Measurement of frailty: development of a primary care framework and validation of an electronic Frailty Index

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By

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Abstract

Frailty measurement in primary care and at transitions of care is needed to enable timely identification of frailty, guide interventions and support proactive, integrated care. However, there is currently no single tool for frailty measurement in these settings.

This thesis comprises a systematic review and two observational studies. The systematic review of frailty measurement tools in primary care and at transitions of care identified few studies for emerging frailty. It was used to develop a framework for a tool, which included components to reflect a multidimensional model, use of routinely collected primary care data and quality of life as a holistic outcome for frailty.

The observational studies used an electronic Frailty Index (eFI) applied to primary care consultation data over a 5-year period (2007-2012) to measure frailty in a population aged 40 years and over (n=9793), selected by osteoarthritis and cardiovascular disease status. The first study described frailty and frailty change over 2 years by socio-demographic and disease status characteristics, including comorbidity severity. The second study linked survey data regarding anxiety, depression, fatigue, social networks and quality of life at two time points 12 months apart for a subset of this population (n=2878). Multiple regression methods were used to investigate whether eFI predicted quality of life and whether this prediction could be improved by the addition of other explanatory factors.

Frailty increased with age, deprivation and comorbidity severity, and increasing frailty was associated with increased frailty change over 2 years. A model that included age, gender, deprivation and eFI was moderately predictive of quality of life at 12-months. This predictive ability was significantly improved by including anxiety, depression, fatigue and healthcare use as additional explanatory factors in the model, although adding social network data did not improve prediction. Further research is required on the lifecourse of frailty across care interfaces.

(300 words)

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Chapter 1: Introduction

Providing safe and effective care to people living with frailty is often considered one of the greatest challenges facing modern health and care services (1). This chapter will firstly introduce the concept of frailty and next outline the leading conceptual models proposed for the condition. It will then go on to consider how frailty relates to other disease states and to systems of care, before discussing the importance of frailty in primary care and at transitions of care. Finally it will explain the necessity of measuring frailty and discuss the features of tools for this purpose.

1.1 Introduction to frailty

1.1.1 What is frailty?

Frailty is defined as a state of increased general vulnerability in which relatively minor stressors are associated with an increased risk of adverse outcomes (1). It is a result of the changes that occur in many different physiological systems during a person's lifetime and it is therefore most common in older age (1). Frailty is a complex and multi-dimensional state, which is related to but distinct from other important concepts, including comorbidity, ageing, disability and dependency (2-9). Frailty is also a dynamic condition, which is modifiable and has the capacity to improve as well as to progress (1,10,11).

1.1.2 Why did the concept of frailty emerge?

The concept of frailty emerged in the context of the increasing recognition that there was a subset of older people particularly prone to adverse clinical outcomes following apparently minor stressors. As well as the impact of these adverse outcomes upon individual older people and their carers, collectively this group had increased health and care needs, which were in turn associated with increased economic and capacity pressures in health and care systems (7,8).

However, the problems these older people experienced could not necessarily be defined in relation to specific diseases or disabilities (3). Furthermore, they often did not respond well to the disease-focused approach widely adopted in modern health and care services, in which guideline driven disease management has tended to result in a move away from generalist, holistic care and towards the creation of diagnostic, clinical and organisational silos of care (12). It became apparent

that this group had sub-threshold age related changes in multiple physiological systems (1) and that whilst they might also have multiple long-term conditions, focusing clinical management solely upon these long-term conditions did not achieve the desired outcomes. This was because in the presence of multimorbidity, the effectiveness of the application of evidence-based guidelines for single conditions becomes limited by the overall complexity of the person's condition (12). This picture is further complicated both by the presence of other underlying age related physiological changes and by the changes in individual priorities and goals of care that can occur in older age (13). The clinical complexity and uncertainty associated with ageing and multi-morbidity could not, therefore, be addressed by increasingly complicated combinations of individual clinical guidelines, but instead the need for the holistic clinical judgment of 'expert generalists' to play a much greater role in the management of this group of people was emphasised (12).

The concept of frailty therefore emerged due to the need for a new paradigm to help identify and meet both the individual and collective needs of an ageing population (3). Although the concept of frailty is now well established, there is still no universal agreement regarding a single model of frailty or other key aspects of condition, including the best approach to frailty measurement (14).

1.1.3 Perceptions of frailty

'Frailty' is a term that is widely used but which can be seen to mean different things to different people. Perceptions of the condition vary depending upon whether the perspective is that of individuals with frailty, their families and carers, health and care professionals, or wider society.

Compared to people living with frailty, families, professionals and carers often use different language when discussing or describing frailty and assign different priorities to the consequences of the condition (15,16). For example, in medical literature frailty is described as 'a state of vulnerability, resulting from a cumulative decline in many physiological systems over a lifetime, in which minor stressors are associated with an increased risk of adverse outcomes' (1). However, a qualitative study by Age UK described people with frailty as: 'people over 65 years, and probably much older, who struggle to do everyday tasks themselves and are becoming increasingly vulnerable to setbacks and difficulties' (15). Furthermore, this study found that people whom professionals and carers identified as frail did not describe themselves as such, instead using expressions such as 'slowing down' and 'being unable to cope' when discussing their condition (15). This variance partly reflects the difference between lay and professional perspectives, but it

also illustrates the absence of common agreement regarding the nature of frailty (17).

Despite variations in how frailty is articulated from different perspectives, a strong common theme is that the condition of frailty is generally defined and conceptualised in negative terms. Within medical literature this perception is frequently reinforced either through direct statements such as 'frailty is the most problematic expression of population ageing' (1), or indirectly, as a result of the language used in relation to frailty and the outcomes and objectives chosen when considering the condition. For example, well established medical models of frailty are defined in terms of deficits, deficiencies and impairments (2,18) and the outcomes considered in relation to frailty often include disability, dependency and mortality (19,20). Furthermore, objectives in the management of frailty are frequently considered in terms of the avoidance of adverse events, particularly events that are significant from the health and care system perspective, rather than in terms of the achievement positive patient focused outcomes and goals of care.

This negative perspective is further reflected in the societal stigmatisation of frailty. For example, the difficulties in meeting the health and care needs of increasing numbers of older people with frailty have been widely discussed in the media, and frequently in catastrophic terms.

1.1.4 Why is the concept of frailty useful?

The usefulness of the concept of frailty depends upon it having meaningful applications that can help to improve individual experience and quality of life for people living with the condition. These applications can be considered in three main categories:

- Individual case management
- Service planning and delivery
- Research and development

The adverse outcomes associated with frailty, such as falls, delirium, hospitalisation and care home admission have complex inter-relationships and significant consequences for individuals. For example, frailty and delirium are commonly found together and this combination is associated with poor outcomes for hospitalised patients (21). Furthermore, these outcomes are also associated with high health and care costs, and are therefore important at a system level. For example, the cost of falls in people aged over 75 is five times that of people aged 60-64 years, with 49% of the extra costs due to cost of admissions and 41% related to increased long term care needs (22). Delirium is also associated with increased costs of care and has been estimated to have an

economic impact of similar magnitude to that of falls and diabetes (23). The application of the concept of frailty is therefore valuable both for individual clinical management and for system and service planning and delivery.

On an individual level, recognising frailty can help to identify opportunities and approaches for intervention. It can also inform clinical decision-making and help set the context for routine management decisions. For example, people with frailty have altered pharmacokinetics and therefore the recognition of frailty has important implications for medicines management (24). It can also support targeted interventions related to potentially modifiable features of frailty, such as sarcopenia and nutrition (25,26). The recognition of frailty can also help to avoid interventions that might be inappropriate in the context of frailty, thus preventing or minimising complications or unintended consequences of healthcare interventions in this group of people (27-29).

Recognition of the concept and consequences of frailty can also make a valuable contribution to the planning and delivery of systems of care and services for older people, through better understanding of population needs, potential interventions and modes of delivery to meet those needs (30). This role is particularly important in the NHS in England currently, in the context of the 'Five Year Forward View' (31), which aims to transform the delivery of care for many population groups, including older people.

The concept of frailty is also highly relevant in the context of research relating to clinical diagnoses and therapeutic interventions for conditions affecting older people, where it can make an important contribution to both the design and interpretation of such studies (32). All three of these applications require not only the recognition of frailty but also the ability to understand, measure and analyse the condition in relation to both individual and external contextual variables. The rest of this chapter therefore discusses a series of areas relevant to development of this understanding, namely: models of frailty; frailty in relation to other diseases and conditions; frailty in relation to systems of care; frailty in primary care and at transitions of care; and tools to measure frailty.

1.2 Models of frailty

A clear conceptual model for frailty is required for the understanding and practical application of the condition. However, universal agreement regarding a single model of frailty has not yet been established (17). This section outlines the three most important alternative models of frailty:

- Phenotype model
- Cumulative deficit model
- Multi-dimensional models

The two most well established models of frailty are the phenotype and the cumulative deficit models, both of which have been validated against adverse health outcomes related to frailty in large cohort studies (33-35). There is overlap in the identification of frailty (1,35) and convergent predictive ability for adverse health outcomes between these two leading models (1,33,34). However, there are important conceptual and practical differences between them (33). Alternative multi-dimensional models for frailty have also been advocated.

1.2.1 Phenotype model

The phenotype model of frailty was first proposed by Fried (2) in order to characterise and present a standardised definition for the clinical syndrome of frailty. This model defined frailty as a clinical syndrome in which three or more of the following five criteria were present: (i) unintentional weight loss, (ii) exhaustion, (iii) weakness (measured by grip strength), (iv) slow walking speed and (v) low physical activity. This phenotype had an overall prevalence of about 7% in community dwelling adults over the age of 65 years and was found to be independently predictive of adverse outcomes such as falls, disability, hospitalisation and death. This study also investigated the nature of the relationships between frailty, disability and comorbidity, and described comorbidity, which is other conditions in addition to frailty, as an aetiological factor in the development of frailty and disability as an outcome of frailty (2).

The phenotype model focuses upon signs and symptoms and takes a categorical approach to frailty using a set of pre-defined criteria. It can therefore be relatively insensitive to changes in frailty. Furthermore, it does not indicate the underlying causes for the phenotypic presentation of frailty and cannot therefore usually guide specific therapeutic interventions. This model considers frailty as a pre-disability state and the predictive ability of this approach can therefore be limited by presence of disability (33). The phenotype model of frailty has been widely used and has been the basis for much research (36,37) since it was first published fifteen years ago.

1.2.2 Cumulative deficit model

The cumulative deficit model of frailty tends to focus upon physical status and determinants of frailty. It is based upon the importance of the accumulated effect of multiple health deficits, present

in the same individual at the same time and related to underlying physiological abnormalities. This approach results in the expression of frailty as a 'frailty index'. This model was first described in 2001 (18) and a standardised procedure for constructing a frailty index was later described (38).

To develop a frailty index, a list of potential deficits is constructed and the 'frailty index' is calculated by dividing the number of deficits identified in any individual by the total number of possible deficits. A minimum of 30 deficits is recommended to construct a valid frailty index (38). There are no pre-defined criteria and a deficit can be any symptom, sign, disease, disability or laboratory abnormality that is associated with age and adverse outcomes, present in at least 1% of population, increases with age and does not saturate at too early an age (38).

This model of frailty does not weight or scale the deficits included. Instead it is underpinned by the concept that the number of abnormal systems, or 'cumulative deficits', is more predictive of frailty than abnormality in any single system (1,38). Key differences exist between this model and the phenotype model. A frailty index is usually a continuous variable and therefore potentially more sensitive to change in frailty over time than the phenotype model. The nature of the deficits contributing to the frailty index can also provide some insight into the underlying causes of frailty and therefore offer some potential to guide interventions. Furthermore, deficits can include disabilities and therefore the ability of this model to reflect frailty is not limited by the presence of disability (33). Alongside the phenotype model of frailty, the cumulative deficit model and associated frailty index construct have also been widely used in frailty research (39-42).

1.2.3 Multi-dimensional frailty models

Although the accumulation of physical health deficits is accepted as an important aspect of frailty (18), frailty is also recognised as a multi-dimensional condition (20,43,44) and has been described in its wider sense as a 'collection of modifiable health and social needs' (15). More recently, therefore, a number of authors have advocated integrated models of frailty, which extend beyond the physiological and physical determinants of frailty (16,45-48). Clear arguments have been made for models of frailty to include psychological, emotional and social domains alongside the well-established physical health domains (16,45-48). The case for including an environmental domain within models for frailty has also been made and is likely to be particularly relevant for people with frailty living in their own homes (48). The inclusion of life course determinants in models of frailty has also been proposed (46). Despite the clear relevance of these arguments to a range of

theoretical, practical and operational aspects of frailty, relatively few current models of frailty take such a broad multidimensional approach or comprehensively include such a wide range of factors (49).

1.3 Frailty and other conditions

1.3.1 Frailty and comorbidity

Frailty is related to but distinct from comorbidity and disability (2), although the conditions very commonly co-exist. Comorbidity refers to the dynamic interactive state that exists when two or more long-term conditions interact together in the same person (50), compared to multimorbidity which is simply the co-existence of two or more such conditions in one individual. Disability is a limitation in activity or participation resulting from impairment, usually referring to physical or mental health impairment (51) .

Attempts to characterise the relationship between these factors have suggested that comorbidity is an aetiological factor in the development of frailty and that disability is an outcome of the condition (2,4). However, evidence has also shown that a disease focused approach to managing multiple long-term conditions on its own is not sufficient to manage frailty (3), implying that frailty is not simply a consequence of comorbidity. Although some relationships between frailty and other long-term conditions have been described (52-54), interactions between frailty and a range of common comorbidities are not yet fully characterised.

The interactions between frailty and other long-term conditions are likely to be complex with multiple causal elements, which in some cases might all be required to achieve a given outcome (simultaneous causal strands) and in others might represent alternative means by which to reach the same end (alternate causal pathways) (55) . Furthermore, interactions between frailty and other long-term conditions also have the potential to be influenced by other factors such as psychological status, social circumstances or environmental conditions. Such influences could be either due to a direct physiological impact upon the interaction of interest, for example biological mediators associated with stress or depression (56), or through an indirect route, for example by impacting upon some aspect of condition management such as the ability to self-care.

1.3.2 Frailty and other conditions and disease states

The relationships between frailty and other conditions and disease states are also complex and not yet fully understood. A wide range of conditions and disease states may play various roles in the development of frailty throughout an individual's life course, from birth onwards (27).

Epidemiological studies, for example, have shown evidence of a relationship between birth weight and grip strength in middle age (57,58), and between postnatal growth and childhood development and motor and cognitive performance in midlife (59,60). Furthermore, they have also provided evidence that factors such as midlife depression, physical activity, chronic symptoms, self-rated health, alcohol intake and body mass index are all associated with the development of frailty in later life (61) .

