticated measurements of physical function would be less feasible.

Conclusion

Frailty is a useful concept and its wider use would be promoted by a consensus on its definition and method of measurement. This thesis provides a better understanding of the multi-dimensional domains of frailty and its concept as a latent vulnerability in older people. It does so by providing a more reliable method of its measurement which demonstrates validity particularly in relation to serious adverse outcomes. This new frailty measure may provide the impetus for similar research in different settings, particularly in developing countries where contextual factors differ. The British FI provides further opportunities to develop strategies for prevention and health promotion at a population level as well improved detection, treatment and intervention of frailty in older people at a clinical level in developing countries.

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Appendix

Questionnaire Number ☐☐

Study Number : ☐☐☐☐

Town: ☐☐

BRITISH WOMEN'S HEART & HEALTH STUDY

BASELINE SURVEY

- This questionnaire asks about your health, your life-style and your social background.

  This will give vital information for our research.

- Most questions can be answered simply by ticking the correct box ☑

- All the information collected will be treated as strictly confidential.

- **Please complete the form today, or as soon as possible, and return in the reply paid envelope.** If you have any difficulties with the questions, please phone us on 0117 928 7327 and leave your phone number so that we can call you back and answer your queries.

Thank you for your help.

British Womens' Heart & Health Study
Department of Social Medicine
Canynge Hall
Whiteladies Road
Bristol BS8 2PR

Please give the following information to help us contact you in the future.

1.0 Your telephone number _____

1.2 Your date of birth ☐☐ ☐☐ ☐☐
Day Month Year

1.3 Today's date ☐☐ ☐☐ ☐☐
Day Month Year

1.4 Your maiden name, if you are married, divorced or widowed:

_____

Name and address of family member or friend we could contact only if necessary:

1.5 Surname _____

1.6 First name _____

1.7 Address _____

_____

_____

_____

1.8 Post code: _____

1.9 Telephone Number: _____

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

2.0 **Health at present**

How would you describe your health at present ?

- Excellent ☐ 1
- Good ☐ 2
- Fair ☐ 3
- Poor ☐ 4

3.0 **Conditions affecting the heart or circulation**

Have you ever been told by a doctor that you have or have had any of the following conditions ?

	Yes	No		If Yes, please give year when first diagnosed, if possible
3.1 Heart attack (coronary thrombosis or myocardial infarction)	☐	☐	3.7	19_____
3.2 Heart failure	☐	☐	3.8	19_____
3.3 Angina	☐	☐	3.9	19_____
3.4 Other heart trouble	☐	☐	3.10	19_____
3.5 High blood pressure	☐	☐	3.11	19_____
3.6 Stroke	☐	☐	3.12	19_____

4.0 **Cancers**

4.1 Have you ever been told by a doctor that you have or have had a cancer?

Yes ☐ No ☐

If yes, please state what kind of cancer(s):

	office use	Please give year when first diagnosed
4.2_____	☐☐☐	4.5 19_____
4.3_____	☐☐☐	4.6 19_____
4.4_____	☐☐☐	4.7 19_____

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

5.0 **Other medical conditions**

Have you ever been told by a doctor that you have or have had any of the following conditions?

	Yes	No	Please give year when first diagnosed, if possible
5.1 Asthma	☐	☐	5.11 19_____
5.2 Bronchitis	☐	☐	5.12 19_____
5.3 Depression	☐	☐	5.13 19_____
5.4 Gastric, peptic or duodenal ulcer	☐	☐	5.14 19_____
5.5 Gout	☐	☐	5.15 19_____
5.6 Gall bladder disease	☐	☐	5.16 19_____
5.7 Osteoporosis	☐	☐	5.17 19_____
5.8 Thyroid disease	☐	☐	5.18 19_____
5.9 Cataract	☐	☐	5.19 19_____
5.10 Glaucoma	☐	☐	5.20 19_____

6.0 **Falls and Fractures**

		Yes	No	
6.1	Have you had a fall in the last 12 months ?	☐	☐	
6.2	*If Yes,* how many times ? _____			
		Yes	No	
6.3	Did you have medical attention for any of these falls ?	☐	☐	
Fractures:		Yes	No	Please give year
6.4	Have your ever fractured or broken your hip?	☐	☐	6.6 19_____
6.5	or, your wrist?	☐	☐	6.7 19_____

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

7.0 **Arthritis**

		Yes	No
7.1	Have you ever been told by a doctor that you have or have had arthritis?	☐	☐

If Yes, please state what kind of arthritis:

	Yes	No	Don't know		Please give year first diagnosed
7.2 rheumatoid arthritis	☐	☐	☐	7.5	19_____
7.3 osteoarthritis	☐	☐	☐	7.6	19_____
7.4 other type of arthritis	☐	☐	☐	7.7	19_____

Which joints are or were affected?

		Yes	No
7.8	hips	☐	☐
7.9	knees/ankles	☐	☐
7.10	shoulders	☐	☐
7.11	hands/fingers	☐	☐
7.12	back/spine	☐	☐

8.0 **Operations**

		Yes	No
8.1	Have you ever had an operation(s)?	☐	☐

If Yes, please give details including the year:

	office use	Please give year of operation(s)
8.2 _____	☐☐☐	8.5 19_____
8.3 _____	☐☐☐	8.6 19_____
8.4 _____	☐☐☐	8.7 19_____

Please list any other operations here:

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

9.0 **Hearing and vision**

Do you have trouble with	Yes	No
9.1 your hearing	☐	☐
9.2 your eyesight *(not simply needing specs)*	☐	☐

If Yes, please give details: office use

9.3 Hearing_____ ☐☐

9.4 Vision_____ ☐☐

10.0 **Diabetes**

	Yes	No	Don't know	Year first diagnosed
10.1 Has anyone in your close family (your parents, brothers, sisters) ever had diabetes ?	☐	☐	☐	
10.2 Have you ever been told by a doctor that you have or have had diabetes?	☐	☐	☐	10.3 19_____
If Yes: 10.4 Are you on a regular diet for your diabetes ?	☐	☐	☐	
10.5 Are you on regular tablets for your diabetes?	☐	☐	☐	
10.6 Are you on regular treatment with insulin?	☐	☐	☐	
10.7 Do you attend a hospital or GP diabetic clinic?	☐	☐	☐	

11.0 **Breathlessness**

		Yes	No	Unable
11.1	Do you get short of breath walking with other people of your own age on level ground?	☐	☐	☐
11.2	On walking uphill or stairs do you get more breathless than people of your own age?	☐	☐	☐
11.3	Do you ever have to stop walking because of breathlessness ?	☐	☐	☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

12.0 **Leg pain**

		Yes	No	Unable
12.1	Do you ever get pain or discomfort in your leg, thighs or buttocks when you walk?	☐	☐	☐

If, No or Unable to walk go on to question 13 "Ankle swelling" on next page.

		Yes	No
12.2	Do you know the cause of the pain?	☐	☐

office use

12.3 *If Yes*, what is the cause? _____ ☐☐

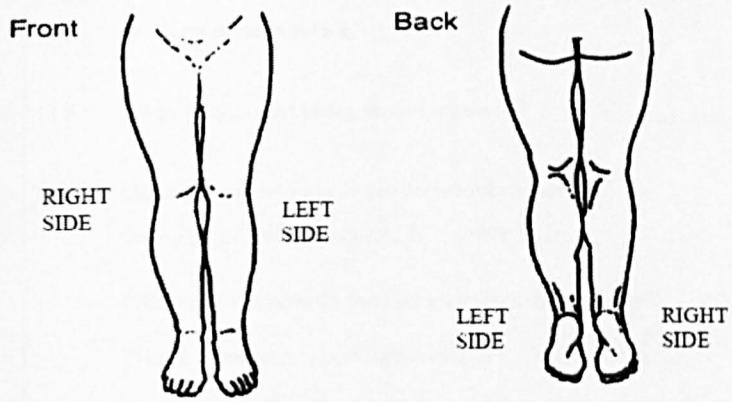
		Yes	No
12.4	Does this pain ever begin when you are standing still or sitting?	☐	☐

		Yes	No	Unable
12.5	Do you get the pain if you walk up hill or hurry?	☐	☐	☐
12.6	Do you get the pain walking at an ordinary pace on the level?	☐	☐	☐

12.7 What happens to the pain if you stand still?

Usually continues more than 10 minutes ☐ 1 Usually disappears in <10 minutes ☐ 2

12.8 Where do you get the pain? **Shade regions affected**



office use ☐☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

13.0 **Ankle swelling**

	Yes	No	Don't know
13.1 Do your ankles swell up regularly ?	☐	☐	☐
13.2 *If Yes*, is this because of varicose veins?	☐	☐	☐

14.0 **Cough and Wheeze**

		Yes	No	Don't know
14.1	Do you usually bring up phlegm (spit) from your chest first thing in the morning in the winter ?	☐	☐	☐
14.2	*If Yes*, do you bring up phlegm like this on most days for as much as 3 months in the winter each year?	☐	☐	☐
		Yes, once	Yes, more often	Never
14.3	In the past 4 years have you ever had a period of increased cough and phlegm lasting for 3 weeks or more?	☐	☐	☐
		Yes	No	Don't know
14.4	Does your chest ever sound wheezy or whistling?	☐	☐	☐
		Yes	No	Don't know
14.5	*If Yes*, does this happen on most days or nights?	☐	☐	☐