Other studies have investigated potential biological mechanisms to explain some of these epidemiological associations. For example, a study to explore a potential role for biological mediators in the association between social isolation and frailty found that recent onset social isolation in early older age was associated with changes in the function of the hypothalamic-pituitary-adrenocortical axis (which is implicated in the biology of ageing), specifically, with diurnal cortisol patterns that increase the risk of morbidity and mortality (56).

The individual contributions and interactions between the many different conditions and disease states associated with frailty still remain largely unknown, as does any variation in their impact at different points along frailty trajectories. The cumulative deficit model implicitly supports the relevance of a life course approach to the role of other diseases and conditions in contributing to frailty. However, there is no comprehensive evidence base to describe the impact of different diseases, conditions and other factors, such as psychological stressors, upon the development of frailty, or how these influences are mediated, interact or vary over a life course. A greater understanding of these factors could make an important contribution to individual care and support, as well as to public health, social policy and wider well-being agendas.

1.4 Frailty and systems of healthcare

Systems of care have complex, important and potentially bidirectional relationships with frailty, meaning that they can have a role in both causal pathways for the condition and in pathways responding to needs associated with the condition. Systems of care are important not only in

providing for the needs of people with frailty, but also because the way in which this care is delivered can be critical in either reducing or exacerbating adverse outcomes or complications associated with frailty. Furthermore, systems of care might also have the potential to interact and influence the progression of the condition of frailty itself.

1.4.1 Systems of healthcare and the consequences of frailty

Meeting the needs of people with frailty and supporting them to achieve individual holistic goals and outcomes of care requires a whole system approach, with integrated and coordinated systems of care delivering health and care interventions which have been demonstrated to be effective (62). Currently, however, the integrated and targeted intervention necessary to meet these needs effectively is frequently not achieved.

Comprehensive Geriatric Assessment (CGA) (63,64), for example, is a holistic multi-dimensional assessment and intervention that has been shown to improve outcomes for people with frailty. However, the delivery of CGA is inconsistent across primary and secondary care boundaries and consistent delivery across the health and social care continuum is very rarely achieved (17).

There is widespread recognition that current NHS systems for acute and urgent care are not well suited to delivering holistic care to frail older people and frequently do not achieve the best outcomes for this group (65). Most NHS hospitals are organised around the disciplines of medicine for dealing with acute care, yet are mostly occupied by older patients with frailty whose needs are poorly met by such systems (66). As a result, this group of patients are particularly likely to experience long lengths of stay and multiple moves between wards in acute hospitals. Such moves frequently lack clinical rationale and are made to ‘serve the system rather than the patient’ (67) . Furthermore, they pose a threat to patient safety by increasing the risks of complications such as delirium, falls and transmission of infection, and reducing the likelihood that the person will receive specialist input such as CGA. These factors are likely to prolong acute hospital episodes and thus increase the risk of further adverse events (67), as illustrated by well-known examples of system failure in the care of older people, such as the Francis Report (68) .

Furthermore, risks to people with frailty posed by suboptimal systems of care extend beyond directly quantifiable medical complications and adverse events, such as falls, delirium and infections (67). Other possible consequences include the loss of personal autonomy and confidence, and loss of trust in the provision of care, all of which can have complex relationships

with, and adverse impact upon, an individual's quality of life and that of their carers (69,70). However, despite this, system redesign has not yet occurred at the pace required to appropriately, effectively and consistently meet the needs of older people with frailty (66).

1.4.2 Systems of care as potential contributors to frailty

Healthcare events, even when well managed and occurring in relatively fit people, can have a non-linear impact upon an individual's health and well-being. This effect is likely to be magnified if there is a suboptimal system response, particularly in the case of people living with frailty.

Acute healthcare events, such as emergency department attendances and unscheduled admissions, are often viewed as outcomes of frailty. It is also recognised that people with frailty can develop 'iatrogenic disability' as a result of hospitalisation (71) and of poor systems of care (67). However, there is another dimension to the relationship between healthcare episodes, systems of care and frailty that requires consideration. That is, the potential for healthcare systems to contribute to frailty development or progression, either through physical consequences or complications (67,68,71), or through psychosocial impacts such as loss of autonomy and disempowerment (69,70). Adverse healthcare experiences related to suboptimal systems of care, particular during episodes of acute care, can be associated with increased individual vulnerability to further adverse events, both in the immediate, medium and longer term. One hypothesis is, therefore, that systems of care have the potential to have a causative or mediating role not only in the consequences and complications of frailty, but also in the progression of the condition of frailty itself. There is a gap in current evidence in this area and these relationships and interactions require further investigation.

1.5 Frailty in primary care and at transitions of care

1.5.1 Recognition of frailty

The vast majority of healthcare activity in the UK occurs in community settings, with around 90% of all healthcare contacts taking place in primary care (72) . Therefore, it is likely that most healthcare contacts related to frailty also take place in primary care. However, to date this activity has not been comprehensively or consistently identified. The recognition of any clinical condition, at both individual and system levels, relies firstly upon making the clinical diagnosis and secondly upon the accurate and reliable recording of this information within clinical records. The lack of a consistent

approach to the diagnosis of frailty and the absence of a clear coding framework for the condition, have hampered the systematic recognition of frailty in primary care.

Read Codes are a coded thesaurus of clinical terms, maintained and managed by the Health and Social Care Information Centre (73). They have been used in the NHS since 1985 to provide a standard vocabulary through which clinicians can record clinical information in IT systems across primary and secondary care. There are two versions, Read codes version 2 (v2) and Clinical Terms Version 3 (CTV3) (74), and there is a procedure for requesting codes to be added or changed. New Read codes for mild, moderate and severe frailty were issued by the Health and Social Care Information Centre in October 2014, as follows:

- CTV3: X76Ao=Frailty; XabdY=Mild frailty; Xabdb=Moderate frailty; Xabdd=Severe frailty.
- Read V2: 2Jd..=Frailty; 2Jd0.=Mild frailty; 2Jd1.=Moderate frailty; 2Jd2.=Severe frailty.

This was an important breakthrough in enabling systematic coding of frailty and degrees of frailty severity across all electronic health records. In combination with increasing recognition of frailty as a clinical diagnostic entity and developing approaches to the measurement of frailty, it created a major opportunity to recognise and quantify frailty in primary care from the point at which it first emerges and is diagnosed, throughout the trajectory until the end of life.

1.5.2 Impact of frailty

The prevalence of frailty is estimated at around 7% in people aged over 65 years and as much as 25% in those aged over 85 years (75). The population is ageing and within our ageing population, people aged over 85 years are the most rapidly increasing group. The number of people with frailty is therefore also growing rapidly and accounts for increasing primary care activity.

Frailty has been shown to be associated with increased costs in secondary care settings and post hospital discharge (22,23,76,77). Furthermore, people with features of frailty, such as older age and multimorbidity, have been shown to have higher consultation rates (78) and higher healthcare utilisation and costs for all types of healthcare contacts, including primary care (79). However, the overall costs of frailty in primary care have been hard to define, because of i) the complex and multidimensional nature of both the condition and the healthcare needs and interventions associated with it, ii) the lack of a consistent approach to identifying and measuring the condition, and iii) the fact that systematic coding for frailty in primary care has only recently been introduced and is not yet in widespread use.

People with frailty have complex and unpredictable trajectories of need, as a result of which they are more likely to require escalation in their level of care and therefore to experience unscheduled transitions of care. They are also more susceptible to the adverse consequences that can arise at such transitions, particularly those related to poor communication or lack of care coordination. Frailty therefore has a considerable impact upon individuals within primary care and at transitions of care.

Frailty also has a wider impact upon primary care and at transitions of care. The need for a holistic, integrated and primary care based model of care for people with frailty is driving significant system transformation, through national policy and initiatives such as the NHS England 'Five Year Forward View' (31) and the British Geriatrics Society 'Fit for Frailty' guidance (80) . Furthermore, the need to identify and implement public health interventions to slow the emergence and progression of frailty also has major implications for primary care (75) .

1.5.3 Outcomes in frailty

Frailty is associated with a greater risk of mortality and the importance of other adverse clinical outcomes such as falls, emergency department attendances, unplanned hospital admissions, longer hospital stays and transitions into 24 hour care has also been emphasised (19). To date, the focus regarding clinical outcomes in frailty has been mainly upon outcomes which impact upon acute and secondary care services and less upon clinical outcomes managed within primary care. However, as a result of the ageing population, the impact of frailty outcomes in primary care is an important and increasing issue and there is an imperative for further research in this area.

However, in addition to consideration of clinically defined outcomes, a central objective of care for people living with frailty must be to improve their quality and experience of life. An understanding of how patient centred outcomes relate to frailty is therefore required and quality of life should be considered as a key outcome for frailty (46). Older people and their carers have emphasised the important contribution of emotional and social factors to overall quality of life (27,46), therefore the assessment of quality of life in frailty should extend beyond the assessment of health and functional capacity (13). Furthermore, the relationship between frailty and quality of life can change over time. For example, as frailty increases the priorities given to the different domains of quality of life change, with non-frail people reporting health as the most important factor whilst people living with frailty placing greatest emphasis upon social contacts (13).

1.5.4 Why measure frailty in primary care and at transitions of care?

The ability to measure frailty in primary care and at transitions of care is important to both individuals in their journeys of care and at system level regarding the organisation and delivery of care. To date, care for people with frailty has been largely reactive and crisis driven, and as a consequence is often fragmented and mainly focused in secondary care settings. Care can be less effective, higher risk and more costly if frailty is not recognised (19). The ability to measure frailty in primary care and at transitions of care could enable the early identification and management of the condition, guide preventative interventions and support a much-needed move towards a more proactive, integrated and holistic approach to care for this population group (19). It could not only help to reduce the numbers of transitions of care for people with frailty but also help to improve the safety, effectiveness and outcomes of any essential transitions.

Frailty measurement in primary care and at transitions of care could also be used to help identify population level needs and support risk stratification, thus informing service development and commissioning decisions. It could also help to support research into frailty and frailty interventions and their implementation in a range of areas such as:

- The relationship between frailty, comorbidity and other conditions (section 1.3, page 7).
- Understanding frailty trajectories and how they can be modified (11), particularly towards the end of life (81) .
- Testing of tools to assess performance of services important to people with frailty, for example patient reported experience measures for intermediate care (82) .
- Developing approaches to maximise engagement of people with frailty in service development and delivery.

1.6 Tools to measure frailty

There is now an acceptance of the need for tools to measure frailty and an increasing debate regarding the nature of such tools and their application in clinical practice (29,83). Potential applications exist at both individual and population levels and include:

- Informing clinical decision-making
- Targeting of specific health and social care interventions
- Evaluation of the impact of specific interventions

- Support of associated clinical commissioning decisions

Instruments to measure frailty will be useful in this context if they are able to i) measure the emergence and degree of frailty, ii) predict frailty progression, iii) measure outcomes in people with frailty.

1.6.1 Properties of measurement tools

In order to support care delivery, tools to measure frailty need to be valid, accurate, reliable and sensitive to change (1,49). In common with other healthcare measurement instruments, frailty measurement tools should be validated in the following dimensions (84):

- Face validity: whether the instrument appears to be relevant and fit for purpose in the experience of the clinicians intending to use it.
- Content validity: whether the instrument includes a range of elements sufficient to reflect the full extent of the concept being measured. In this case, to adequately reflect the multi-dimensional nature of frailty and the factors involved in frailty emergence and progression.
- Construct validity: whether the instrument behaves as would be expected if it were measuring the intended concept.
- Criterion validity: how the sensitivity and specificity of measurement results obtained using the instrument compare to the results of measurement using a previously established 'gold standard' measure of the concept of interest e.g. CGA for frailty.
- Predictive validity: the ability of the instrument to accurately predict future outcomes associated with the concept of interest.

It is also important to specify which aspects of frailty a tool is designed to measure and in what context, and to ensure that the tool has been validated for that purpose and in that context (49).

To have clinical relevance, frailty measurement tools must be validated in relation to outcome measures which are i) meaningful for people with frailty and their carers, ii) adequately reflect the complexity of an individual's circumstances (16) and iii) include both standardised and personalised outcome measures (3). They should also be able to demonstrate a dose response relationship between frailty and the outcomes of interest (19). Finally, frailty measurement tools also need to be able to detect clinically significant and bidirectional changes in frailty (in other words the ability to detect both increasing and decreasing frailty) over clinically meaningful timescales.

1.6.2 Components of tools to measure frailty

The selection of components for inclusion in a frailty measurement tool will have a key impact upon the properties of the final tool. The range of included components needs to be broad enough to reflect the full concept of frailty, but narrow enough to allow the tool to be practically applicable.

The components need to appear relevant and appropriate to the measurement of frailty and to reflect the full range of elements that are important in the conceptual model of frailty chosen to underpin the frailty measurement tool. The components chosen to contribute to a frailty measurement tool have a practical requirement to be measureable in their own right, but their inclusion should be based upon their content and predictive validity and not just determined by the ease with which they can be measured.

The methods by which the individual components of the tool are brought together are also critical to the quality and accuracy of the final measurement tool (85,86). This is illustrated by a study in which both self-report and test-based measures were each used to construct a frailty measurement tool (87). In this study, combining the self-report and test-based measures gave the measure of frailty that was the strongest predictor of frailty outcomes, yet it was not clear if this was due to the types of items included in the combined measure, the interactions between them, or simply that this tool included more items in total than either the self-report or test-based measurement tool alone.

The theoretical and methodological challenges of reducing complex data into a single measurement scale have been described, highlighting the need for a scale to be constructed through a valid numerical transformation if a reliable measurement tool is to be achieved (85,86) .

1.6.3 Methodology to develop tools to measure frailty

The methodological steps required in the development and validation of a tool to measure frailty can therefore be summarised as follows:

1) Define the context in which the tool is intended for use, for example, in primary care, secondary care, at transitions of care or in all settings of care.
2) Define the purpose of tool, in other words, whether it is intended to predict frailty, to measure frailty or to predict outcomes in frailty.
3) Define the conceptual model of frailty most relevant and applicable to the context and purpose of the frailty measurement tool.

4) Define the components that will most accurately and fully reflect the chosen model of frailty.
5) Define how each of these components will be measured.
6) Define how these components will be brought together within the construct of the measurement tool.
7) Validate the properties of the measurement tool.

Following development and validation of a tool, two further steps are required in order to establish a clinical prediction model, e.g. for frailty, namely impact analysis and implementation (19,88). It has been observed that, in general, studies often report the development and validation of tools, but impact analysis and implementation are more rarely reported (19,88) .