15.0 **Treatment with aspirin**

		Yes	No
15.1	Do you take aspirin regularly?	☐	☐
If Yes,			
15.2	Is this on doctor's advice?	☐	☐

15.3 When did you start taking aspirin regularly ? 19 _____

15.4 On how many days each week do you take aspirin?

daily ☐ 1 alternate days ☐ 2 other ☐ 3

15.5 What dose of aspirin do you take each day that you take it?

75mg/1/2junior ☐ 1 125mg/junior ☐ 2 300mg/adult ☐ 3 other ☐ 4

15.6 For what condition are you taking aspirin ?

Please state _____ office use ☐☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

16.0 **Hormone replacement therapy (HRT)**

		Yes	No	Don't know
16.1	Have you ever taken HRT?	☐	☐	☐
If Yes,				
	16.2 Are you still taking it?	☐	☐	
	16.3 How long have you (or did you) taken it ? _____ years			
If stopped now,				
16.4	How long ago did you stop taking it? _____ years			
				office use
16.5	Which preparation do/did you use? _____			☐☐

17.0 **Vitamin or mineral tablets**

		Yes	No
17.1	Do you take any vitamin or mineral tablets or supplements?	☐	☐
			office use
If Yes, please give details: _____	17.2		☐☐

18.0 **Weight**

18.1 What is your present weight ? _____Stones _____ Pounds

18.2 What is your current dress size? _____

18.3 What was your weight as a young woman aged 21? _____Stones _____ Pounds

18.4 What was your dress size as a young woman aged 21?_____

18.5 Have you dieted during your adult life?

☐ 1 yes, regularly ☐ 2 yes, on and off ☐ 3 no

18.6 Has your weight changed in the last four years?

☐ 1 not changed ☐ 2 increased ☐ 3 decreased ☐ 4 up/down ☐ 5 don't know

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Weight (continued)

18.7 *If your weight has increased or decreased in the last 4 years,*

how much weight have you gained or lost? _____stones _____ lbs

		Yes	No
18.8	*If you have lost weight*, was this intentional? (eg. dieting)	☐	☐

19.0 **Smoking**

		Yes	No	
19.1	Have you ever smoked cigarettes regularly (at least 1/day)?	☐	☐	**If No, go to 19.8**
If Yes: 19.2	Do you smoke cigarettes at present?	☐	☐	

If Yes:

19.3 How many cigarettes do you smoke a day? _____ cigarettes

19.4 If hand-rolled, how much tobacco do you use a week ?

_____ounces 19.5 _____grams

If No, go to 19.6

19.6 How old were you when you started smoking regularly? _____years

19.7 Have you changed your cigarette smoking habits over the last 4 years ?

☐ 1 Yes, increased ☐ 2 Yes, cut down ☐ 3 Yes, given up ☐ 4 No

		Yes	No
19.8	Do you currently smoke tobacco in any other form (e.g. pipe, cigar)?	☐	☐

		Yes	No
If No, 19.9	Have you ever regularly done so?	☐	☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Smoking (continued)

For ex-smokers

		Yes	No
19.10	Were you previously a regular cigarette smoker?	☐	☐

If Yes.

19.11 How many cigarettes did you usually smoke each day ?_____cigarettes

19.12 At what age did you give up? _____ years old

19.13 Why did you give up? Tick one main reason only.

☐ 1 Personal choice ☐ 2 Financial reasons ☐ 3 Health precaution

☐ 4 Doctor's advice ☐ 5 Illness or ill-health ☐ 6 Other reasons

19.14 Does/did your husband/partner smoke cigarettes?

☐ 1 Yes ☐ 2 No ☐ 3 Ex-smoker ☐ 4 Not applicable

20.0 **Alcohol Intake**

20.1 Would you describe your present alcohol intake as

Daily/most days	☐ 1
Weekends only	☐ 2
Once or twice a month	☐ 3
Special occasions	☐ 4
Never	☐ 5

20.2 One drink is **HALF** a pint of beer, a **SINGLE** whisky, gin etc., or **ONE GLASS** of wine or sherry. How much do you usually drink each day ?

More than 6 drinks a day	☐ 1
3-6 drinks a day	☐ 2
2 drinks a day or less	☐ 3
None	☐ 4

20.3 How many alcoholic drinks do you take during an **average week**? _____drinks

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Alcohol (continued)

20.4 What type of drink do you usually take ?

- Beers, Lagers ☐ 1
- Sherry, wine ☐ 2
- Spirits ☐ 3
- Variety of beer, wines or spirits ☐ 4
- Low alcohol drinks ☐ 5

		Yes	No	If Yes, glasses per week
20.5	Do you drink white wine?	☐	☐	_____glasses/week
20.6	Do you drink red wine?	☐	☐	_____glasses/week

20.7 Have you changed your alcohol intake in the last four years?

- No ☐ 1
- Yes, increased ☐ 2
- Yes, cut down ☐ 3
- Yes, given up ☐ 4

*If you have **CUT DOWN** or **GIVEN UP***

20.8 Was this due to: Tick one main reason only.

- ☐ 1 Personal choice
- ☐ 2 Financial reasons
- ☐ 3 Health precaution
- ☐ 4 Doctor's advice
- ☐ 5 Illness or ill-health
- ☐ 6 On medication
- ☐ 7 Other reasons

For those not drinking at present

		Yes	No
20.9	Did you drink in the past ?	☐	☐

If Yes,

20.10 would you describe your previous alcohol intake as

- Daily/most days ☐ 1
- Weekends only ☐ 2
- Once or twice a month or special occasions ☐ 3

20.11 How many alcoholic drinks did you take during an average week? _____ drinks/week

20.12 How many years ago did you stop? _____years ago

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

21.0 **Your diet**

21.1 Do you eat any special diet? Yes ☐ No ☐

21.2 *If Yes*, please specify

☐ 1 low fat ☐ 2 high fibre ☐ 3 vegetarian ☐ 4 diabetic ☐ 5 sliming/low calorie ☐ 6 other

21.3 What kind of bread do you eat?

☐ 1 White ☐ 2 Brown ☐ 3 Wholemeal ☐ 4 Various

21.4 Spreading fat: What kind do you use at home?

☐ 1 Butter ☐ 2 Margarine (Hard) ☐ 3 Margarine (Soft) ☐ 4 Low calorie spread (e.g. Delight) ☐ 5 Various ☐ 6 None

How often do you eat the following foods? (Please tick the appropriate box for each food item)

	1	2	3	4	5	6
	More than once a day	Once a day	Most days	One or two days a week	Less than once a week	Never
21.5 Fresh fruit summer						
21.6 Fresh fruit winter						
21.7 Salads in summer						
21.8 Salads in winter						
21.9 Green vegetables						
21.10 Fish (all kinds)						
21.11 Poultry (eg. chicken, turkey)						
21.12 Red meat (eg. beef, pork, ham, bacon)						
21.13 Processed meat (eg. burgers, sausages, pies, pasties, pate)						
21.14 Cereals						
21.15 Nuts						
21.16 Cheese						

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Your diet (continued)

21.17 What kind of cooking fat do you usually use at home?

☐ 1 Lard, butter, animal fat ☐ 2 Vegetable oil ☐ 3 Olive oil ☐ 4 Various fats ☐ 5 Other fats

21.18 What type of milk do you usually use?

☐ 1 Full cream ☐ 2 Semi-skimmed ☐ 3 Skimmed ☐ 4 Dried ☐ 5 Tinned ☐ 6 None ☐ 7 Other

22.0 **Physical Activity**

22.1 Which of the following forms of transport do you use most often? Please tick only one box

☐ 1 Car ☐ 2 Public Transport ☐ 3 Cycle ☐ 4 Walk ☐ 5 Not applicable

22.2 Do you make regular journeys every day or most days either walking or cycling?

☐ 1 No ☐ 2 Walk ☐ 3 Cycle ☐ 4 Both

22.3 Which of the following best describes your usual walking pace?

☐ 1 Slow ☐ 2 Steady average ☐ 3 Fairly brisk ☐ 4 Fast (at least 4miles/hr)

22.4 *If you cycle regularly*, how long do you spend cycling in an average week? _____ hours/week

22.5 Do you take physical activity such as running, swimming, dancing, golf, tennis, squash, jogging, bowls?

☐ 1 No ☐ 2 Occasionally (less than monthly) ☐ 3 Frequently (once a month or more)

*If you take part in these physical activities **frequently***, (once a month or more):
How many **times** a month on average do you take part in these activities?

22.6 Summer _____ times/month

22.7 Winter _____ times/month

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Physical activities (continued)

In a **typical week** during the past year, how many hours did you spend each week in the following activities? Write 0 if no activity.

Walking to work, shopping and leisure	22.8	Summer_____ hours/week
	22.9	Winter _____hours/week
Cycling, including to work and leisure	22.10	Summer_____hours/week
	22.11	Winter _____hours/week
Gardening, light eg. pruning, watering	22.12	Summer_____hours/week
	22.13	Winter _____hours/week
Gardening, heavy eg. digging, mowing	22.14	Summer_____hours/week
	22.15	Winter _____hours/week
Physical exercise eg. fitness, aerobics,	22.16	Summer_____hours/week
swimming, jogging, tennis	22.17	Winter _____hours/week
DIY eg. on house, car	22.18	_____hours/week
Housework activities, light eg. cooking washing up, dusting	22.19	_____hours/week
Housework, heavy, eg. hoovering, floors window cleaning	22.20	_____hours/week

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Physical activity (continued)

22.21 In a **typical week** in the last year, did you do any of these activities vigorously enough to cause breathlessness, sweating or a faster heart beat? Yes ☐ No ☐

22.22 *If Yes*, for how many minutes each week did you perform vigorous activity?_____minutes/week

22.23 In a typical week in the last year, how many flights of stairs do you climb a day? _____flights/day

22.24 Compared with your activity level of three years ago, are you doing

☐ 1 More ☐ 2 Same ☐ 3 Less

22.25 *If less*, please give the reason_____ office use ☐

22.26 Compared with other woman of your age, are you:

☐ 1 Much more active ☐ 2 More active ☐ 3 Similar ☐ 4 Less active ☐ 5 Much less active

23.0 **Your health overall**

Thinking about your health TODAY which of the following is the most applicable.

23.1
- I have no pain or discomfort ☐ 1
- I have moderate pain or discomfort ☐ 2
- I have extreme pain or discomfort ☐ 3

23.2
- I have no problems with performing my usual activities ☐ 1
- I have some problems with performing my usual activities ☐ 2
- I am unable to perform my usual activities ☐ 3

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Your health overall (continued)

23.3 I have no problems with washing and dressing ☐ 1
I have some problems with washing and dressing ☐ 2
I am unable to wash and dress myself ☐ 3

23.4 I have no problems in walking about ☐ 1
I have some problems in walking about ☐ 2
I am confined to a chair/wheelchair ☐ 3

23.5 I am not anxious or depressed ☐ 1
I am moderately anxious and/or depressed ☐ 2
I am extremely anxious and/or depressed ☐ 3

23.6 Compared to five years ago, is your memory

☐ 1 Improved ☐ 2 Same ☐ 3 Almost as good ☐ 4 Worse ☐ 5 Much worse

24.0 **Disability**

Yes No

24.1 Do you have any long-standing illness, disability or infirmity ? ☐ ☐
('long-standing' means anything which has troubled you over a period of time or is likely to do so)

If Yes

Yes No

24.2 Does this illness or disability limit your activities in any way? ☐ ☐

24.3 What is the **main** medical problem causing this disability? If you have several medical problems, please give the most severe one.

office use

_____ ☐☐

Yes No

24.4 Do you receive a disability or other allowance for this? ☐ ☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Disability (continued)

Do you currently have difficulty carrying out any of the following activities on your own as a result of a long term health or medical problems, or due to old age?

		Yes	No	Please give the year this first started	
24.5	Going up or down stairs	☐	☐	24.11	19_____
24.6	Bending down	☐	☐	24.12	19_____
24.7	Straightening up	☐	☐	24.13	19_____
24.8	Keeping your balance	☐	☐	24.14	19_____
24.9	Going out of the house	☐	☐	24.15	19_____
24.10	Walking 400 yards	☐	☐	24.16	19_____

Do you currently use any aids or appliances to help with day to day activities?

		Yes	No
24.17	Walking stick	☐	☐
24.18	Walking frame	☐	☐
24.19	Wheelchair	☐	☐
24.20	Toilet raised seat	☐	☐
24.21	Bath board/shower	☐	☐
24.22	Extra rails in bathroom	☐	☐
24.23	Stair lift	☐	☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Health problems

Is your present state of health causing problems with any of the following ?

		Yes	No
24.24	Job (paid employment)	☐	☐
24.25	Household chores	☐	☐
24.26	Social life	☐	☐
24.27	Sex life	☐	☐
24.28	Interests and hobbies	☐	☐
24.29	Holidays and outings	☐	☐
24.30	Family relationships	☐	☐

25.0 **Your present circumstances**

25.1 Are you:

☐ 1 Single ☐ 2 Married ☐ 3 Widowed ☐ 4 Divorced/separated ☐ 5 Other

25.2 Are you at present

- living alone ☐ 1
- living with a husband or partner ☐ 2
- living with other family member(s) ☐ 3
- living with other people ☐ 4

25.3 Do you have a car available for use in your household ? Yes ☐ No ☐

25.4 Your accommodation: are you

- an owner occupier ☐ 1
- renting from a local authority ☐ 2
- renting privately ☐ 3
- other (please specify) ☐ 4

_____

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Education and employment

25.5 How old were you when you finished full time education. _____ years old

25.6 At present are you

- a housewife ☐ 1
- retired ☐ 2
- employed, full time ☐ 3
- employed, part time ☐ 4

25.7 If you are **retired**, is this due to

- normal retiring age ☐ 1
- early retirement, voluntary ☐ 2
- early retirement, compulsory ☐ 3
- illness/disability ☐ 4
- other reasons ☐ 5
- not applicable ☐ 6

25.8 If you are **retired**, please give the year in which you retired 19 _____

25.9 What job have you done for the longest period of time ?

_____ ☐ 25.10 ☐☐

25.11 Would you describe this work as

- Manual ☐ 1
- Non-Manual ☐ 2

Concerning your husband or partner:

25.12 Has your husband or partner ever suffered with any of the following? Please answer even if you are now widowed or divorced/separated.

	Yes	No
Heart attack	☐	☐
Stroke	☐	☐
Cancer	☐	☐

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Concerning your husband or partner (continued):

25.13 At present is your husband/partner

- retired ☐ 1
- employed, full time ☐ 2
- employed, part time ☐ 3
- unemployed, seeking work ☐ 4
- unemployed, not seeking work ☐ 5
- not applicable (eg. widowed) ☐ 6

25.14 If he is are **retired**, is this due to

- normal retiring age ☐ 1
- early retirement, voluntary ☐ 2
- early retirement, compulsory ☐ 3
- illness/disability ☐ 4
- other reasons ☐ 5
- not applicable ☐ 6

25.15 If he is retired, in which year did retired ? 19 _____

25.16 If he is **unemployed**, is this due to

- redundancy ☐ 1
- illness/disability ☐ 2
- other reasons ☐ 3

25.17 What job has your husband or partner done for the longest period of time? Please answer even if he is now deceased, or you are now divorced or separated.

_____ ☐ 25.18 ☐☐

25.19 Would you describe this work as

- Manual ☐ 1
- Non-Manual ☐ 2

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Pensions

25.20 What type of financial income do you (and your husband/partner) have or will you have on retirement ?

state pension only	☐ 1
occupational pension, fixed amount	☐ 2
occupational pension, index linked	☐ 3
private pension	☐ 4
occupational and private pensions	☐ 5
don't know	☐ 6

Contact with relatives and friends

How often do you see or speak to :-

Please tick the appropriate box in each row

		Every day 1	Every week 2	Every few months 3	Every year 4	Rarely or never 5	Does not apply 6
25.21	Your children						
25.22	Brothers/sisters						
25.23	Friends						
25.24	Neighbours						

Is the amount of contact you have with each of these:-

Please tick the appropriate box in each row

		Too little 1	About right 2	Too much 3	Does not apply 4
25.25	Your children				
25.26	Brothers/sisters				
25.27	Friends				
25.28	Neighbours				

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

26.0 **Your earlier life and health**

Recent research suggests that your weight at birth may be important in later life. We need to ask you some questions about your early life.

26.1 How much did you weigh when you were born?

Write 00/00 if you don't know. _____lbs _____ozs

As a child, did the home you lived in longest have:

		Yes	No	Don't know
26.2	A bathroom	☐	☐	☐
26.3	Hot water	☐	☐	☐
26.4	Your own bedroom	☐	☐	☐
26.5	Use of a car	☐	☐	☐

Your periods

26.6 At what age did your periods **start** ? _____

26.7 At what age did your periods **stop** ? _____

26.8 Did your periods stop naturally ☐ 1

because of an operation ☐ 2 office use

(please give details) _____ 26.9 ☐

26.10 Have you ever taken the oral contraceptive pill ? Yes ☐ No ☐

26.11 *If Yes*, which type of pill did you take?

Combined pill	1	☐
Progestogen only (mini-pill)	2	☐
Don't know	3	☐

26.12 *If Yes*, for how long did you take it ? _____years

26.13 In what year did you last take the pill ? 19_____

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

27.0 **Your pregnancies**

27.1 How many pregnancies did you have? Give number _____

27.2 How many live births did you have? Give number _____

For you first born child, please give the following details: If no live births, please go to 27.7

27.3 Boy ☐ Girl ☐ 27.4 Born on time ☐ Early ☐ Late ☐

27.5 Birthweight _____ lbs _____ ozs

Did you have any of the following complications during any of your pregnancies?