1.7 Summary

This chapter has identified and discussed a number of key aspects of frailty that are relevant to individual case management, to services and systems of care, and to the public health agenda. In particular, it has highlighted the importance of conceptual models of frailty, the properties and application of tools to measure the condition, and the importance of frailty in primary care and at transitions of care.

Chapter 2: Background

2.1 Conceptualising frailty in primary care and at transitions of care

2.1.1 Is frailty a long-term condition?

There is a developing narrative around the proposition that frailty has many of the characteristics of a long-term condition and should therefore be conceptualised as such (10,32). The advantages of this approach are firstly in supporting the practical management of the condition and secondly in supporting research into interventions for the condition, particularly those in primary care.

Conceptualising frailty in this way offers the opportunity to link its management to an operational framework for the management of long-term conditions that is well defined and well established in primary care in the UK (32). This systematic approach supports a focus on proactive management, aimed at maximising capability and minimising the need for acute reactive interventions. It is built upon a preventative and proactive approach to care which uses routine identification and coding of the condition to create disease registers to support co-ordinated and consistent person-centred care. The approach is primary care and community based and extends beyond traditional medical management to include supporting and enabling self-care, including through behaviour change (32). It supports a longitudinal person-centred approach to management, providing better support for individuals throughout their journey of care, rather than taking a cross-sectional approach driven by specific health events or service interactions. However, in order to operationalise the management of frailty through the long-term condition model, a number of conditions need to be met. Clear diagnostic and prognostic frameworks for the condition are required, alongside methods to measure the severity of the condition and a suite of evidence-based interventions that can be appropriately implemented at different stages of disease progression.

One of the key challenges associated with conceptualising frailty as a long-term condition is therefore how to develop a ‘medical diagnostic model’ and related measurement system that adequately reflects the complexity of the condition. Diagnostic models for ‘traditional’ long-term conditions, for example diabetes, are usually defined by fixed criteria in relation to physiological measurements and progress is usually monitored through biological and physiological variables

(89). However, as discussed (section 1.2, page 4) there is no universally agreed model for frailty, and therefore no unified diagnostic framework or measurement approach for the condition. Existing approaches focus predominantly on the physical characteristics of frailty (90), whilst at the same time acknowledging the importance of a holistic approach to management (17). The question therefore arises whether other components relevant to the holistic presentation of frailty should be integrated alongside physical components of the condition within a model of frailty. Or, alternatively, whether the model of frailty should focus upon physical aspects of frailty with the other components considered as contextual factors relevant to the management of the condition, rather than part of the condition itself.

2.1.2 A multi-dimensional framework for the definition of frailty

Frailty can be described as a 'collection of modifiable health and social needs' (15) and a multi-dimensional approach to frailty is particularly appropriate in primary care, aligning with the 'biopsychosocial' model of general practice (46). Such a model would support a holistic and contextual approach to a person's care, rather than focusing only upon the measurement and management of illness and disease (3,28). Constructing a multi-dimensional framework for frailty in primary care and at transitions of care requires an understanding of:

- Which components should be included in the model, for example clinical measurements.
- How the importance of these components varies, both between individuals and over time.
- How this relates to the development of a scale or index for frailty.
- How the different components interact in relation to frailty outcomes.
- How the components are linked to each other and to outcomes in frailty.

2.1.2.1 Components to reflect the multi-dimensional nature of frailty

The identification of the range of components needed to comprehensively reflect the multi-dimensional nature of frailty requires a systematic approach, which could be aligned into two main categories: i) biological components, ii) environmental components.

The accumulation of physical health deficits as a consequence of underlying physiological change is universally accepted as an important feature of frailty (1,18). These physical conditions, which include long-term conditions, acute health events and physiological changes related to ageing, are clearly biological components of frailty. However, mental health conditions and cognitive changes are also important biological components of the condition (91-93).

Broader holistic components are important to frailty and include both those concerning the social environment (45,46), for example social contact and social participation, and those related to the physical environment (48), for example deprivation, housing conditions and available assistive technology. Section 1.4 (page 8) discussed the relationship between frailty and systems of care but also highlighted the lack of evidence in this area. Systems of care could therefore be proposed as a potential environmental component in a multi-dimensional model of frailty, and a plausible 'contribution story' (94) can be made to support this hypothesis, although further research is required to characterise this role.

The strength of the evidence base for these potential components in a multi-dimensional model of frailty is variable (43,44). It is strongest for the well-established biological components of frailty (1,18) and increasingly supports those in the social environment (45,46). Evidence of the importance of the physical environment (48) is also beginning to emerge but there appears to be a gap in evidence with respect to systems of care (65-67,69-71).

The influence of each component within the overall multi-dimensional model of frailty will vary between different individuals and for the same individual over time. As well as identifying components that comprehensively reflect the multi-dimensional nature of frailty, components should also be considered in terms of their ability to add most value to the overall model of frailty in exchange for the simplest additional information.

2.1.2.2 Interactions between components and their links to outcomes in frailty

A multi-dimensional model of frailty depends on the relationships between the components within the framework, as well as the significance of individual components (43,44,46). Within this framework it is necessary to understand the influence of different components and causal pathways, and the nature and significance of the interactions between these elements and their relationships to outcomes in frailty.

To be relevant for inclusion in the multi-dimensional model of frailty, all components must be in some way associated with outcomes related to frailty, such as acute hospital admission, care home admission, costs of care, quality of life and other patient-centred outcomes. For some components, clear causal links can be identified with these outcomes, for example, increasing physical dependency and care home admission (95). However, for other components, whilst associations

with outcomes related to frailty exist, for example, between social relationships and mortality, pathophysiological relationships and causal pathways might not be clearly identified (96) .

The relationships and interactions between components are complex and their nature and importance can vary between different components and individuals and over time. In addition, some factors show bidirectional relationships with frailty (27), for example the relationships between frailty, falling and emotional distress, anxiety and depression (91,92) and between frailty and disability (3). Furthermore, some factors exert their influence through multiple mechanisms and over extended periods of time, for example socioeconomic factors acting via both biological and social mediators. There is a also a strongly time dependent element to the interactions within a multi-dimensional model of frailty (97).

Although the importance of considering the complex interactions between different factors contributing to frailty has been recognised (16,20,28,49), existing models of frailty tend to take a simple cumulative approach to combining the components of frailty. It is not yet clearly understood whether components of frailty contribute through a model of alternate causal pathways or one of simultaneous causal strands (55,94), and further research is therefore required to define the complex interactions between components of frailty.

2.1.3 The dynamics of frailty in primary care and at transitions of care

Frailty is a dynamic condition. A person can move between frailty states over time and such changes can occur rapidly or gradually depending upon individual circumstances (1,11,29) . Transitions in frailty may be easier to recognise when they relate to a significant health event such as a fall and more difficult to acknowledge when they occur as part of a gradual decline in health and functional ability (1,11). Frailty transitions are important because they are opportunities at which the progression of frailty might be prevented, reversed or delayed (3,11,43,45). However, it is acknowledged that transitions towards increasing frailty occur more frequently than improvements and it is not uncommon to find individuals who experience a rapid cycle of decline (1). Increasing our understanding of the emergence, transitions and trajectories of frailty is therefore an important part of developing a meaningful model for frailty in primary care and at transitions of care.

A conceptual model that adequately reflects the multi-dimensional nature of frailty and the dynamics and complexity of the condition is required to underpin the development of a

measurement system for frailty in primary care and at transitions of care and in order to support the operationalisation of a multi-dimensional concept of frailty in healthcare delivery.

Currently there are gaps in this evidence along frailty trajectories. There is a need to characterise frailty and frailty change across a range of populations and in different settings of care in order to better understand frailty in primary care and at transitions of care. These include, for example, the need to describe frailty in general primary care populations and in disease specific populations, as well as in populations residing in care homes and populations with acute or transitional care requirements. By starting with the characterisation of frailty in the general primary care population and moving on to describe the condition in more specific primary care population subgroups, there is an opportunity to identify patterns of frailty associated with particular transitions of care and along particular frailty trajectories.

2.2 Developing a measurement system for frailty in primary care and at transitions of care

The case for the measurement of frailty in primary care and at transitions of care has been made (section 1.5.4, page 13) and tools to measure frailty introduced (section 1.6, page 13). This section considers current frailty measurement tools and the potential for further development in this area.

2.2.1 Current tools to measure frailty in primary care and at transitions of care

Historically, there has been no consistent or coordinated approach to frailty measurement and a range of frailty measurement tools have been developed for different purposes (30). Some of these tools have been developed or applied in primary care (98,99) .

2.2.2 Conceptual basis of current tools

The conceptual basis of tools that have been used to measure frailty in primary care varies, including some tools based upon the phenotype model of frailty, for example the SHARE frailty instrument (36), some which generate a frailty index based upon the cumulative deficit model of frailty, including a frailty index calculated from routinely collected primary care data (100,104) and others based upon a multidimensional model of frailty including the Tilburg Questionnaire (101). Comprehensive Geriatric Assessment (CGA) is the ‘gold standard’ for the clinical assessment of frailty (64). However, although CGA is well established in some specialist settings, it is a detailed and time intensive multi-disciplinary process and has therefore been rarely used in primary care.

2.2.3 Nature and purpose of current tools

Tools used to measure frailty in primary care include those based on assessments using questionnaires (101), those using clinical assessment (36,103) and others using routinely collected data(104). Frailty tools in primary care have been used to screen for frailty (41,105), to measure frailty status (106) and to predict outcomes in frailty (107,108).

2.2.4 Components included in current tools

Frailty measurement tools used in primary care very often include biological components of frailty, both physical health components such as disease status (109) and mental health components such as cognitive impairment (101). They are also seen to include environmental factors, representing both the social environment and the physical environment (48).

2.2.5 Outcomes considered in current tools

Current tools used to measure frailty in primary care have considered the prediction of outcomes associated with frailty including outcomes related to systems and episodes of care, such as admissions to hospital and to nursing homes (103), and individual outcomes such as quality of life (101), disability (2) and death (2).

2.2.6 Additional considerations for further development

2.2.6.1 Outcomes, components and interactions

Tools to measure frailty should include quality of life as a key outcome (46). Frailty tools must therefore measure those components that impact upon this primary outcome of interest, and not simply those components that are easiest to understand and to quantify, or are most routinely available. Frailty tools must not just measure characteristics interpreted as significant from a professional perspective. The 'culture of assumption', which has been identified as having a causative role in previous failures in the care of older people with frailty, must be avoided (66,68) and instead ways must be found to include patient identified and patient focused components.

Furthermore, frailty tools must not only measure relevant components, including contextual factors, in the determination of frailty, but also find ways of scaling their impact and understanding the interactions between them. This is essential if the role and contribution of different components of the frailty construct are to be individually and collectively understood and important in the context of implementing clinical interventions for frailty. However, there are theoretical and methodological challenges in constructing valid numerical transformations to bring together the complex data

representing a range of different components of frailty to form a single measure of this complex multi-dimensional concept.

There is a risk that the nature of the components included in a frailty measurement tool, and the relative significance attributed to each of them, could be distorted by the extent to which we understand the components and/or the ease with which they can be recognised and measured. For example, physical and physiological factors have tended to have a dominant role in clinical instruments for the identification and measurement of frailty. However, this dominance might reflect bias caused by the fact that from a clinical perspective they are the most easily identifiable and well-characterised components, rather than reflecting rigorous testing for their relative significance in relation to other potential components of a multidimensional framework for frailty. The relative significance of the different components included in a frailty measurement tool should therefore be tested and compared before they are combined to create a single instrument.

Similar consideration should be given to ensure that the methods used to measure and combine the different components do not create bias in component selection. For example, there is increasing interest in the use of routine datasets in the measurement of frailty, particularly using routine primary care data to generate a frailty index (1,100,104). This is an appealing and powerful concept, underpinned by robust methodological detail and current technical ability to generate such an index (38,100). However, it also risks bias in favour of components of frailty well represented in routine data and risks the exclusion or under representation of components that are absent from, or less well coded in, primary care records.

2.2.6.2 Unifying approaches

There has been a tendency for frailty to be viewed differently from different professional perspectives, including between professionals based in different settings of care and between different professionals within a single care setting. This has previously been reflected in the concept ‘different tools for different purposes’ (30) and has led to the development of a range of frailty instruments, often for use either in specific service settings (for example in the emergency department (110)) or with specific groups of people (for example people with cancer (99)). This approach to frailty measurement is primarily aimed at enabling the targeting of service specific specialist interventions. However, it also reflects the fragmented service-centric perspective from which care is often delivered to people with frailty. As a result, individually satisfactory or even high

quality services can together fail to deliver good care from a person-centred perspective, due to poorly aligned or conflicting objectives and poor coordination or communication between different services across the wider system of care. This puts people with frailty at greater risk of adverse events, particularly at transitions of care.

An increasing argument is therefore developing for the benefits of a single frailty instrument that can be recognised and used by a range of professionals (16). This change in approach has been associated with a shift in perspective that seeks to expand the identification and measurement of frailty beyond specialist and secondary care settings and embed this concept within routine primary care (32). It is also concordant with a national drive towards more integrated systems of care (31), which demand improved communication and coordination of care. The development of a single frailty measurement tool suitable for multi-professional and multi-agency use is a challenging but feasible ambition. This approach is assisted by the increasing systematisation and standardisation of clinical care delivery and enabled by technological developments that enhance communication and allow information to be shared more easily. However, a shared definition and conceptual model of frailty is an absolute prerequisite for a unified approach to frailty measurement.

The components included in a frailty measurement tool can therefore make an important contribution to supporting and enabling integrated care. Instruments focussing upon physical frailty alone risk fragmentation of care (43,46). However, a comprehensive multi-dimensional frailty instrument could serve as a common language between professionals and support the delivery and evaluation of integrated, person-centred care (16). This approach is particularly suited to general practice (46) and would support a holistic and contextual approach to a person's care, rather than focusing only upon the measurement and management of illness and disease (3,28). Some components of such an instrument could still be specific to diseases or conditions, to interactions with specialist services or elements of care, or to the optimal management of underlying medical conditions. However, these components would be integrated into the holistic overall measurement of a person's condition, taking account of complexity, uncertainty and competing risks, rather than measuring individual components in a disconnected and potentially disproportionate manner. This approach has the potential to be of particular value towards the end of life, in the context of changing individual goals, objectives and priorities of care.

A key strength of a shared multi-professional frailty measurement tool developed in relation to holistic frailty outcomes would be that it would support a change in focus away from professionally driven and service-centric outcomes of care and towards shared, person-centred outcomes of care. A tool that could support shared decision-making and help to bring professional objectives and perspectives into line with those of the individuals with frailty, rather than delivering services in line with preconceived professional perspectives, would be invaluable. This would represent a transformation in approach to the management of frailty. Thus there is a compelling case to support the rapid development of a comprehensive multi-dimensional instrument for the identification and measurement of frailty in primary care and at transitions of care, which is shared and understood by all stakeholders, including patients, their carers and a range of professionals.