		Yes	No
27.3	High Blood Pressure	☐	☐
27.4	Sugar in the urine	☐	☐
27.5	Diabetes	☐	☐
27.6	Swelling of the hands or feet	☐	☐
27.7	Pre-eclampsia	☐	☐

28.0 **Family history**

Your father

28.1 Is your father still alive Yes ☐ No ☐

If No, 28.2 How old was he when he died?_____years

28.3 What were you told was the cause of his death. Please tick only one cause.

Heart attack	☐ 1	Other cancer	☐ 6
High blood pressure	☐ 2	Accident or injury	☐ 7
Stroke	☐ 3	Other cause	☐ 8
Respiratory disease	☐ 4	Don't know	☐ 9
Cancer of lung	☐ 5		

28.4 What job did your father do for the longest period of time? office use

_____ ☐ 28.5 ☐☐

28.6 Would you describe this job as: Manual ☐ 1 Non-manual ☐ 2

Please answer the following questions by filling in the appropriate box with a tick ☑ or writing the answer in the space provided.

Your mother

		Yes	No
28.7	Is your mother still alive	☐	☐

If No, 28.8 **How old was she when he died?_____years**

28.9 What were you told was the cause of her death. Please tick only one cause.

Heart attack	☐ 1	Other cancer	☐ 6
High blood pressure	☐ 2	Accident or injury	☐ 7
Stroke	☐ 3	Other cause	☐ 8
Respiratory disease	☐ 4	Don't know	☐ 9
Cancer of breast	☐ 5		

Family history of heart attacks and stroke

Are any of your relations affected by heart attacks and strokes either now or before they died?

		Yes	No	Don't know
Mother				
28.10	Heart attack	☐	☐	☐
28.11	Stroke	☐	☐	☐
Father				
28.12	Heart attack	☐	☐	☐
28.13	Stroke	☐	☐	☐

		Yes	No	Don't know	No sisters or brothers
Sisters					
28.14	Heart attack	☐	☐	☐	☐
28.15	Stroke	☐	☐	☐	☐
Brothers					
28.16	Heart attack	☐	☐	☐	☐
28.17	Stroke	☐	☐	☐	☐

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.

CHECK CAREFULLY THAT YOU HAVE ANSWERED EACH PAGE AND THEN RETURN IT IN THE REPLY PAID ENVELOPE PROVIDED.

MRC ASSESSMENT OF ELDERLY PEOPLE IN GENERAL PRACTICE

DETAILED ASSESSMENT

Patient Name Label

Barcode Label

Date of birth

Day 0 1 2 3 4 5 6 7 8 9

Month 0 1 2 3 4 5 6 7 8 9 10 11 12

Year 0 1 2 3 4 5 6 7 8 9

Sex: Male ☐ Female ☐

Marital status

- ☐ Single
- ☐ Married
- ☐ Separated/divorced
- ☐ Widowed
- ☐ Living with a partner

PLEASE TICK APPROPRIATE BOX:-

- ☐ Interview completed with subject
- ☐ Totally proxy interview *(Reasons for proxy)*
- ☐ Partly proxy interview *(Reasons for proxy)*
- ☐ Subject unable to complete interview *(No proxy)*
- ☐ Subject not found *(Reason not found)*
- ☐ Subject refused interview
- ☐ Subject died
- ☐ Subject moved to long stay care
- ☐ Subject admitted to hospital
- ☐ Subject moved away *(New address)* *(New GP/FHSA)*

Nurse number 0 1 2 3 4 5 6 7 8 9 10 1

Nurse name

Date of interview

Day 0 1 2 3 4 5 6 7 8 9

Month 0 1 2 3 4 5 6 7 8 9 10 11 12

Year 0 1 2 3 4 5 6 7 8 9

Place of interview

- Surgery ☐
- Residential home ☐
- Own home ☐
- Other *(Specify)* ☐

Visit start time *(use 24 hour clock)*

Hours 0 1 2 3 4 5 6 7 8 9

Minutes 0 1 2 3 4 5 6 7 8 9

Interview start time *(use 24 hour clock)*

Hours 0 1 2 3 4 5 6 7 8 9

Minutes 0 1 2 3 4 5 6 7 8 9

After 3 minutes rest, take the patient's sitting blood pressure. Repeat sitting blood pressure after another 3 minutes rest, and then take standing blood pressure after 3 minutes rest.

Record to the nearest 2mmHg.

	Sitting		Average corrected sitting reading	Standing
	First	Second		
Systolic			True Systolic	
Diastolic			True Diastolic	
Zero error				

Calculations

Action:
Repeat in 1 week if average sitting systolic is >=180mmHg, or average sitting diastolic is >=100mmHg. To repeat for either, standing systolic must be >=140mmHg.

Repeat blood pressure:

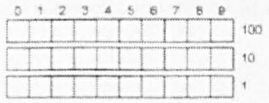
	Sitting		Average corrected sitting reading	Standing
	First	Second		
Systolic			True Systolic	
Diastolic			True Diastolic	
Zero error				

Calculations

Immediate Action:
(Any age) If average repeat sitting systolic >=220mmHg or sitting diastolic >=115mmHg, inform GP within 4 hours.

Action:
Refer to team if subject is less than 80 years old and average repeat sitting systolic >=180mmHg or sitting diastolic >=100mmHg. To refer for either, standing systolic pressure must be >=140mmHg.

2(a) Pulse rate



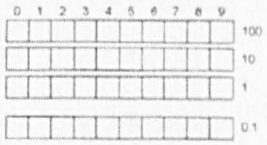
Immediate Action:
If pulse <40 or >130, inform GP within 4 hours.

Action:
Refer to team if pulse 40-49 or 110-129.

2(b) Continuously irregular pulse? Yes ☐ No ☐

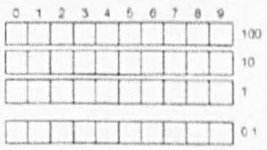
Action:
If yes, do ECG if surgery has facilities. Refer to team if ECG reports atrial fibrillation, atrial flutter or runs of ventricular extrasystoles. If surgery has no ECG facility, refer to team.

3 Measure patient's standing height to the nearest 0.1cm.



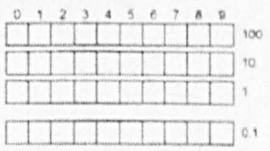
cm

4 Measure patient's weight without coat and shoes to the nearest 0.1 kilogram.



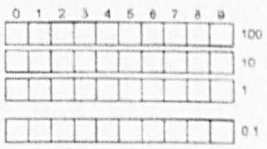
Kg

5(a) Measure patient's demi span to nearest 0.1cm.



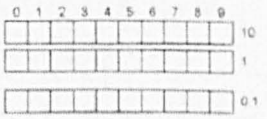
cm

5(b) Repeat demi span measurement to nearest 0.1cm.



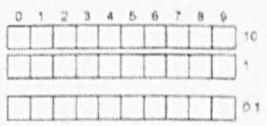
cm

6(a) Measure patient's mid-arm circumference to nearest 0.1cm.



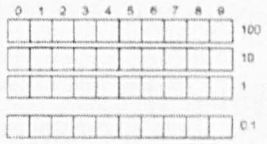
cm

6(b) Repeat mid-arm circumference measurement to nearest 0.1cm.



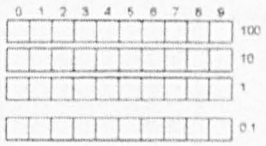
cm

7(a) Measure patient's waist circumference to nearest 0.1cm.



cm

7(b) Repeat waist circumference measurement to nearest 0.1cm.

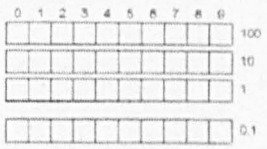


cm

8(a) Measure patient's hip circumference to nearest 0.1cm.

cm

8(b) Repeat hip circumference measurement to nearest 0.1cm.



cm

Please indicate if there were any special circumstances that might have affected any of the above anthropometric measurements. Yes ☐ No ☐

Please record these special circumstances in the space below, (see training notes).

"I am now going to ask you some questions about your recent health, that is, over the past month."

9(a) *Have you ever had any pain or discomfort in your chest?*
Yes ☐
No ☐ ←go to (i)

9(b) *Do you get this pain or discomfort when you walk uphill or hurry?*
Yes ☐
No ☐ ←go to (i)

9(c) *Do you get it when you walk at an ordinary pace on the level?*
Yes ☐
No ☐

9(d) *When you get any pain or discomfort in your chest, what do you do?*
Stop ☐
Slow down ☐
Continue at the same pace ☐ ←go to (i)

9(e) *Does it go away when you stand still?*
Yes ☐
No ☐ ←go to (i)

9(f) *How soon?*
10 minutes or less ☐
More than 10 minutes ☐ ←go to (i)

9(g) *Where do you get this pain or discomfort?* (Tick all places mentioned)

	Yes	No
Sternum	☐	☐
Left chest	☐	☐
Left arm	☐	☐
Other	☐	☐

If "other", specify ☐

9(h) *Are you receiving treatment for this?*
Yes ☐
No ☐

Action: If No, refer to team

9(i) *Have you ever had a severe pain across the front of your chest lasting for half an hour or more*
Yes ☐
No ☐

10(a) *Are you wearing a hearing aid now?*
Yes ☐ ←go to (c)
No ☐

10(b) *Do you have a hearing aid at home for your own use?*
Yes ☐
No ☐ ←go to (e)

10(c) *Do you use the hearing aid regularly?*
Yes ☐
No ☐

10(d) *Does it help?* A lot ☐ A little ☐ Not at all ☐

Only ask (e) if "No" to (a) and (b). Otherwise go to Q11.

10(e) *Have you ever tried one?*
Yes ☐
No ☐ ←go to 11

10(f) *Did it help?* A lot ☐ A little ☐ Not at all ☐

11 *"I am now going to do some checks on your hearing by whispering some letters and numbers. Please keep looking forward".*

Stand behind subject at a distance of 6 inches. Take a deep breath in, breathe right out and then whisper at one item per second: *"3,A,2"*. Ask the subject to repeat this. The test is passed if the sequence is repeated correctly. If they respond incorrectly or not at all, the test is repeated once more using *"1,F,3"*.

Passed first time ☐ Passed second time ☐ Failed ☐

Action:
If patient fails, examine the ears.

Examination of the ears

Nothing abnormal ☐

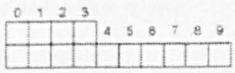
Wax ☐

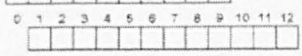
Other (specify) ☐

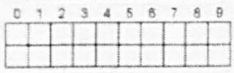
Action:
If wax not present and hearing has not been investigated in the **last year**, refer for audiometry. If wax is present, arrange for drops and syringing. Repeat whispered voice test 1 week after syringing.

Repeat whispered voice test.

Date

Day 

Month 

Year 

Passed first time ☐ Passed second time ☐ Failed ☐

Action:
If patient still fails and hearing has not been investigated in the **last year**, refer for audiometry.

12 *"As people grow older it is quite normal to find they sometimes have trouble with their bladder or bowels. I'd like to ask you some questions about it."*

12(a) **Ask all:** *Do you ever wet yourself if you are not able to get to the toilet as soon as you need to, or when asleep, or if you cough or sneeze?*

Yes ☐
No ☐ ←go to 13
Catheter ☐ ←go to (d)

12(b) **If yes,** *how often does this happen?*

More than once a day ☐*
Once a day ☐*
Three or more times a week ☐*
Once or twice a week ☐*
Less than once a week ☐

12(c) **If yes,** *is it just a few drops or more than that?*

Just a few drops ☐
More than that ☐*

Action: If *incontinent of urine (more than a few drops) once a week or more, do MSU. If infected MSU refer to team; if not infected refer to continence advisor/community nurse.

12(d) **If catheter,** *do you have any problems with this?*

Yes ☐
No ☐

Action: If yes, refer to continence advisor/community nurse

13(a) **Ask all**: *Do you ever soil or mess yourself?*

Yes ☐
No ☐ ←go to 14

13(b) **If yes,** *how often do you have soiling accidents?*

More than once or twice a day ☐ *
Once or twice a day ☐ *
Three or more times a week ☐ *
Once or twice a week ☐ *
Once or twice a month ☐
Less than once a month ☐

Action: If 3 or more times a week, refer to team. If once or twice a week, refer to continence advisor/ community nurse.

14 **Men only, women go to Q15.**

14(a) ***In the last month*** *have you usually had to get up to pass water during the night?*

Yes ☐
No ☐ ←go to (d)

14(b) **If yes,** *how often per night?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐ 1 times

Twice a night or less - go to (d)
More than twice - go to (c)

14(c) **If more than twice,** *have you seen your doctor about this problem in the last month?*

Yes ☐
No ☐

Action: If No, refer to team.

14(d) ***In the last month*** *have you had difficulty in passing your water?*

No difficulty ☐ ←go to 16
Some difficulty ☐ ←go to 16
A lot of difficulty ☐ *

14(e) **If a lot of difficulty,** *have you seen your doctor about this problem in the last month?*

Yes ☐
No ☐

Action: If a lot of difficulty passing water ***and*** not seen doctor in the last month, refer to team.

Women only. Men go to 16.

15a *How old were you when you had your first menstrual period?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐ 1 years

15b *How old were you when you had your last menstrual period?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐ 1 years

15c *Did your periods stop naturally, because of surgery, or for some other reason?*

Naturally ☐
Surgery ☐
Other (specify) ☐ ←

15d *Have you ever been pregnant (including miscarriages and stillbirths)?*

Yes ☐
No ☐ ←go to 16

15e *How many children, including stillbirths, have you had?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐ 1

16 **Ask all patients:**

16(a) ***In the last month*** *have you been more constipated than usual?* Yes ☐ No ☐ ←go to 17

16(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ ←go to 17 No ☐

16(c) **If no,** *is it a problem for you?* Yes ☐ No ☐

Action: If it is a problem, refer to team

17(a) ***In the last month*** *have you had repeated attacks of diarrhoea?* Yes ☐ No ☐ ←go to 18

17(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ ←go to 18 No ☐

17(c) **If no,** *is it a problem for you?* Yes ☐ No ☐

Action: If it is a problem, refer to team

18 ***In the last month*** *have you had alternating attacks of diarrhoea and constipation?* Yes ☐ No ☐

19(a) ***In the last month*** *have you had blood in your motions?* Yes ☐ No ☐ ←go to 20

19(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, send stool specimen to laboratory for analysis. If it is positive for blood, refer to team.

20(a) ***In the last month*** *have your motions been black?* Yes ☐ No ☐ ←go to 21

20(b) *Are you taking iron tablets?* Yes ☐ ←go to 21 No ☐

20(c) **If no,** *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, send stool specimen to laboratory for analysis. If it is positive for blood refer to t[illegible]n.

21 *Can you chew satisfactorily?* Yes ☐ No ☐

Action: If No, refer to dentist.

22(a) *Do you have a problem with swallowing?* Yes ☐ No ☐ ←go to 23

22(b) **If yes,** *have you seen your doctor about this?* Yes ☐ No ☐

Action: If No, refer to team.

23(a) ***In the last month*** *have you vomited blood or vomit that looks like coffee grounds?* Yes ☐ No ☐ ←go to 24

23(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, refer to team.

24(a) *Have you coughed up blood?* Yes ☐ No ☐ ←go to 25

24(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, refer to team.

25(a) *Do you **usually** bring up any phlegm from your chest first thing in the morning in the winter?* Yes ☐ No ☐

25(b) *Do you **usually** bring up any phlegm from your chest during the day - or at night - in the winter?* Yes ☐ No ☐

If Yes to 25(a) or 25(b), ask 25(c). If not, go to 25(d).

25(c) *Do you bring up phlegm like this on most days for as much as three months each year?* Yes ☐ No ☐

25(d) *In the past three years, have you had a period of increased cough and phlegm lasting for three weeks or more?* Yes ☐ ←one period Yes ☐ ←2 or more periods No ☐

25(e) *Does your chest sound wheezy or whistling on most days (or nights)?* Yes ☐ No ☐

25(f) *Do you get short of breath walking with people of your own age on level ground?* Yes ☐ No ☐

25(g) *Are you short of breath on talking?* Yes ☐ No ☐ ←go to 26

25(h) **If yes** to Q25(g), *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, refer to team.

26(a) *Do you have swelling of your legs up to your knees on getting up in the morning?* Yes ☐ No ☐ ←go to 27

26(b) **If yes,** *have you seen your doctor about this in the last month?* Yes ☐ No ☐

Action: If No, refer to team.

27 *In the last **six months**, how many falls have you had **at home**?* None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ More than 4 ☐

Action: More than 4, refer to team

28 *Over the last **six months** have you noticed unexplained weight loss of more than half a stone?* Yes ☐ No ☐

Action: If Yes, refer to team.

29 *Compared with other people of your own age would you say that your health is generally: excellent, good, fair or poor?*

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

30 *Compared to other people of your age, would you describe yourself as:*

- Very physically active ☐
- Fairly physically active ☐
- Not very physically active ☐
- Not at all physically active ☐

31 Here are some activities which people sometimes find difficult. For each one ask, "Do you do the following by yourself or could you do the following by yourself if you had to? And if unable to do it alone, do you receive enough help?"

		No difficulty	Some difficulty	Unable to do it alone but help is usually available	Unable to do it alone and not enough help is available
31a	Cut your own toe nails	☐	☐	☐	☐ *
31b	Dress yourself including zips or buttons	☐	☐	☐	☐ *
31c	Cook a hot meal	☐	☐	☐	☐ *
31d	Do light housework or simple repairs	☐	☐	☐	☐ *
31e	Go up and down stairs and steps (if necessary using a frame, tripod or stick)	☐	☐	☐	☐
31f	Wash all over (including bathing or showering)	☐	☐	☐	☐ *
31g	Walk 50 yards down the road (if necessary using a frame, tripod or stick)	☐	☐	☐	☐
31h	Do shopping	☐	☐	☐	☐ *

Action: Any * refer to the appropriate service.