2.2.6.3 Summary

The challenge of developing an instrument for the measurement of a broad multi-dimensional concept such as frailty, within which the causal relationships between risk factors and key outcomes are not always clearly understood, cannot be under-estimated. It has been pointed out that 'only the most general concept of frailty could retain this flexibility' (30). Perhaps, however, it is a more general approach to the concept, models and measurement of frailty that is needed in order to support the achievement of holistic goals of care for people with the condition. Importantly, looking towards a more general overall framework for the measurement of frailty does not deny the importance of the definition and measurement of individual components within the wider concept of frailty and is not counter to continued efforts to improve tools and techniques for this purpose. Rather it promotes the view that the full potential impact of understanding and assessing individual components of frailty in increasing detail can only be realised when these measures are also appropriately combined into a more general and dynamic view of the condition. The concept therefore emerges not of 'different tools for different purposes' (30) but of a shared frailty tool with multiple layers of resolution, which can be applied with differing focus depending upon the specific context and desired outcomes of care.

2.3 Operationalising a multi-dimensional concept of frailty in healthcare delivery

Frailty in primary care is a dynamic and multi-dimensional concept arising from the interactions within and between key components (28). It is characterised by complexity (28) and several dimensions of complexity can be described, including structural complexity (the components contributing to frailty), temporal complexity (changes over time) and complexity of 'multiple stakeholders' (individuals, families, carers, professionals), all with different perspectives (55,94). To be effective, frailty measurement systems and operational models of frailty need to reflect and respond to this complexity, in all its dimensions.

2.3.1 Understanding the nature and complexity of an individual's needs

A multi-dimensional model of frailty has important operational implications in helping to understand a person's needs, both individually and collectively, and how they relate to the vulnerability associated with frailty (1). Different needs will arise at different times in connection with the different components of frailty and will have different trajectories and impact upon individual vulnerability. However, they can all be described operationally through a multi-dimensional model of frailty.

For example, a person's number of long term conditions typically increases over time and this can increase vulnerability, both directly, through a progressive deterioration in physical health, and indirectly, for example through the risks associated with poly-pharmacy. Furthermore, a person's psychological status can also vary over time, for example, with periods of anxiety or loss of confidence making a person more vulnerable to adverse outcomes such as falls or self-neglect. An individual's vulnerability is also related to their social and physical environment. For example, support from a family member or the provision of an appropriate care package can reduce vulnerability, whilst vulnerability can be increased by poor maintenance of a property or external factors such as extremes of hot or cold weather.

Finally, the manner in which care is delivered can have an impact, with chaotic and/or reactive care, or care delivered at an inappropriate level of acuity, likely to increase vulnerability when compared to planned and coordinated care delivered at the appropriate level of acuity. This impact can either be associated with the direct outcomes of care or might be mediated through other factors such as complications of acute hospitalisation, or anxiety and loss of confidence associated with failure of coordination and delivery of services across a range of providers.

The operationalisation of a multi-dimensional model of care allows these needs to be individually identified, understood and responded to, but also offers the 'added value' of considering them in combination, thus offering the opportunity for more effective provision of holistic, person-centred care.

2.3.2 Integrated pathways of care

In order to develop effective pathways of care, frailty must be considered in the broader context of the conditions and experience of people's lives. Operationalising a multi-dimensional model of frailty can help understanding of the development, transitions and trajectories of frailty. Important questions include defining the construct through which frailty emerges or progresses (55) and understanding the likelihood of non-linear relationships and interactions between the components of frailty, and between a person living with frailty and their wider society and environment. Non-linear interactions include critical tipping points where small changes can have a disproportionate impact, either positive or negative, upon outcomes, and points of leverage where positive intervention can be reinforcing (94). It is also important to consider emergent outcomes (94) along frailty trajectories, which may lead to a change or reprioritisation of an individual's desired goals and outcomes of care as their condition or circumstances change.

A key operational application of a multi-dimensional model of frailty is to help answer these questions and thereby enable the design of proactive interventions and integrated pathways of care delivery. It will help identify, inform and develop pathways of care appropriate for:

- Every stage of frailty, from diagnosis to end of life.
- All phases of care, including proactive, routine and responsive care.
- In all places of care, whether at home, or in community, acute or other setting.

2.3.3 Measurement and management of frailty

A number of important operational implications emerge from the understanding of frailty as a modifiable health state (1,10) and the acceptance that at times it can be appropriate for a person's frailty to help inform clinical decision-making concerning their care (28,29). If an individual's place on the 'frailty-fitness continuum' (29) is to be used in treatment decisions and this position is modifiable (1), then it must be understood whether or not the individual is in their state of least possible frailty at the time of assessment and decision making. If they are not, the following must be considered i) how their degree of frailty might be improved, ii) what timescale this would involve,

iii) how this timescale relates to that of the clinical decision being made, and iv) what impact any change in frailty status might have upon that decision. Operationalising this approach therefore also demands accurate, effective and reliable tools for the measurement of frailty and clarity regarding the use of such tools.

2.3.4 Person-centred goals of care

A multi-dimensional model of frailty helps to emphasise the need for holistic and person-centred goals of care. It also reinforces the need to monitor the effectiveness of care delivery against the achievement of these outcomes and not purely against system or process-based measures.

Within a multi-dimensional model of frailty the dynamic interactions between the different components are critical to the overall quality of life, even when there is no pathophysiological link between the two. Change will take place within individual frailty components and may be large or small, sudden or gradual, predictable or unexpected. This change might represent an improvement or deterioration and change in one component might be potentiated or mitigated by change in another.

Conceptualising and operationalising frailty through a multi-dimensional model in primary care can therefore help to identify critical tipping points where small changes in one or other domain can have a disproportionate adverse impact upon an individual's overall experience and quality of life. Equally, it can help identify points of potential leverage, which can help to maximise the positive impact of specific interventions. Furthermore, it identifies the value of innovative approaches to care which think and move laterally across and between different components of frailty, to help overcome or circumvent challenges in the quest for attainment of person-centred goals of care.

Operationalising a multi-dimensional frailty model also has the potential to improve communication between individuals, carers and professionals, and to help develop understanding and acceptance of the complexity and uncertainty associated with this stage of life. This supports individual choice and decision making, enables a better individual understanding of the risks and benefits in different areas of life related to these choices, and promotes the supportive care environment needed to enhance individual quality of life. This approach therefore has potential to help us understand how we can better promote resilience to the challenges which are frequently associated with older age, thus helping people to identify and achieve individual person-centred goals of care and experience the best possible quality of life.

2.3.5 Systems of care

Operationalising a multi-dimensional model for frailty both enables and demands four key approaches across systems of care. These are:

- Systems must include not only health and care organisations, but also individuals, families, carers, and people and organisations in wider communities and society.
- Professional activity across all organisations and all professional groups must be coordinated and aligned to work in partnership with individuals to support, but not direct, identification and achievement of person-centred goals of care.
- System effectiveness should be measured against shared person-centred goals of care and not against individual service, organisational or processed based outcomes.
- Established evidence based interventions that are known to reduce vulnerability in relation to individual components of frailty should be delivered consistently and appropriately.
- Innovative holistic and integrated approaches to care should be developed through multi-professional, multi-organisational approaches, alongside but not instead of existing evidence based interventions.

2.4 The gap between research and operational reality

There are significant gaps between research evidence and operational reality in three key areas related to the multi-dimensional model of frailty, namely frailty measurement, frailty interventions and frailty service delivery.

There is a pressing need for a frailty measurement tool that comprehensively reflects a multi-dimensional model of frailty. However, at present there is variable evidence regarding the components that should be included in such a tool, the measurement approaches for individual components, and theoretical methodological approaches by which these components can be combined to give a single measurement for frailty. The ambitious concept is that of a single measurement tool that includes sensitive components enabling it to identify frailty and frailty change rigorously, to have the ability to be used throughout patient journeys and to have the ability to predict a range of outcomes in frailty. However, currently, there are few operational settings in which frailty is regularly measured, frailty measurement approaches are variable and frailty

measurement is usually connected with isolated episodes of care rather than as part of a systematic and coordinated pathway of care.

The majority of current evidence for interventions in frailty relates to discrete interventions directed towards the physical component of frailty, with much less evidence available regarding other approaches. Furthermore, even when there is good evidence for interventions, there are still significant operational challenges in designing and implementing services to deliver these interventions. This is illustrated by the gap between the extent of the evidence base in support of CGA and the extent of implementation (17). Some authors have investigated the design of services to deliver complex interventions in frailty and the fidelity of their implementation, but operationally substantial challenges remain in this area (114-116). The interfaces between theoretical constructs, conceptual models, academic research, clinical practice and 'real life' will continue to be key challenges requiring careful negotiation in the interpretation and operationalisation of frailty.

2.5 Study rationale and research questions

Frailty requires a holistic view with focus upon improved understanding of the key components of frailty and the interactions between them. This will enable a more proactive approach to care, support the identification of critical tipping points and non-linear relationships in frailty trajectories, and help to achieve positive impact upon quality of life for people with frailty. It will also support a wider understanding and acceptance, amongst individuals and across society, of the complexities and uncertainties associated with this stage of life, and help to emphasise that an individual's quality and experience of life can be improved if a more holistic approach to frailty is adopted, both conceptually and operationally.

The aims of this project were therefore to:

i) Identify key components that should be included in a tool to measure frailty in primary care and at transitions of care

ii) Investigate how these components can be applied in these settings

iii) Investigate how they relate to quality of life in frailty.

The research questions covered three key areas accordingly.

2.5.1 Structure of frailty measurement tools

What are the key components of a tool to measure frailty in primary care and at transitions of care?

- Should environmental components be included alongside biological components in such tools, particularly components representing the physical environment, the social environment and systems of care?

2.5.2 Application of frailty measurement tools

How can these components be applied in primary care and at transitions of care?

- Can routinely collected primary care data adequately represent the key components required in a tool to measure frailty in primary care and at transitions of care?
- Does the application of these components vary according to socio-demographic and comorbidity variables?
- Is the application of these components time dependent?

2.5.3 Quality of life as an outcome in frailty measurement

How does this approach to frailty measurement relate to the key outcome of quality of life for people with frailty?

- Is frailty measured in this way associated with quality of life?
- Is the association between frailty measured in this way and quality of life improved by modelling to include other components?
- Can frailty measured in this way predict quality of life over a 12-month period?
- Is the ability of frailty measured in this way to predict quality of life over a 12-month period improved by modelling to include other components?

2.6 Hypotheses

The hypotheses tested in this project in connection with these research questions were:

2.6.1 Stage one hypotheses

a) Physical environment, social environment and systems of care are important components of frailty in determining primary care and at transitions of care outcomes.

b) Routinely collected primary care data improves frailty measurement in determining primary care and at transitions of care outcomes.

2.6.2 Stage two hypotheses

a) Socio-demographic factors of increasing age, female gender and increasing deprivation are associated with increasing frailty in the primary care population.
b) Socio-demographic factors of increasing age, female gender and increasing deprivation are associated with increasing frailty change in the primary care population.
c) Chronic disease status and increasing comorbidity disease severity is associated with increasing frailty in a primary care population.
d) Chronic disease status and increasing comorbidity disease severity is associated with increasing frailty change in a primary care population.

2.6.3 Stage three hypotheses

a) Increasing frailty scores in the primary care population based on routinely collected primary care data is associated with worsening quality of life.
b) Increasing frailty scores in the primary care population based on routinely collected primary care data is associated with worsening change in quality of life over a 12-month time-period.
c) The inclusion of psychological, fatigue and social network components strengthens the association between frailty score and worsening quality of life.
d) The inclusion of psychological, fatigue and social network components strengthens the association between frailty score and worsening change in quality of life over a 12-month time-period.

2.7 Study types

This project was designed in three phases and comprised three separate studies.

2.7.1 A systematic review of frailty tools in primary care and at transitions of care

A systematic literature review was conducted to investigate tools used to measure frailty in primary care and at transitions of care. It characterised the structure and function of these tools by investigating their conceptual basis, which components of frailty they included and which outcomes of frailty they considered, how they were applied and used, and whether they had been validated in clinical practice. This review provided a detailed understanding of the structure and function of

existing tools used for measuring frailty in primary care and at transitions of care and provided the basis for the subsequent studies in this project.

2.7.2 A cohort study to characterise frailty in a primary care population

A cohort study was conducted to characterise frailty in a primary care population. An electronic frailty index was used to measure frailty in an anonymised primary care consultation dataset, for a population defined with respect to defined comorbidity groups (secondary analysis of data from a previous study). The study characterised frailty in this cohort according to socio-demographic variables and comorbidity groups, and investigated changes in frailty over a two-year period according to these different characteristics. The results of this study were used in the third phase.

2.7.3 A cohort study to investigate relationships between frailty, other explanatory factors and quality of life

A cohort study was conducted to investigate the relationship between frailty, other variables and quality of life in a primary care population. An electronic frailty index calculated from routine primary care data was used to measure frailty in an anonymised primary care consultation dataset, which also contained anonymised linked survey data for psychological status, social network measures, levels of fatigue and change in quality of life data at two time points, twelve months apart (secondary analysis of data from a previous study). The study investigated the association between the electronic frailty index and quality of life, and its ability to predict quality of life over a 12-month period. It also investigated whether the strength of this association and predictive ability could be improved by modelling to include other components.

Chapter 3: Frailty tools in primary care and at transitions of care: a systematic review

3.1 Introduction

Practical applications for the measurement of frailty in clinical practice need to be underpinned by conceptual models derived from frailty measurement as an established research concept (1,29,30,49). Development of practical applications has tended to focus on specialist and elderly care settings, but there is increasing recognition of the need for the measurement of frailty as it emerges in primary care (1,3,28) and at transitions of care. The link between primary care and transitions is important because it supports the proactive and integrated care likely to be of most benefit to people with frailty (16), the need for which is driving much current NHS policy (31).

The primary care population is usually where frailty initially emerges and as it becomes established people with the condition often experience recurrent healthcare contacts. Yet there are no well-established tools for identifying the emergence of frailty in order to assist primary care teams to deliver services that better meet their needs and prevent deterioration (42). The more accurately these measurement tools represent the models of frailty most relevant to primary care, the more they will help in identifying critical tipping points and the more effective will be the points of potential intervention in frailty trajectories. Frailty tool components could combine clinical factors as potential predictors and healthcare use as predictors of change. Inclusion of routinely collected clinical data provides the opportunity to (i) include transitions in models and (ii) target 'groups' of people that are at high risk for frailty emergence and progression.

Previous systematic reviews investigating frailty measurement have either focused on the nature of the instruments, rather than their applicability in clinical settings (49,118,119), or have investigated specific approaches to the identification and measurement of frailty in primary care, such as the use of the frailty index (41), screening instruments (120) or simple instruments, such as the gait speed test (105). However, the focus of this review was to identify tools that have been used to measure frailty in primary care and at transitions of care and investigate to what extent the components included in these tools reflect the multi-dimensional model most relevant to primary care and at transitions of care. The three specific objectives of this systemic review were to: (i)

determine which tools had been used to measure frailty in primary care and at transitions of care and whether they had been used to measure frailty status, predict outcomes in frailty or predict frailty in the non-frail; (ii) determine which components were included in these frailty tools, particularly whether healthcare use measures and routinely collected data were included, and (iii) assess whether these tools had been validated for use in clinical practice. This review was carried out by two reviewers and reported on studies published in English from any geographical location.

3.2 Aims and Objectives

3.2.1 Aims

The aim of this systematic review was to examine current evidence on the use of tools to measure frailty in primary care and at transitions of care. The purpose of the evidence synthesis was to examine which aspects of frailty had been measured using these tools, which components of frailty had been included in these tools and whether these tools had been validated in clinical practice.

3.2.2 Objectives

Three specific objectives of this systemic review were:

1) To determine which tools had been used to measure frailty in primary care and at transitions of care and to determine which tools had been use to:
    a) Measure frailty status.
    b) Predict frailty in the non-frail.
    c) Predict outcomes in frailty.
2) To determine which components were included in these frailty tools and particularly whether healthcare measures and routinely collected data were included.
3) To determine whether tools used to measure frailty in the specified settings had been validated using clinical comprehensive geriatric assessment and/or outcomes associated with frailty, and to identify whether these tools met the following (section 1.6.1, page 14):
    a) Face validity
    b) Construct validity
    c) Criterion validity
    d) Predictive validity

3.3 Methods

A systematic review was conducted of research studies in this field in order to identify the scope, content, strengths and weaknesses of existing tools for the measurement of frailty in primary care and at the transitions of care. The medical literature databases MEDLINE, EMBASE and CINHAL were searched to identify studies published from the start date of each database through to 29th January 2014, which reported the development or testing of tools to measure frailty in primary care or at transitions of care. The selection of articles was carried out according to clearly defined inclusion and exclusion criteria. Data was extracted from the selected articles using a standardised template. Quality assessment of the selected articles was also completed. This data was then used to produce a narrative synthesis of the available evidence regarding the use of tools to measure frailty in the specified settings. The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROPSERO) on 5th February 2014. The PROSPERO registration number is CRD42014006560 and the protocol is available on the PROSPERO website (www.crd.york.ac.uk/PROSPERO).

3.3.1 Inclusion and Exclusion Criteria

The clinical condition under investigation in this review was 'frailty'. The aspect of frailty under investigation was the measurement of frailty and the settings in which this was investigated were primary care (with a focus on general practice) and at transitions of care (specifically the interface between general practice and hospital-based settings). The inclusion and exclusion criteria in this systematic review were developed based upon the Centre for Reviews and Dissemination guidance for undertaking reviews in health care (121) framework which uses the following domains: population, intervention or exposure, comparators, outcomes and study design. In this review they were represented by the following; population, measurement exposure, external validation of the measurement tool, outcomes and study design.

3.3.1.1 Population

Frailty can occur in people under the age of 65 years but is more usually a condition associated with older age. There is a developing literature concerning the measurement of frailty (1,29,30,49)

but much of this work has been based in specialist care settings, such as acute hospital wards, or in the context of specific diseases or conditions, for example cancer or fractured neck of femur. However, there is an increasing need for the measurement of frailty in primary care (1,3,28) and at transitions of care because this approach supports a focus on proactive management aimed at maximising capability and minimising the need for acute reactive interventions in the management of frail patients with complex needs. The settings of interest in this review were therefore primary care and transitions of care.

The study population for this review was older people (aged 65 years and over) in any community setting. Studies focused on the measurement of frailty and which were wholly based in primary care or involved the interface or transition between secondary and primary care were included.

Studies based entirely in secondary or specialist care, or dealing exclusively with older people with one particular disease or condition (e.g. cancer or heart failure), or sharing one specific predefined aspect of frailty were excluded.

3.3.1.2 Measurement Exposures

The specific exposure of interest in this review was the measurement of frailty. Tools to measure frailty include a range of components and the components of frailty measurement tools of interest in this review were:

1) Clinical measurements (for example blood test results and anthropometric data such as Body Mass Index and blood pressure measurements)
2) Routinely collected data (for example demographic, diagnostic and prescribing data)
3) Physical health factors (for example conditions, symptoms and functional ability)
4) Psychological factors (for example mental health and cognitive problems)
5) Healthcare use (for example primary care contacts, use of community services and hospital care episodes)
6) Social factors (for example living alone and receiving social care support)
7) Clinical assessment (including history and physical examination)
8) Environmental factors (for example housing conditions)

Studies were included in this review if they reported the use of tools to measure frailty and if these tools included one or more of the above components of frailty.

3.3.1.3 External Validation of Measurement Tool

The external validation of frailty measurement tools was assessed in two ways in this review. Firstly it examined whether the tools had been externally validated using any form of Comprehensive Geriatric Assessment. Comprehensive Geriatric Assessment (CGA) is a well researched complex intervention used in the assessment and management of older people with frailty (64). It is a holistic and multidimensional diagnostic process designed to determine a frail older person's medical conditions, mental health, functional capacity and social circumstances. An individual's level of frailty can be demonstrated through CGA (63). In addition to acting as a mechanism for the diagnosis and assessment of frailty, comprehensive geriatric assessment also generates a clinical management plan, which can be used to guide subsequent interventions (63,64). External validation against Comprehensive Geriatric Assessment was considered to be the 'gold standard' in this review.

Secondly it examined whether the frailty measurement tools had been externally validated using clinical outcomes known to be associated with frailty. In other words, the review considered whether the outputs of the measurement of frailty had been compared to individual outcomes known to be associated with frailty, such as mortality, unscheduled secondary care activity, admission to nursing home and functional decline (1).

3.3.1.4 Outcomes

The primary outcome under investigation was that one or more of the following aspects of frailty had been measured using the tool under investigation, namely:

a) Frailty status
b) To predict frailty in the non-frail
c) To predict outcomes in frailty

3.3.1.5 Study Designs

The review included descriptive and observational studies, which focussed on the measurement of frailty, including cohort, case control and cross sectional studies. English language publications were included and studies published in other languages were excluded. Studies published as full articles were included. Studies where only the abstract was available and those published as research letters were excluded. Inclusion and exclusion criteria are show in Table 3.1.

Table 3.1: Inclusion and exclusion criteria for articles in systematic review

Criteria	Specification for Inclusion	Specification for Exclusion
Population	Aged 65 years or older. General population of older people. Primary care or transitions of care. Any geographical location.	Study limited to a specified disease, condition or predefined aspect of frailty. Set in secondary or specialist care.
Measurement Exposure	Frailty measurement tool including one or more of the specified components of frailty.	
External Validation	CGA Specified clinical outcomes associated with frailty.	
Outcomes	Tool was used to measure frailty.	
Study Design & Publication	Descriptive and observational studies. Full article available. English language publication	Full article not available or published only as a research letter. Non-English language publication.

3.3.2 Search Strategy

The design of the search strategy for this review included the selection of databases, the selection of appropriate search terms and a strategy for additional searches.

3.3.2.1 Literature databases

The principal databases used to identify the studies for inclusion in this review were:

- Medical Literature Analysis and Retrieval System Online (MEDLINE)
- Excerpta Medica Database (EMBASE)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

MEDLINE and EMBASE are well-recognised international databases for medical publications. CINAHL also includes publications in the field of nursing and allied healthcare professions. The Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Database of Abstract Reviews and the International Prospective Register of Systematic Reviews (PROSPERO) were also searched for this review**.**

The publication period in the main searches was from the start date of each database involved through to the date upon which all the main searches were run (29th January 2014). The searches were re-run on 13th August 2014, when data extraction was complete for articles identified by the initial searches, so that relevant newly published articles could also be considered for inclusion.

3.3.2.2 Search terms

Search terms must be carefully selected and combined in order to produce a search strategy which is sensitive enough to include all important published evidence in the chosen field, yet specific enough to yield a list of articles which can be practically and realistically reviewed in a systematic manner. The three key aspects considered were the selection of the search terms, the database fields within which to search and the way in which the search terms were combined.

Search terms were developed using Medical Subject Headings (MeSH) to identify each of the key aspects of the studies to be included in this review. Medical Subject Heading terms are standardised terms used to index articles in literature databases. The terms are grouped and organised into a logical hierarchy which enables a systematic approach to the identification of relevant publications in any given subject area. A search can be made broader by adding '*' to a stem MeSH term, for example in this case 'frail*'. The search will then yield all articles indexed with

any derivation of the stem term without having to search for the full terms individually. In this case, for example, this expansion included all terms such as frail, frailty, frail elderly, frail older people. Search terms made up of more than one word but which need to be considered as single phrases rather than separate words should be indicated inside quotation marks (“x“).

Search terms were needed to identify each of the three key aspects of articles to be selected by the review, namely the population setting (primary care and transitions of care), the condition (frailty) and the intervention (measurement [of frailty]). Terms for the condition of frailty proved relatively straight-forward to identify, as did those for healthcare measurement. However, the selection of terms relating to the setting proved more problematic. Terms for general practice and primary care were clearly identifiable. However, no clearly indexed terms were found for ‘transitions of care’ and a free text search for the phrase yielded unmanageably large numbers of articles. As the aspects of interest were care transitions or interfaces with primary care, it was considered that there would be reference to primary care somewhere within any relevant articles and the decision to use primary care search terms across ‘any field’ was therefore made.

The terms selected were:

Condition	frail*
Aspect	tool, score, instrument, measure, assessment, outcome, indicator, index
Setting	"primary health care", "primary care", "primary medical care", "general practice", "family practice"

A term may be searched for within specific fields in a database such as ‘author’, ‘title’ or ‘title and abstract’, or across ‘any field’. Field selection has a major impact on the sensitivity and specificity of the results yielded by the search strategy. The preferred option was to maximise the scope of the search by using the ‘any field’ option, but the concern was that this would yield an unmanageably large number of articles. However, test searches demonstrated that the number of articles identified using this approach could be manageably progressed through the systematic review process. Therefore the ‘any field’ option was selected for all three search strings.

The final decision relating to the search terms was the way in which they should be combined. Search terms can be linked within search strings by functions such as AND, OR and NOT. This established syntax allows a series of search strings, which can be of varying individual complexity, to be developed and linked together to form the final overall search strategy.

The final combination of search terms selected for application across 'any field' was:

[Frail*] AND

[tool OR score OR instrument OR measure OR assessment OR outcome OR indicators OR index] AND

["primary health care" OR "primary care" OR "primary medical care" OR "general practice" OR "family practice"]

The search strategy (Table 3.2) was tested and validated by running the searches across the selected databases and checking that the results identified a number of key articles already known to be of importance in this field.

Table 3.2: Search terms and combinations for database searches

Criteria	Combination of Search Terms		Field Selection
Condition: Frailty	Frail*	AND	Any field
Aspect: Measurement [of frailty]	Tool	OR	Any field
	Score	OR	
	Instrument	OR	
	Measure	OR	
	Assessment	OR	
	Outcome	OR	
	Indicators	OR	
	Index	AND	
Setting: Primary care	"primary health care"	OR	Any field
	"primary care"	OR	
	"primary medical care"	OR	
	"general practice"	OR	
	"family practice"		

3.3.2.3 Additional Searches

Other sources searched for articles relevant for inclusion in this review were:

- Reference lists from included studies and from key contextual articles on frailty.
- Identifying articles that had cited included articles, known as citation searching.

The measurement of frailty in the specified setting was also discussed with key UK authors in the field, including Professor John Young and Dr Andrew Clegg of the Bradford Institute for Health

Research, both in person and by email. This resulted in access to unpublished data and two unpublished reports.

3.3.3 Screening and selection of articles

This stage consisted of the removal of duplicate articles (DKM), followed by title and abstract screening (DKM) and then final article assessment and selection (DKM and UTK), according to the specified inclusion and exclusion criteria described in (section 3.3.1, page 36 and table 3.1, page 39). The approach was designed to minimise bias in the selection of articles and differences in selection between the two reviewers were resolved by discussion and consensus agreement.

3.3.4 Data extraction

Data was extracted using a structured data extraction protocol, agreed by both reviewers. The data extraction form was designed both to minimise bias and facilitate subsequent data synthesis and analysis. The data extraction form organised the data under the following main categories:

1) Study source
2) Conceptual basis of frailty measurement tool
3) Methods
4) Outcomes
5) Participants
6) Components of tool
7) Elements of components of tool
8) Validity assessment of tool
9) External validation of tool
10) Described uses of tool

A number of specific data items were collected within each of these categories (Table 3.3). Where a study reported the testing of more than one frailty tool, relevant data was extracted for each tool. The data extraction form was piloted on a small number of articles prior to the full review, in order to make sure that all relevant data was captured in an appropriate format and that there was consistency and agreement of approach between the two reviewers. The data was then extracted by the first reviewer and validated by the second reviewer for a selection of articles.

Table 3.3: Data extracted from each article included in the final review

Data	Description
Study source • Author • Year	 First author surname Year of publication
Conceptual basis of tool	Frailty Index - from routine data OR Frailty Index - composite OR Phenotype Model OR Multi-dimensional Model
Methods • Name of tool • Mode of administration • Study design • Inclusion • Exclusion • Recruitment Period • Follow up period • Reference geriatric assessment • Frailty outcomes considered Quality of life Disability / functional decline Hospital admissions Fractures / falls GP visits Emergency department visit Out of hours GP visit Nursing home admission Death	 Name of any tool used (if specified) Self-reported questionnaire OR Professionally administered questionnaire OR Clinical review OR Extraction of data remote from patient OR Combination Descriptive / cohort / case-control / cross- sectional Study inclusion criteria Study exclusion criteria Months or years Months or years Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No

Table 3.3 (continued)	
Data	**Description**
Participants • Setting • Sample size • Age • Country	 Primary care / transitions of care / both Number of people in study Range included Country
Components included in the tool • Clinical measurements • Routinely collected data • Physical health factors • Psychological factors • Healthcare use • Social Factors • Clinical assessments • Environmental factors	 Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No Yes / No
Elements included in components of tools A cumulative list was created listing any elements used within each component in any of the tools	
Validity assessment of tool (84,122) • Face validity • Construct validity • Criterion validity • Predictive Validity	 Not assessed / Assessed Not assessed / Assessed Not assessed / Assessed Not assessed / Assessed
External validation of tool • To Comprehensive Geriatric Assessment • To frailty outcomes	 Yes / No Yes / No
Described uses of tool • To measure frailty status • To predict frailty in the non-frail • To predict outcomes in frailty	 Yes / No Yes / No Yes / No

3.3.5 Quality Assessment

The methodological quality of all the articles selected for inclusion in the review was assessed using the latest version of the Quality Assessment Diagnostic Accuracy Studies (QUADAS-2) tool (123,124). The QUADAS framework has been identified for the quality assessment of diagnostic accuracy studies. It was considered appropriate for the quality assessment of studies in this review because although frailty is not a single disease entity it is increasingly regarded as a diagnostic entity that should be managed as a long-term condition (10,32) and the studies in this review concerned the diagnosis and measurement of this condition.