Introduction:
I am now going to ask you some questions which involve memory, reading and writing type exercises.
Nurse Instruction:
Remember not to prompt the patient. Ask the questions exactly as they are written.

32 **Orientation** (Ask the following questions)

			Correct	Incorrect
32a	*What is the date today?* *Code whether date, month and year are correct).*	Date	☐	☐
32b		Year	☐	☐
32c		Month	☐	☐
32d	*What day of the week is it today?*	Day	☐	☐
32e	*What is the season?* **(Seasons:** (Jan/Feb = Winter (March = Winter or Spring (Apr/May = Spring (June = Spring or Summer (July/Aug = Summer (Sept = Summer or Autumn (October = Autumn (Nov/Dec = Autumn or Winter	Season	☐	☐
32f	*What is the name of this place? Where is it located?* For home visits ask, *"What is the full address of this place?"*	Place	☐	☐
32g	*What floor of this building are we on?*	Floor	☐	☐
32h	*What is the name of this city/town/village?*	Town	☐	☐
32i	*What county are we in?*	County	☐	☐
32j	*What country are we in?*	Country	☐	☐

33 **Immediate Recall**

Instruction to Patient:
"I am now going to say three words. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them in a few minutes.

Name these three objects taking 1 second to say each:

"Apple" "Table" "Penny"

Rate the first attempt. If any errors or omissions are made on the first attempt, repeat all the names until patient learns all three up to a maximum of 5 repeats.

First Repetition

	Correct	Incorrect
Apple	☐	☐
Table	☐	☐
Penny	☐	☐

34 **Attention and Calculation**

34a *"Now I would like you to take 7 away from 100".*
"Now take 7 away from the number you get".
"Now keep taking 7 away until I tell you to stop".

Rate as correct each time the difference is 7, even if a previous answer was incorrect. Do not repeat the number you were given.

	Correct	Incorrect
Subtraction 1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐
5	☐	☐

34b **If 34a is not done, ask 34b.**
NB Only count score for 34b if 34a not done.

Ask the subject to spell the word "world" backwards
The score is the number of letters in correct position.
For example, "dlrow" is 5, "dlorw" is 3.

	Correct	Incorrect
d	☐	☐
l	☐	☐
r	☐	☐
o	☐	☐
w	☐	☐

35 **Recall**

"What were the three words I asked you to repeat a little while ago?" (33)

	Correct	Incorrect
Apple	☐	☐
Table	☐	☐
Penny	☐	☐

36 **Language**

"Now I am going to ask you to do some things, so please listen carefully. Some may seem very simple, but please bear with us."

If, for physical or educational reasons, the patient is not able to complete this section, leave all coding boxes blank and make a note of the reasons for omission. Then go to the end of this section (Deriving total score).

36a **Naming**

	Correct	Incorrect
Show the subject a wrist watch and ask, *"What is this called?"* — Watch	☐	☐
Show a pencil and ask, *"What is this called?"* — Pencil	☐	☐

Answer is only correct if object is accurately named.

36b **Repetition**

	Correct	Incorrect
*"I am now going to say something and I would like you to repeat it after me": **"No ifs, ands, or buts".*** — Repetition	☐	☐

Only one presentation is allowed, so it is essential that you read the phrase clearly and slowly, enunciating all the s's.

36c **3-Stage command**

*"I am now going to give you a piece of paper. When I do, take the paper in your **RIGHT** hand, fold the paper in half with **BOTH** hands and put the paper down on your **LAP"**.*
Hand the paper to the patient's midline.

If the full sequence is not completed, repeat the whole instruction.

	Correct	Incorrect
Takes paper in right hand	☐	☐
Folds paper in half	☐	☐
Puts paper on lap	☐	☐

36d **Reading**

Hold up the card which reads **"Close your eyes"**, so the subject can see it clearly. Say, *"Please read what is here and do what it says".*

	Correct	Incorrect
Closes eyes	☐	☐

Score as correct only if patient actually closes eyes.

Writing

36e Give the subject a blank piece of paper and say,
"Write a complete sentence on the piece of paper".
Spelling and grammar are not important. The sentence must have a subject and a verb.

	Correct	Incorrect
Writes sentence	☐	☐

Copying

36f *"Here is a drawing. Please copy the drawing on the paper".*
Give intersecting pentagons card.

Answer is correct if the two five-sided figures intersect to form a four-sided figure and if all the angles in the five-sided figures are preserved.

	Correct	Incorrect
Draws pentagons	☐	☐

Deriving total score

	Yes	No
Language section (Q36) completed:	☐	☐

Total score: 0 1 2 3 4 5 6 7 8 9 (10 / 1)

a. For patients who did not complete the language section on physical/educational grounds, tick "No" for "language section completed".
Give one point for every correct answer and fill in the number grid.

NB Only include scores for Q34b (world spelled backwards) if Q34a (subtraction) not conducted.

Action: If the total score is less than 12, refer to the Community Psychiatric Nurse or Memory Clinic.

b. For all other patients, tick "Yes" for "language section completed". Sum the total of correct answers and fill in the number grid.

NB Only include scores for Q34b (world spelled backwards) if Q34a (subtraction) not conducted.

Action: If the total score is less than 17, refer to the Community Psychiatric Nurse or Memory Clinic.

Comments on MMSE (Q32-36):

37 *Has a doctor ever told you that you had any of the following? If yes, was that in the last year?*

	No	Yes, within last year	Yes but before last year
Pneumonia	☐	☐	☐
Emphysema	☐	☐	☐
Asthma	☐	☐	☐
Arthritis/Rheumatism	☐	☐	☐
Eczema	☐	☐	☐
Stomach ulcer/other digestive ulcer	☐	☐	☐
Haemorrhoids or piles	☐	☐	☐
High blood pressure	☐	☐	☐
Heart attack	☐	☐	☐
Stroke	☐	☐	☐
Leg ulcer	☐	☐	☐
Varicose veins	☐	☐	☐
Gout	☐	☐	☐
Depression needing treatment	☐	☐	☐
Thyroid trouble	☐	☐	☐
Cataract	☐	☐	☐
Glaucoma	☐	☐	☐
Fractured spine	☐	☐	☐
Fractured hip	☐	☐	☐
Parkinson's disease	☐	☐	☐
Cancer (if yes, ask where)	☐	☐	☐ ← Site
Infection in bladder or kidneys	☐	☐	☐

Men only

Trouble with your prostate gland	☐	☐	☐

38a *Have you ever been told by a doctor that you have sugar diabetes?* Yes ☐ No ☐ go to 39

38b *When were you first told you had diabetes? (give year)* 19 ☐☐ (0 1 2 3 4 5 6 7 8 9)

38c *What treatment are you on for your diabetes?*
(Tick all that apply)
Diet alone ☐
Tablets ☐
Insulin injections ☐
No treatment ☐

38d *Do you test your blood for sugar?* Yes ☐ No ☐

If yes, ask *"how often do you do this?"*
About once a day ☐
About once a week ☐
About once a month ☐
Less than once a month ☐

38e *Do you test your urine for sugar?* Yes ☐ No ☐

If yes, ask *"how often do you do this?"*
About once a day ☐
About once a week ☐
About once a month ☐
Less than once a month ☐

38f *Who do you normally see about your diabetes?*
(Can be more than one person)
Family doctor/GP ☐
Hospital doctor ☐
Practice/District nurse ☐
No one ☐

38g *In the **last year**, have you had your feet examined?* Yes ☐ No ☐ D/K ☐

38h *In the **last year**, have you had your eyes examined?* Yes ☐ No ☐ D/K ☐

38i *In the **last year**, have you discussed your diet with a dietician?* Yes ☐ No ☐ D/K ☐

Nurse instruction:
Questions (j) and (m) should be asked **only to patients on tablets or insulin.**

38j *Have you ever had a low blood sugar (a "Hypo")* Yes ☐ No ☐ D/K ☐

Ask all patients on tablets or insulin Q38k to m.

38k *If you have a low blood sugar, should you increase your diabetes treatment?* Yes ☐ No ☐ D/K ☐

38l *If you have a low blood sugar, should you take a sugary drink or snack?* Yes ☐ No ☐ D/K ☐

38m *If you have the 'flu, should you stop taking your diabetes tablets/insulin?* Yes ☐ No ☐ D/K ☐

39a *I would like to ask you some questions about your housing.*

Who do you live with?

- Alone ☐
- Spouse ☐
- Son/Daughter ☐
- Other relative ☐
- Friend ☐
- Other (specify) ☐ _____

39b *What kind of accommodation do you live in?*

- Council rental ☐
- Private rental ☐
- Housing Association ☐
- Home owner ☐
- Sheltered accommodation ☐)
- Local Authority residential home ☐)
- Private residential home ☐) go to 40
- Local Authority nursing home ☐)
- Private nursing home ☐)

If living in own or rented accommodation, ask:

39c	*In the last year have you had difficulty keeping your home warm?*	Yes * ☐	No ☐
39d	*Do you have central heating?*	Yes ☐	No ☐

39e	**If yes,** *in which rooms?*	All	Some	None
	Living rooms	☐	☐	☐
	Bedrooms	☐	☐	☐

39f	*Do you have an indoor toilet?*	Yes ☐	No ☐ *
39g	*Do you have a relative, neighbour or friend whom you can call on for help when required?*	Yes ☐	No ☐ *
39h	*Is there anyone available if you need help at night?*	Yes ☐	No ☐ *

Action: If 3 or more *, refer to Social Services.

40a *When you need to talk about private matters or when you are worried or stressed, who can you really count on or feel at ease with?* (May give more than one answer).

- No one ☐ *
- Spouse ☐
- Friend ☐
- Neighbour ☐
- Relative ☐
- Home Help/other paid help ☐
- Warden ☐

40b	*During the last year have you experienced?* (May give more than one answer)	*Yes	No
	Death or separation from a loved one	☐	☐
	Serious illness in a loved one	☐	☐
	Moving your residence	☐	☐

40c	*Do you ever have difficulty in making ends meet, I mean, is it difficult to find the money to pay your bills?*	Yes * ☐	No ☐
40d	*Do you have difficulty in managing your own finances, I mean things like paying for bills, working out change etc?*	Yes * ☐	No ☐

Action: If 2 or more *, refer to Social Services.

41 *I am now going to ask you some questions about how you've been feeling over the* ***past few weeks.*** *For each question, please choose the answer that best applies to you.*

		Not at all	No more than usual	Rather more than usual	Much more than usual
41a	*Have you lost much sleep over worry?*	☐	☐	☐	☐
41b	*Have you had difficulty in staying asleep once you are off?*	☐	☐	☐	☐
41c	*Have you felt constantly under strain?*	☐	☐	☐	☐
41d	*Have you been getting edgy and bad-tempered?*	☐	☐	☐	☐
41e	*Have you been getting scared or panicky for no good reason?*	☐	☐	☐	☐
41f	*Have you found everything getting on top of you?*	☐	☐	☐	☐
41g	*Have you been feeling nervous and strung-up all the time?*	☐	☐	☐	☐

42 ***These questions are about how you've been feeling over the last week. For each question, please choose the answer that best applies to you.***

		Yes	No
42a	*Are you basically satisfied with your life?*	☐	☐ *
42b	*Have you dropped many of your activities and interests?*	* ☐	☐
42c	*Do you feel that your life is empty?*	* ☐	☐
42d	*Do you often get bored?*	* ☐	☐
42e	*Are you in good spirits most of the time?*	☐	☐ *
42f	*Are you afraid that something bad is going to happen to you?*	* ☐	☐
42g	*Do you feel happy most of the time?*	☐	☐ *
42h	*Do you often feel helpless?*	* ☐	☐
42i	*Do you prefer to stay at home rather than going out and doing new things?*	* ☐	☐
42j	*Do you feel you have more problems with memory than most?*	* ☐	☐
42k	*Do you think it is wonderful to be alive now?*	☐	☐ *
42l	*Do you feel pretty worthless the way you are now?*	* ☐	☐
42m	*Do you feel full of energy?*	☐	☐ *
42n	*Do you feel that your situation is hopeless?*	* ☐	☐
42o	*Do you think that most people are better off than you are?*	* ☐	☐

42p Count the number of asterisked replies:
If score is 7 or less, go to 43. **Total Score:** 0 1 2 3 4 5 6 7 8 9 (10) (1)

If score is more than 7, ask:

42q *Are you receiving treatment for these feelings?* Yes ☐ No ☐ ←go to 42s

42r *How long have you been having this treatment* For more than 6 months ☐ 6 months or less ☐

42s **Action:**
Refer to team if score more than 7 **and** no treatment **or** more than 6 months on present treatment.

43a *Do you smoke cigarettes (including hand rolled) at present?* Yes ☐ No ☐ ←go to (c)

43b *How many cigarettes do you smoke a day?* 0 1 2 3 4 5 6 7 8 9 (10, 1) Cigarettes go to (f)

or how many ozs of tobacco do you smoke a day? 0 1 2 3 4 5 6 7 8 9 (1, 0.1) Ozs of tobacco go to (f)

43c **If current non-smoker** ask, *have you ever smoked cigarettes?* Yes ☐ No ☐ ←go to 44

43d *How many cigarettes did you smoke a day?* 0 1 2 3 4 5 6 7 8 9 (10, 1) Cigarettes

or how many ozs of tobacco did you smoke a day? 0 1 2 3 4 5 6 7 8 9 (1, 0.1) Ozs of tobacco

43e *How old were you when you stopped smoking?* 0 1 2 3 4 5 6 7 8 9 (10, 1) Years

Ask all current and ex-smokers:

43f *How old were you when you started smoking?* 0 1 2 3 4 5 6 7 8 9 (10, 1) Years

44a *During the last year have you taken an alcoholic drink?* Yes ☐ No ☐ ←go to (f)

44b *During the past week how many drinks have you had of each of the following?*
Record number, including zero.

Spirits - number of singles 0 1 2 3 4 5 6 7 8 9 (10, 1)

44c Wine, Sherry or Port - number of glasses 0 1 2 3 4 5 6 7 8 9 (10, 1)

44d Beer - number of half pints 0 1 2 3 4 5 6 7 8 9 (10, 1)

44e *Compared with 5 years ago, would you say that on the whole you drink more, less, or about the same nowadays?*
More nowadays ☐ Less nowadays ☐ About the same ☐

44f **If a non-drinker** ask, *have you always been a non-drinker or did you stop drinking for some reason?*
Always a non-drinker ☐ Used to drink but stopped ☐ ←go to 45

44g **If stopped drinking,** *why did you stop?* (Tick all that apply)

	Yes	No
Illness, doctor's advice	☐	☐
Concerned about health	☐	☐
Too expensive	☐	☐
Other	☐	☐

If "Other", please specify: ☐

45a *Do you have any problems with your eyesight?* Yes ☐ No ☐

45b *Do you wear glasses?* (If patient is wearing glasses, don't ask, just tick) Yes ☐ No ☐ ←go to (c)

45c **If yes,** *do you wear them all the time, for reading only or other reason?* Wears glasses all the time ☐ Wears glasses for reading only ☐ Other, please specify ☐ ← ☐

45d *Are you registered as blind or partially sighted?* Blind ☐ Partially sighted ☐ No ☐

46 **Visual Acuity**

Test with patient wearing usual glasses. Using Glasgow chart, measure the patient's vision at 3 metres. If the patient cannot see the biggest letters, then measure at 1 metre. Measure both eyes first, then each eye separately. Scores can be plus or minus. The greater the score, the worse the vision.

46a

Both eyes	**Left eye**	**Right eye**
Plus ☐ Minus ☐	Plus ☐ Minus ☐	Plus ☐ Minus ☐
0 1 2 3 4 5 6 7 8 9 1	0 1 2 3 4 5 6 7 8 9 1	0 1 2 3 4 5 6 7 8 9 1
0.1	0.1	0.1
0.01	0.01	0.01
0.001	0.001	0.001
Measured at 3 metres ☐	Measured at 3 metres ☐	Measured at 3 metres ☐
Measured at 1 metre ☐	Measured at 1 metre ☐	Measured at 1 metre ☐
Unable to read at 1 metre ☐	Unable to read at 1 metre ☐	Unable to read at 1 metre ☐

If a minus score, or score less than 0.5, go to Q47, If score is 0.5 or greater, re-test using pinhole.

46b **Pinhole score:**

Left eye	**Right eye**
Plus ☐ Minus ☐	Plus ☐ Minus ☐
0 1 2 3 4 5 6 7 8 9 1	0 1 2 3 4 5 6 7 8 9 1
0.1	0.1
0.01	0.01
0.001	0.001
Measured at 3 metres ☐	Measured at 3 metres ☐
Measured at 1 metre ☐	Measured at 1 metre ☐
Unable to read at 1 metre ☐	Unable to read at 1 metre ☐

Action:
If pinhole score improves to less than 0.5, refer to the optician.
If pinhole score is 0.5 or more, ask if investigated in the last year: → Yes ☐ No ☐
If No, refer to ophthalmologist.

47a *Do you have any leg or foot ulcers?* Yes ☐ No ☐ ←go to 48

47b *Are they/Is it being treated?* Yes ☐ No ☐

47c *Are they/Is it healing alright?* Yes ☐ No ☐

Action:
If ulcer(s) not treated or not healing with present treatment, refer to Community Nursing services

48a *Do you have any other problems with your feet?* Yes ☐ No ☐ ←go to 49

48b **If yes,** examine feet and specify: (Tick all that apply)

	Yes	No
Bunions	☐	☐
Corns	☐	☐
Ingrowing toe nail	☐	☐
Very long toenails	☐	☐
Other problem	☐	☐

If "Other problem", please specify ☐

48c **If yes,** *are you receiving chiropody?* Yes ☐ No ☐

Action: If no, refer for chiropody.