This tool consists of four domains covering:

1) Patient selection
2) Index test used, which in this case is the measurement of frailty using the frailty measurement tool under investigation in the study.
3) Reference standard used, which in this case is either CGA or the prediction of outcomes associated with frailty, or both.
4) Flow and timing, which is the flow of patients through the study and in particular the timing of the index and reference testing.

Each of these four domains was assessed in terms of the risk of bias and the first three were also assessed for concerns regarding applicability. Signalling questions were included in the tool to help reviewers to identify aspects of the study design related to the potential for bias and to make judgements regarding the risk of bias. The signalling questions used to guide quality assessment in the different domains are described in Table 3.4.

Table 3.4: Signalling questions for QUADAS assessment of selected articles

QUADAS Domain	Signalling questions
Patient selection	
a) Risk of bias	Was a consecutive or random sample enrolled? Did the study avoid inappropriate exclusions?
b) Concerns regarding applicability	Are there concerns that included patients/setting do not match the review question?
Index test (Measurement of frailty using the tool under investigation)	
a) Risk of bias	Were index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre-specified?
b) Concerns regarding applicability	Are there concerns that the index test, its conduct or interpretation differ from the review question?
Reference standard (Comprehensive Geriatric Assessment and/or prediction of outcomes associated with frailty)	
a) Risk of bias	Is the reference standard likely to correctly classify the target condition? Were reference standard results interpreted without knowledge of the index test results?
b) Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?
Flow and timing	
a) Risk of bias	Was there an appropriate interval between the index test and reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?

These components are all relevant to the quality assessment of studies investigating frailty measurement tools. Patient selection is important because some factors associated with frailty can directly or indirectly have an impact upon an individual's participation in research studies to assess these tools. Both index and reference standards are complex entities in relation to the assessment of tools for the measurement of frailty and therefore also important in the quality assessment of such studies. Frailty is a dynamic condition that changes over time. Therefore the flow and timing of index and reference testing in relation to the measurement of frailty is also extremely important. All four components of the QUADAS tool were systematically applied to the studies of frailty tools identified. The format used to record the results of the quality assessment using the QUADAS tool is shown in Table 3.5.

Table 3.5: Framework for recording QUADAS assessment of studies

QUADAS Domain	Outcome of Assessment
Patient selection – risk of bias	Low / High / Unclear
Patient selection – concerns regarding applicability	Low / High / Unclear
Index test – risk of bias	Low / High / Unclear
Index test – concerns regarding applicability	Low / High / Unclear
Reference standard – risk of bias	Low / High / Unclear
Reference standard – concerns regarding applicability	Low / High / Unclear
Flow and timing – risk of bias	Low / High / Unclear

3.3.6 Data analysis and synthesis

This systematic review resulted in a narrative synthesis of the available evidence regarding the use of tools to measure frailty in primary care and at transitions of care.

Firstly, a descriptive analysis was presented summarising the characteristics of the studies reported in the selected articles. The total number of studies reviewed was reported. Some of the studies reported the use of more than one tool and some tools were reported in more than one study: therefore the total count of the frailty tools described and tested in these studies was presented, as was the total number of different frailty tools described across all the studies.

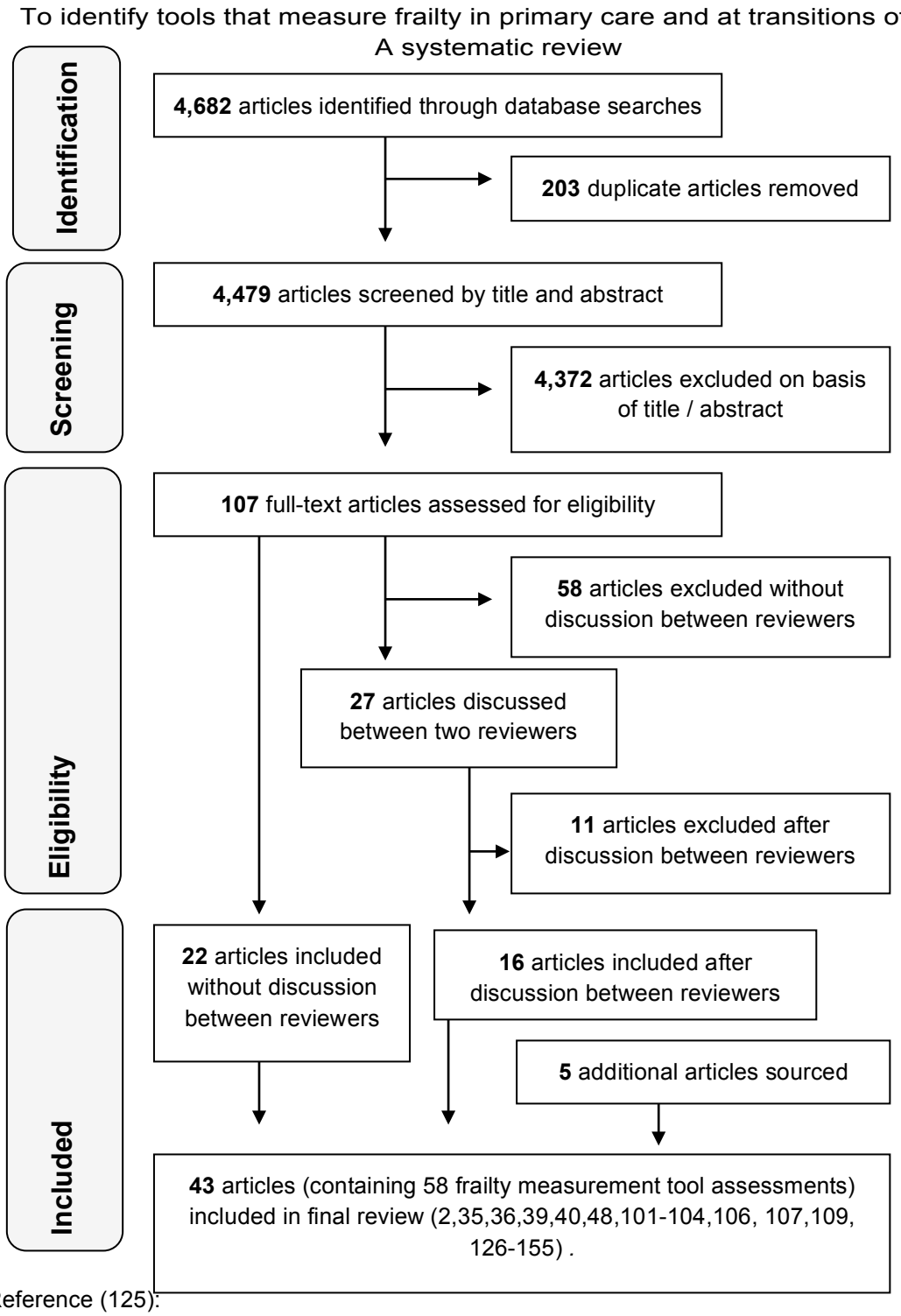
The clinical setting and location of the studies were described, along with the sizes of the study populations and the follow up period of the studies. The conceptual basis and the mode of administration of the frailty measurement tools identified were described. The different components used in the frailty tools reported were described and the combinations of components used in the different tools was analysed. A cumulative list and classification of the elements within the components of the frailty tools described was also produced. The aspects of frailty that the frailty measurement tools had been used to measure were also reported.

The extent of the use of comprehensive geriatric assessment as the reference standard for the external validation of the frailty measurement tools was assessed, as was the nature and extent of external validation using other outcomes associated with frailty. The extent of the assessment of internal validity of the frailty measurement tools for criterion validity, construct validity, predictive validity and face validity was reported. Finally, the results of the quality assessment were reported, indicating the number of studies that were found to have low, high or unclear risk of bias or concerns regarding applicability for each domain.

3.4 Results

3.4.1 Study Selection

Figure 3.1: PRISMA Flow Diagram



Reference (125):

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

A flow diagram for the selection of studies in this systematic review is show in Figure 3.1. The database searches identified a total of 4,682 articles (EMBASE 448, MEDLNE 303 and CINAHL 3931). Of these, 203 were identified as duplicates and were removed, leaving 4,479 distinct articles. These 4,479 articles were screened by title initially and, where uncertainty existed from screening of the title, abstracts were also screened. As a result of this screening by title and abstract, 4,372 articles were excluded and 107 remained for further review. The full text of these 107 articles was reviewed and as a result 22 articles were included and 58 articles were excluded without discussion between the two reviewers. The remaining 27 articles were discussed between the two reviewers, as result of which a further 11 articles were excluded and 16 retained for review. A further 5 articles were included from other sources, thus the final number of articles selected for inclusion in the review was 43 (2,35,36,39,40,48,101-104,106,107,109,126-155) .

3.4.2 Characteristics of studies

The characteristics of the included studies are summarised in Table 3.6.

There were 37 (2,36,40,48,101-104,106,107,109,126-138,140-142,144-151,153,155) studies which reported on a single frailty tool and a further 6 (35,39,139,143,152,154) which reported on more than one tool. Three of these studies reported on 2 tools (39,139,143) and there was one study each reporting on 3 (35), 4 (154) and 8 (152) frailty tools simultaneously. This gave a total of 58 frailty tool assessments from the 43 studies (2,35,36,39,40,48,101-104,106,107,109,126-155). Some frailty tools were reported upon by more than one study. All studies were included for all frailty tools provided that the articles met the inclusion criteria. Multiple studies were included for the same frailty tool because the studies had differing and distinct characteristics, for example reporting upon different aspects of the tools or testing them in different populations or against different outcomes.

Seven papers were identified in the original literature search that included an age limit for the study population at the start of the study of less than 65 years but greater than or equal to 50 years (36,48,104,107,131,133,152). After discussion between the two reviewers, these studies were considered to be important in this field and they were included in the review.

The 58 frailty tool assessments were reported from three continents, with 59% based in Europe (36,39,48,101-104,107,126-130,132-136,140,143,144,148,149,152,153,155), 33% in North

America (2,35,40,106,109,131,136,137,139,141,142,145-147,150,151) and 8% in Asia (138,154) . The sample size in the frailty tool assessments ranged from 100 up to 33,629. The study population was less than 1,000 in 24% (101,126-128,132,133,137-139,145-148); 1,000-5,000 in 43%(35,39,40,102-104,106,109,129,130,135,140,142-144,149,151,154,155); 5,001-10,000 in 9% (2,35,134,136,150); and greater than 10,000 in 24% (35,36,48,107,131,141,152) of studies. All of the studies included in the review reported upon the measurement of frailty in primary care and community settings.

There were inclusion criteria based on geographical location of residence, defined for example by municipal or electoral registers, in 35 (60%) of the studies (2,35,36,39,48,101-103,106,107,126, 130,137,138,141-144,146,147,151-153,155). Registration with specific General Practices was an inclusion criterion in 6 (10%) studies (104,127,128,131,132,135), whilst 3 (5%) studies included only people registered with particular health insurance providers (133,136,150). Participants were included on the basis of their place of employment in one study (134), by their attendance at a specific support centre for older people in another (145), and through response to a public recruitment announcement asking for volunteers in another (129). The participants of 11 (19%) studies were included only if their functional abilities allowed them to attend a study assessment centre and/or complete a physical and/or cognitive screening test prior to entry into the study (133,136,150).

People with Parkinson's Disease and/or depression and/or cognitive impairment and/or stroke were excluded from 6 (10%) of studies (2,35,106,133,145,148). A further 6 (10%) of studies excluded participants with visual impairment and/or mobility impairment sufficient to prevent them from walking across a consultation room and/or those with bilateral hip replacements (139,154). People resident in nursing homes were excluded from 5 (9%) of studies (131,135-137,140). One study excluded people who were already receiving community support (132), one excluded those already under the care of a geriatrician (127) and two studies excluded those people on a palliative trajectory (127,148).

The majority, 41 (70%) of the studies for the assessment of frailty measurement tools were cohort studies (2,35,36,103,104,106,107,126,130,131,133,134,138-143,146,147,149-155), with a further 12 (21%) cross sectional studies (39,48,101,102,109,127,135-137,144,148), 1 (2%) case control studies (40) and 4 (7%) other studies including pilot studies (128,129,132,145).

The follow up period for the assessment of the frailty measurement tools against outcomes related to frailty ranged from 0 to 10 years. Of the reported assessments, 12 (21%) were cross sectional studies and had no defined follow up period (39,48,101,102,109,127,135-137,144,148), 13 (22%) had follow up periods of 2 years or less(36,101,104,107,109,126,131,136,137,139,141), 25 (44%) had follow up periods of 3-5 years (40,103,106,130,133,134,138,142,143,146,152,154,155) and 7 (12%) had follow up periods of 6-10 years (2,39,140,147,150,151) .

The year of publication ranged from 1980 to 2014 but the distribution of the publication of relevant articles across those years reflected the rapid growth of interest in the measurement of frailty in recent years. Only 5 (8%) of the frailty tool assessments were published before the year 2000 (132,135-137,145), 8 (14%) were published 2001-2005 (2,40,106,129,130,149,150,153), 16 (28%) were published in the period 2006-2010 (35,36,101,103,109,139,140,142-144,146,151) and 29 (50%) published since 2011 (39,48,102,104,107,126-128,131,133,134,138,141,147,148,152, 154,155) .