49a *Do you have any ulcers or sores anywhere on your body?* Yes ☐ No ☐ ←go to 50

49b **If yes,** examine for pressure sores and record if present:

	Yes	No
Sacrum	☐	☐
Buttock	☐	☐
Heel	☐	☐
Other	☐	☐

If "Other", please specify ☐

49c *Are they/Is it being treated?* Yes ☐ No ☐

49d *Are they/Is it healing alright?* Yes ☐ No ☐

Action:
If ulcer(s) not treated or not healing with present treatment, refer to Community Nursing services.

50 *In the last year have you had knee pain for most days (more than 14) of any month?* Yes ☐ No ☐

51a *"Please can you show me the tablets or medicine that you are currently taking."* For each one ask, *"How many of these or how much do you take each day?*

Any tablets or medicines shown? Yes ☐ No ☐

Print from container

51b

Name of tablet, medicine etc	Total daily dosage	Units	Dosage as required	Units

51c Number of different medications: 0 1 2 3 4 5 6 7 8 9 (10, 1)

51d **Check drug list for interactions.**
Are there any interactions? Yes ☐ No ☐

Action:
If possible drug interaction, refer to team.

Thank you very much for your time and help. All I need to do now is take a blood test and check your urine".

Take blood and test urine (MSU if incontinent and stool specimen if necessary)

52 **Blood Test**

Has the patient been fasting (not eaten in the last 12 hours) before the blood sample was taken? Yes (Fasting) ☐ No ☐

	Blood Constituent	Patient Result		Refer to Team	Immediate Action (inform GP) (within 8 hours)
✓	Haemoglobin		g/dl	<9 or >18	<8.0
	White cell count		x 10^9/l	<3 or >16	<2 or >17
	Platelets		x 10^9/l	<100 or >900	<80
	TSH		mU/l	<0.1 or >4	>16
✓	Glucose		mmol/l	>7.5 (fasting) or >12 (not fasting)	>15
	Sodium		mmol/l	<129	<125 or >152
	Potassium		mmol/l	<3.3	<3.0 or >6.0
	Urea		mmol/l	>18	>24
✓	Creatinine		µmol/l	>250	>350
	Total protein		g/l		
✓	Albumin		g/l	<30	<25
	Calcium		mmol/l	<2.0 or >2.7	>2.8
	Phosphate		mmol/l		
	Bilirubin		µmol/l	>35	>50
	Alkaline phosphatase		iU/l	>350	
	AST		iU/l	>80	>120
	Uric acid		mmol/l	>0.8	

53 Dip stick results

	Positive (record number of +s)				Negative	**Action** if result is positive
	+	++	+++	++++		
Glucose	☐	☐	☐	☐	☐	Refer to team
Protein	☐	☐	☐	☐	☐	MSU
Blood	☐	☐	☐	☐	☐	MSU

54 **Where applicable:** MSU (tick appropriate box) Infected ☐ Not infected ☐

Immediate Action: If grossly infected, plus acute symptoms, inform GP within 8 hours.

Action: If infected, refer to team

55 **Where applicable:** Stool specimen

Report shows presence of occult blood Yes ☐ No ☐

Action: If occult blood present, refer to team.

56a Any other serious condition which, in the nurse's opinion needs further assessment? Yes ☐ No ☐

56b **If yes,** give details:

57a Are there any assessor's comments relevant to the assessment? Yes ☐ No ☐

57b **If yes,** give details:

Emergency referral Yes ☐ No ☐

Interview finish time (24 hour clock)

Hours 0 1 2 3 4 5 6 7 8 9

Minutes 0 1 2 3 4 5 6 7 8 9

Visit finish time (24 hour clock)

Hours 0 1 2 3 4 5 6 7 8 9

Minutes 0 1 2 3 4 5 6 7 8 9

Referral Agencies
(tick all that patient has been referred to)

- ☐ GEM/PCT
- ☐ Dentist
- ☐ Chiropodist
- ☐ Ophthalmologist
- ☐ Optician
- ☐ Audiometry
- ☐ Community Psychiatric Nurse
- ☐ Memory Clinic
- ☐ Continence Advisor
- ☐ Community Nursing Services
- ☐ Social Services
- ☐ Occupational therapist
- ☐ Dietician
- ☐ Other

Variables used to derive the large and abridged version of the CHS FI using the BWHHS study cohort

Large CHS FI (51 variables)

1. Low Haemoglobin
2. High cholesterol
3. Low albumin
4. High creatinine
5. High glucose
6. Low BMI
7. High BMI
8. Waist hip ratio
9. High blood pressure (measured)
10. Orthostatic hypotension (measured)
11. Sinus Tachycardia (>100 bpm)
12. Eye sight trouble
13. Hearing trouble
14. Cataract
15. Glaucoma
16. Asthma
17. Arthritis
18. Angina
19. Ankle oedema
20. Bronchitis
21. Cancer
22. Cerebrovascular disease
23. Anxious or depressed
24. Depression
25. Diabetes Mellitus
26. Gout
27. High blood pressure (self report of diagnosed)
28. Falls
29. Hip fracture
30. Memory problems/dementia
31. Myocardial infarction
32. Stroke
33. Thyroid disease
34. Ulcers
35. Unable to walk out of house/difficulty in going out
36. Difficulty in walking about
37. Difficulty walking 400 yards
38. Difficulty going up and down stairs
39. Difficulty doing household chores
40. Difficulty washing and dressing oneself
41. Status activity level
42. Shortness of breath
43. Increased cough
44. Increased and often wheeze
45. Morning phlegm
46. Most days phlegm
47. Ever had chest pain
48. Chest discomfort
49. Chest pain
50. On level pain
51. On uphill pain

Abridged CHS FI (36 variables)

1. BMI
2. Waist hip ratio
3. High blood pressure (measured)
4. Orthostatic hypotension (measured)
5. Sinus Tachycardia (>100 bpm)
6. Eye sight trouble
7. Hearing trouble
8. Cataract
9. Glaucoma
10. Asthma
11. Arthritis
12. Angina
13. Bronchitis
14. Cancer
15. Anxious or depressed
16. Depression
17. Diabetes Mellitus
18. High blood pressure (self report of diagnosed)
19. Falls
20. Memory problems/dementia
21. Myocardial infarction
22. Stroke
23. Thyroid disease
24. Ulcers
25. Unable to walk out of house/difficulty in going out
26. Difficulty in walking about
27. Difficulty going up and down stairs
28. Difficulty doing household chores
29. Difficulty washing and dressing oneself
30. Status activity level
31. Shortness of breath
32. Increased cough
33. Increased and often wheeze
34. Morning phlegm
35. Ever had chest pain
36. Chest discomfort

Variables used to derive the large and abridged version of the CHS FI using the MRC assessment study cohort

Large CHS FI (44 variables)

1. Low Haemoglobin
2. High cholesterol
3. Low albumin
4. High creatinine
5. High glucose
6. Low BMI
7. High BMI
8. Waist hip ratio
9. High blood pressure (measured)
10. Orthostatic hypotension (measured)
11. Sinus Tachycardia (>100 bpm)
12. Eye sight trouble
13. Hearing trouble
14. Cataract
15. Glaucoma
16. Asthma
17. Arthritis
18. Emphysema
19. Cancer
20. Anxious or depressed
21. Depression
22. Diabetes Mellitus
23. Hip fracture
24. High blood pressure (self report of diagnosed)
25. Falls
26. Memory problems/dementia
27. Myocardial infarction
28. Stroke
29. Thyroid disease
30. Ulcers
31. Unable to walk out of house/difficulty in going out
32. Difficulty going up and down stairs
33. Difficulty doing household chores
34. Difficulty washing and dressing oneself
35. Status activity level
36. Shortness of breath
37. Increased cough
38. Increased and often wheeze
39. Morning phlegm
40. Most days phlegm
41. Ever had chest pain
42. Chest discomfort
43. On level pain
44. On uphill pain

Abridged CHS FI (35 variables)

1. BMI
2. Waist hip ratio
3. High blood pressure (measured)
4. Orthostatic hypotension (measured)
5. Sinus Tachycardia (>100 bpm)
6. Eye sight trouble
7. Hearing trouble
8. Cataract
9. Glaucoma
10. Asthma
11. Arthritis
12. Angina
13. Bronchitis
14. Cancer
15. Anxious or depressed
16. Depression
17. Diabetes Mellitus
18. High blood pressure (self report of diagnosed)
19. Falls
20. Memory problems/dementia
21. Myocardial infarction
22. Stroke
23. Thyroid disease
24. Ulcers
25. Unable to walk out of house/difficulty in going out
26. Difficulty in walking about
27. Difficulty going up and down stairs
28. Difficulty doing household chores
29. Difficulty washing and dressing oneself
30. Status activity level
31. Shortness of breath
32. Increased cough
33. Morning phlegm
34. Ever had chest pain
35. Chest discomfort