Table 3.6: Summary of characteristics of included studies

Characteristics of Studies	Study references
Location	
• Europe	(36,39,48,101-104,107,126-130,132-136,140,143,144,148,149,152,153,155)
• North America	(2,35,40,106,109,131,136,137,139,141,142,145-147,150,151)
• Asia	(138,154)
Sample Size	
• <1,000	(101,126-128,132,133,137-139,145-148)
• 1,000-5,000	(35,39,40,102-104,106,109,129,130,135,140,142-144,149,151,154,155)
• 5,001-10,000	(2,35,134,136,150)
• >10,000	(35,36,48,107,131,141,152)
Inclusion Criteria	
• Municipal or electoral registers	(2,35,36,39,48,101-103,106,107,126,130,137,138,141-144,146,147,151-153,155)
• Registration with specific GP	(104,127,128,131,132,135)
• Specific health insurance providers	(133,136,150)
• Functional abilities	(133,136,150)
Exclusion Criteria	
• Parkinson's disease /depression /cognitive impairment/stroke	(2,35,106,133,145,148)
• Visual or mobility impairment/ bilateral hip replacements	(139,154)
• Nursing home residents	(131,135-137,140)
Study Design	
• Cohort	(2,35,36,103,104,106,107,126,130,131,133,134,138-143,146,147,149-155)
• Cross sectional	(39,48,101,102,109,127,135-137,144,148)
• Case control	(40)
• Other	(128,129,132,145)
Follow up period	
• Not applicable	(39,48,101,102,109,127,135-137,144,148)
• 2 years or less	(36,101,104,107,109,126,131,136,137,139,141)
• 3-5 years	(40,103,106,130,133,134,138,142,143,146,152,154,155)
• 6-10 years	(2,39,140,147,150,151)
Year of Publication	
• Before 2000	(132,135-137,145)
• 2001-2005	(2,40,106,129,130,149,150,153)
• 2006-2010	(35,36,101,103,109,139,140,142-144,146,151)
• 2011 or later	(39,48,102,104,107,126-128,131,133,134,138,141,147,148,152,154,155)

3.4.3 Quality of studies

The QUADAS assessment tool was used to classify the risk of bias and concerns regarding applicability as low, high or unclear for all the specified domains for the all included studies. The number of studies that found high, low or unclear risks of bias or concerns regarding applicability for each domain are summarised in Table 3.7 and illustrated in Figures 3.2 and 3.3.

Table 3.7: Summary of results of QUADAS assessment for all included studies

QUADAS Domain	Outcome of Assessment Number of studies (%)		
	High	**Low**	**Unclear**
Patient selection			
• risk of bias	30 (52%)	22 (38%)	6 (10%)
• concerns regarding applicability	3 (5%)	53 (90%)	3 (5%)
Index test			
• risk of bias	4 (7%)	45 (77%)	9 (16%)
• concerns regarding applicability	0 (0%)	48 (83%)	10 (17%)
Reference standard			
• risk of bias	4 (7%)	43 (74%)	11 (19%)
• concerns regarding applicability	3 (5%)	37 (64%)	18 (31%)
Flow and timing			
• risk of bias	3 (5%)	36 (62%)	19 (33%)

Figure 3.2: Proportion of Studies with high, low and unclear risk of bias in each of the QUADAS domains

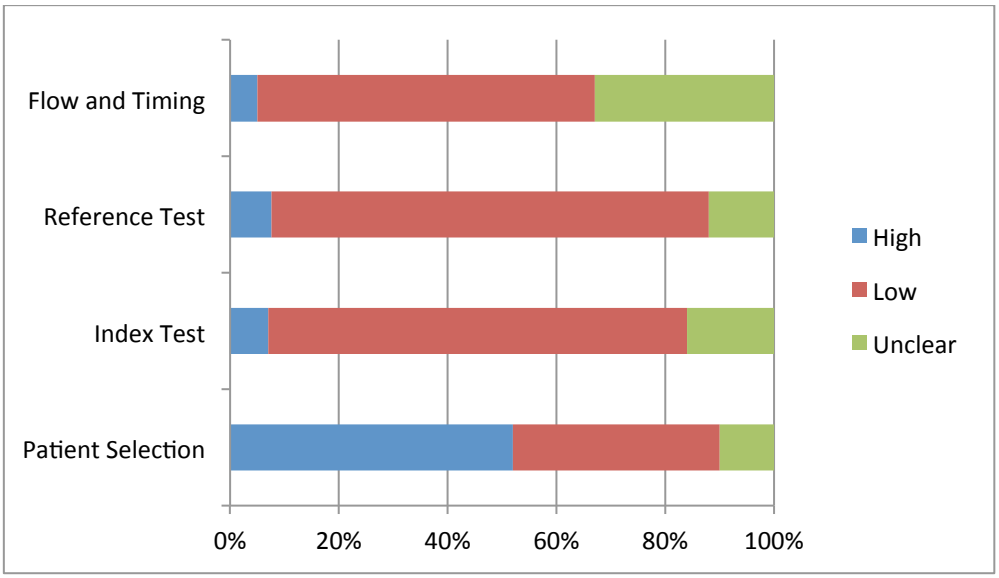
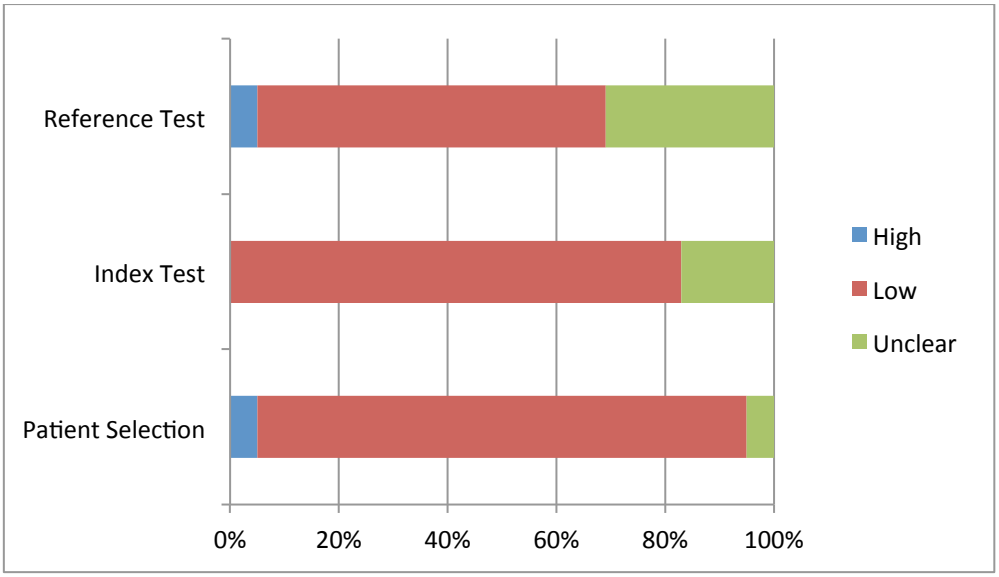


Figure 3.3: Proportion of Studies with high, low and unclear concerns regarding applicability in each of the QUADAS domains



3.4.4 Characteristics of frailty measurement tools identified

The characteristics of the frailty measurement tools in this study are summarised in Table 3.8.

Table 3.8: Summary of characteristics of included studies

Characteristics	Study references
Conceptual Basis	
• Frailty Index (routine data)	(104,131)
• Frailty Index (composite)	(35,40,109,138,141-143,151,152,154)
• Phenotype	(2,35,36,39,106,107,129,133,134,139,145,147,152,155)
• Multidimensional	(35,39,48,101-103,126-128,130,132,135-137,140,143,144,146,148-150,152,153)
Mode of Administration	
• Clinical review	(2,36,39,103,106,107,129,138,143,149,154,155)
• Professionally administered questionnaire	(109,130,141,147)
• Self-reported questionnaire	(48,101,102,126,132,133,135-137,142,144-146,148,150,151,153)
• Combination of clinical review and questionnaire	(35,40,127,128,134,139,140,152)
• Extraction of data remote from patient	(104,131)
Components of Frailty Measurement tools	
• Clinical measurement	(35,36,39,40,103,106,107,134,138-141,143,149,152,154,155)
• Routinely collected data (only)	(104,131)
• Physical health factors	(2,35,36,39,40,48,101-103,106,107,109,126-130,132-155)
• Psychological factors	(35,40,48,101-103,106,109,126-130, 132,133, 135,137,138, 140,141,143-146,148-152,154)
• Healthcare use	(132,136,137,142,152)
• Social factors	(35,40,48,101-103,106,126-130,132,135-138,142,148,153)
• Clinical assessment	(2,35,39,40,103,106,127,128,138,139,142-3,149,152,154,155)
• Environmental factors	(48)
External validation of frailty tools	
Using CGA	(40,101,106,127,132,135,137-141,143,145,148)
Using other frailty outcomes	
• Quality of life	(101,102,126,148)
• Disability / functional decline	(2,39,101-103,107,126,133,138,139,144,146-150,154)
• Hospital admissions	(2,39,101,103,126,133,134,136,138-142,144,153,155)
• Fractures / falls	(39,103,139)
• GP visits	(101,126,144)
• Emergency department visits	(104,139,144,153)

• Out of hours GP visit • Nursing home admission • Death	(104) (39,40,104,106,130,131,136,141) (2,36,39,40,103,104,106,109,130,131,133,138,140-143,146,147,150-152,154,155)
Uses of frailty tools	
• To measure frailty status • To predict outcomes in frailty	(2,35,36,39,40,48,101,102,104,106,107,109,126-135,137-153,155) (2,36,39,40,101,103,104,106,107,109,126,130,131,133,134,136-144,146,147,149-155)
Assessment of internal validity	
• Face validity • Construct validity • Criterion validity • Predictive validity	(101,128,132) (2,35,36,48,101,102,104,106,127,139,141-144,151,152) (2,35,40,48,101,102,104,129,134,135,137,139-144,149-152,154,155) (2,36,39,40,101,103,104,106,107,109,126,130,131,133,134,136-144,146,147,149-155)

3.4.4.1 Conceptual basis of tools

The conceptual basis of the frailty models in the reviewed studies and the total number of different tools in each category are presented in Table 3.9.

Table 3.9: Conceptual basis of frailty measurement tools in this study

Conceptual Basis of the Measurement Tool	Number of assessments reviewed in each category	Number of individual tools assessed in each category
Frailty Index (routine data)	2 (3%)	2
Frailty Index (composite)	12 (21%)	12
Phenotype Model	20 (35%)	16
Multi-dimensional Model	24 (41%)	15
Totals	58 (100%)	45

The conceptual model upon which the measurement tools were based was a Frailty Index using routine data only in 2 (3%) studies (104,131), a composite Frailty Index in 12 (21%) studies (35,40,109,138,141-143,151,152,154), phenotype in 20 (35%) (2,35,36,39,106,107,129, 133,134,139,145,147,152,155) and a multi-dimensional model in 24 (41%) of studies assessed. The total number of different tools described in the reviewed studies was 45. Eight specific measurement tools were assessed in more than one of the studies reviewed (4 were assessed in two studies, 3 were assessed in 3 studies and 1 was assessed in 4 studies).

3.4.4.2 Mode of administration

The mode of administration of the tool was by clinical review for 17(29%) of tools (2,36,39,103,106,107,129,138,143,149,154,155), by questionnaire in 21(36%) cases (4(7%) were professionally administered (109,130,141,147) and 17(29%) were self-reported (48,101,102,126, 132,133,135-137,142,144-146,148,150,151,153)), by a combination of clinical review and questionnaire in 18 (31%) cases (35,40,127,128,134,139,140,152) and by extraction of data remote from the patient in 2 (4%) cases (104,131), as shown in Table 3.10.

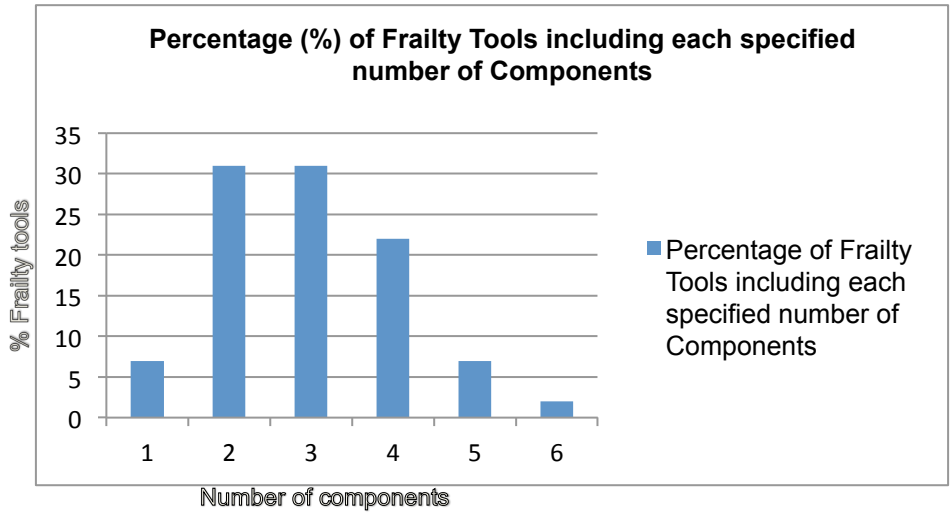
Table 3.10: Mode of administration of frailty measurement tools included in the review

Mode of administration	Number (%)
Clinical review	17 (29%)
Questionnaire	
a) Professionally administered	4 (7%)
b) Self-reported	17 (29%)
Combination of clinical review and questionnaire	18 (31%)
Extraction of data remote from patient	2 (4%)

3.4.4.3 Components of frailty tools

The components of frailty tools under investigation are described in section 3.3.1.2, page 38. The number of components included in the different frailty tools reviewed ranged from 1 to 6, with 36 (62%) of the tools studied being comprised of two or three components. The distribution of the number of components included in the tools studied is shown in Figure 3.4.

Figure 3.4: Percentage (%) of frailty tools including different numbers of components



The frequency with which the different components were represented across the range of frailty tools reviewed is listed in Table 3.11.

Table 3.11: Table to show the frequency of inclusion of different components of frailty across the frailty tools reviewed

Component of Frailty Measurement	Tools including component	Tools not including component
Clinical Measurement	23 (40%)	35 (60%)
Routinely Collected Data (only)	2 (3%)	56 (97%)
Physical Health Factors	56 (97%)	2 (3%)
Psychological Factors	36 (62%)	22 (38%)
Healthcare Use	7 (12%)	51 (88%)
Social Factors	23 (40%)	35 (60%)
Clinical Assessment	21 (36%)	37 (64%)
Environmental Factors	1 (2%)	57 (98%)

3.4.4.4 Elements included in the components of frailty tools

A cumulative list was created which categorised the elements identified within each component of the frailty measurement tools reviewed, as shown in table 3.12.

Table 3.12: Components, categories and elements of tools reviewed

Clinical Measurements		
Anthropometric Data	**Specific Tools and Tests**	**Blood Tests**
• Height • Weight • Body Mass Index • Pulse • Blood Pressure • Peak expiratory flow rate • Waist hip ratio • Functional reach • Calf circumference	• Geriatric Depression Scale • Tinetti gait and balance score • Physical Activity Score for Elderly • Romberg test • Brachial-ankle index by doppler • Knee extension strength • Timed up and go test • Walking speed • Grip strength • Mini Mental State examination	• Hb • WCC • Lipids • CRP • d-dimer • Testosterone • Albumin

Routinely Collected data			
Diagnostic Codes	**Prescribing Data**	**Symptom Codes**	**Demographic Data**

Physical Health Factors		
Diseases and Diagnoses	**Functional ability / impairment**	**Symptoms**
• COPD • Cancer • Diabetes • Stroke • Respiratory function • Cardiovascular function • IHD • Arthritis • Fractures • Specific diseases	• Level of physical activity • Slowness • Strength • Weakness • Endurance • Activities of daily living • Instrumental activities of daily living	• Difficulty with balance • Poor hearing • Poor vision • Cough • Shortness of breath • Urinary incontinence • Bowel incontinence • Pain • Poor health • Weight loss • Falls • Tiredness/exhaustion

Table 3.12 (continued):

Psychological Factors	
Mental Health • Depression • Anxiety • Hallucinations • Behaviour problems	**Cognitive Function** • Problems with memory • Cognitive problems • Reasoning • Disorientation • Dementia
Symptoms • Trouble sleeping • Loss of confidence • Loss of ability to cope • Feeling pressure • Satisfaction with endurance / strength • Nervous or anxious	**Descriptive** • Self-perceived health • Sense of mastery • Is health causing concern? • Emptiness • Mental well being • Unhappy / sad / down • Motivation

Healthcare Use		
Secondary Care Use • Emergency department attendance • Number of days in hospital in previous 2 years • Hospital admission in the last year	**General** • Special equipment provided • Prescription items dispensed in a year	**Place of Care** • Nursing Home admission

Clinical Assessments
• Sit to stand time • Dexterity - full use of 2 hands and 10 fingers • Put on and take off cardigan • Clinical assessment of balance • Vision • Ability to recognise face at 4m • Hearing • Speech • Verbal fluency

Table 3.12 (continued):

Social Factors	
Defined / External	**Personal / Perceptual**
• Moved during last year • Type of housing • Eat a hot meal every day • Help with meals • Have formal home care support with ADLs • Lives alone • Bereavement in the last year • Financial issues • Education level • Smoking • Do you look after anyone?	• Loneliness • Do you get on well with those close to you? • Is there a relative or friend you can rely on? • Are you missing people? • Can you go out by yourself? • Support from family • Support from community • Do you have a good social network?

Environmental Factors	
Specific	**General / Descriptive**
• Stairs to get into house • Toilet upstairs • Difficulty heating house	• Housing conditions • Insufficient comfort • Too far to facilities • Don't like the neighbourhood

3.4.5 External Validation of frailty tools identified

In this review 13 (22%) of the reported assessments were cross sectional studies and had no defined follow up period, 13 (22%) had follow up periods of 2 years or less, 25 (44%) had follow up periods of 3-5 years and 7 (12%) had follow up periods of 6-10 years. Follow up periods are relevant when considering follow up and external validation using outcomes associated with frailty. With regard to external validation, 14 (24%) of the tools had been validated using both CGA and the prediction of other outcomes associated with frailty, 2 (3%) using CGA alone, 37 (64%) using other outcomes alone, and 5 (9%) of the tools had not been validated against either CGA or other outcomes.

3.4.5.1 Comprehensive Geriatric Assessment

The frailty tools reported had been validated using some form of Comprehensive Geriatric Assessment (CGA) in 16 (28%) of cases and had not been validated using a CGA in 42 (72%) of cases.

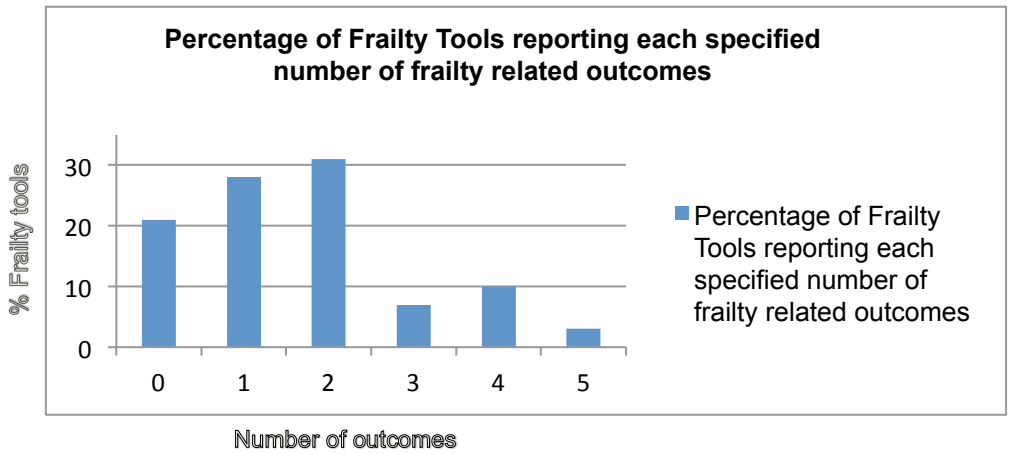
3.4.5.2 Outcomes associated with frailty

In this study 51 (88%) of the tools had been validated using outcomes associated with frailty and 7 (12%) had not. The following frailty related outcomes were reported in the studies reviewed

1) Quality of life
2) Disability / functional decline
3) Hospital admissions
4) Fractures / falls
5) GP visits
6) Emergency department visit
7) Out of hours GP visit
8) Nursing home admission
9) Death

The number of frailty related outcomes reported for the different frailty tools reviewed ranged from 0 to 5, with 34 (59%) of studies reporting one or two outcomes. The distribution of the number of frailty related outcomes reported in the studies is shown in Figure 3.6.

Figure 3.6: Percentage (%) of tools reporting different numbers of frailty outcomes



The frequency with which the different frailty related outcomes were represented across the range of frailty tools reviewed is listed in Table 3.13.

Table 3.13: Table to show the frequency of inclusion of different outcomes related to frailty across the frailty tools reviewed

Frailty related outcome	Tools including the outcome	Tools not including the outcome
Quality of life	4 (7%)	54 (93%)
Disability / functional decline	22 (38%)	36 (62%)
Hospital admission	18 (31%)	40 (69%)
Fractures / falls	5 (9%)	53 (91%)
GP visits	3 (5%)	55 (95%)
Emergency Department visit	5 (9%)	53 (91%)
Out of hours GP visit	1 (2%)	57 (98%)
Admission to Nursing Home	9 (16%)	49 (84%)
Death	35 (60%)	23 (40%)

3.4.6 Uses of frailty tools identified

Frailty tools had been used to measure frailty status in 56 (97%) of cases and to predict outcomes in frailty in 14 (24%) of cases. None of the tools had been used to predict frailty in the non-frail.

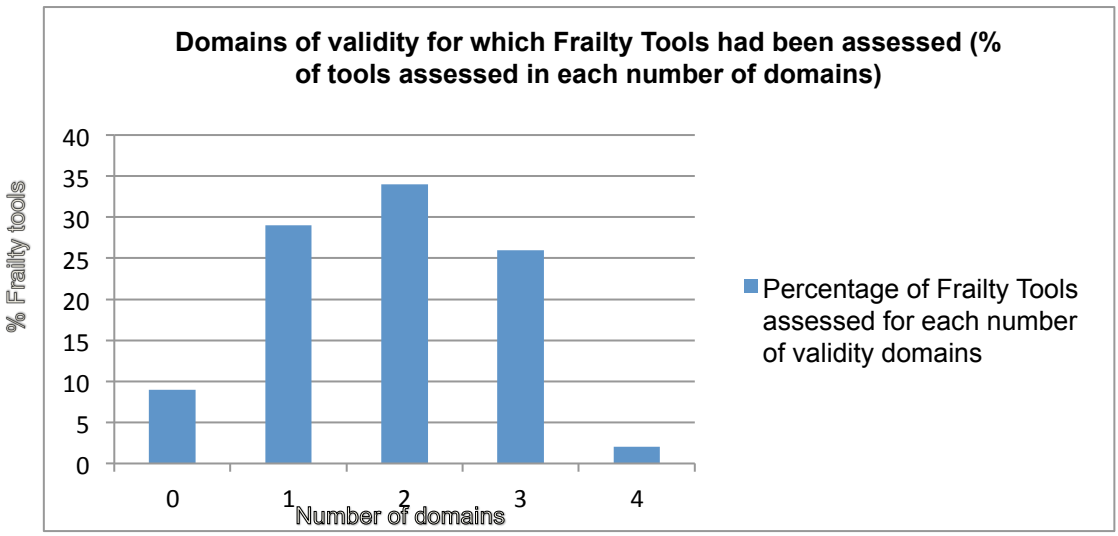
3.4.7 Assessment of internal validity of frailty measurement tools

The assessment of the internal validity of the frailty tools reported was reviewed for face, construct, criterion and predictive validity (section 1.6.1, page 14). Validity assessment was highest for the assessment of criterion validity at 62%, followed by 45% for construct validity, 24% for predictive validity and 5% for face validity. Only one study reported validity assessment across all four domains and 5 studies (9%) did not report validity assessment in any of the domains. Validity assessment for 1 domain was reported in 17 (29%) of cases, for 2 domains in 20 (34%) and for 3 domains in (18%) of cases. Assessment of the different domains of validity across the range of frailty measurement tools reviewed is listed in Table 3.14 and illustrated in Figure 3.8.

Table 3.14: Table to show the frequency of validity assessment for different domains of validity across the frailty tools reviewed

Domain of Validity Assessment	Tools assessed in this domain	Tools not assessed in this domain
Face Validity	3 (5%)	55 (95%)
Construct Validity	26 (45%)	32 (55%)
Criterion Validity	36 (62%)	22 (38%)
Predictive Validity	14 (24%)	44 (76%)

Figure 3.8: Proportion (%) of frailty tools for which each number of domains of validity had been assessed.



3.5 Discussion

3.5.1 General findings

There has been rapid growth in research regarding the measurement of frailty in primary care and at transitions of care in recent years, with 50% of the studies identified in this review having been published since 2011 and 92% published since the year 2000. The research activity identified in this review has been concentrated in Europe and North America, with 92% of studies in this review set in these regions. However, it is possible that this finding is to some extent an artefact resulting from the inclusion criteria of 'English language publications' in the article selection for this review.

3.5.2 Conceptual basis of frailty measurement tools

The conceptual basis of the frailty measurement tools identified in this review was equally divided between the three main models of frailty, with one third based on a frailty index (cumulative deficit) model, one third on a phenotype model and one third on a multi-dimensional model. This division reflects the current lack of consensus regarding a single conceptual definition of frailty and is consistent with other published evidence in illustrating that there is currently no agreed 'best approach' to the measurement of frailty in primary care and no single frailty measurement tool with clear and decisive advantages over others in this setting.

3.5.3 Mode of administration of frailty measurement tools

In this review, 35 (60%) of the tools measured frailty through some form of direct clinical review, with 17 of these relying entirely on direct clinical review and 18 involving a combination of direct clinical review and questionnaire assessment. A further 21 (36%) of the frailty measurement tools assessed used a questionnaire format of which 4 were professionally administered questionnaires and 17 were self-reported questionnaires. Only 2 (4%) of the studies in this review reported frailty measurement tools based entirely on routinely collected data.

Frailty measurement tools using direct clinical review of the individual concerned have the advantage of giving the opportunity to consider and include a depth of clinical information that cannot be obtained through remote methods such as questionnaires or routinely collected data. However, frailty measurement tools involving direct clinical review have the disadvantage of being more costly and time consuming than measurement tools that operate more remotely from clinicians. They also have the disadvantage of potential variability in application between different clinicians. This type of tools might therefore be less suitable for population screening and more suitable as part of a targeted intervention programme.

Frailty measurement tools involving questionnaires, whether professionally administered or self-reported, have the advantage of offering the opportunity to focus upon the individual's perception of their own current health and well-being status and any associated health and care needs. They also offer an excellent opportunity to measure the individual's quality of life, although this review shows that currently quality of life has only been formally considered as an outcome in a small number of frailty measurement tools. Self-report questionnaires are less costly to administer than

frailty measurement tools using direct clinical review, although this cost differential is likely to be reduced or event absent between professionally administered questionnaires and direct clinical review. In health economic terms, earlier detection of frailty may well be cost effective because frailty management could become less costly to health services through early intervention.

However, there are also some clear disadvantages in a questionnaire approach to the measurement of frailty, particularly in the case of self-report questionnaires. The measurement of frailty in this way is not suitable for individuals with functional impairments that prevent them from understanding or completing the questionnaire. These functional impairments are frequently a consequence of physical and/or mental health conditions that are likely to be more common in individuals with, or at risk of, frailty. Therefore, individuals who are more likely to be frail are also more likely to have medical conditions that make it difficult or even impossible to measure their frailty using tools involving self-report questionnaires.

Frailty measurement tools using routinely collected data have the advantage that once established they can be remotely, comprehensively and consistently applied to the population of interest, thus maximising inclusion and minimising selection bias. The use of frailty measurement tools using routinely collected data also has the advantage of being low cost in comparison both to measurement tools involving direct clinical assessment and to those using professionally administered or self-report questionnaires. Frailty measurement tools using routinely collected data have the disadvantage that they rely on the quality of the coding at the point of data entry into the electronic patient record. Furthermore, much of the current focus of the development of frailty measurement tools using routinely collected data is upon data collected in primary care and challenges remain in the routine linking and inclusion of secondary care and social care data with primary care systems.

Frailty measurement tools administered in different ways therefore have various strengths and weaknesses when considered for use in a range of populations and purposes. Previously this has tended to lead to an approach of ‘different tools for different purposes’ (30), with various frailty instruments developed for use in different contexts. However, the disadvantage of this approach is that it can tend both to reflect and to perpetuate the fragmented and service-centric perspective from which care is often delivered to people with frailty.

This review identifies that there is a gap in current approaches, which could be filled by taking a unified approach that seeks to combine the strengths of the differing modes of administration and minimises their limitations. An 'ideal' frailty measurement tool could be envisaged to take a 'progressive', 'dynamic' or 'responsive' approach to the measurement of frailty. This could potentially combine an initial screening stage benefiting from the inclusivity and consistency of measurement using routinely collected data with progression to a more detailed and targeted measurement of frailty, including both clinical and quality of life assessments, for those individuals identified most likely to have frailty and complex needs.

3.5.4 Components of frailty measurement tools

Tools to measure frailty included a range of components and the components of frailty used in the measurement tools identified in this review were analysed. The components of the measurement tools of interest in this review were: routinely collected data, physical health factors, clinical measurements, clinical assessments, psychological factors, healthcare use, social factors and environmental factors.

Conceptual definitions of frailty based upon medical sciences have tended to be dominated by physical health domains, with much focus on the physical aspects and determinants of frailty (1). Physical and biological factors are pre-eminent in our clinical understanding of frailty and therefore it is not surprising that physical and physiological factors play a dominant role in the tools for the measurement of frailty identified in this review. Physical health components were represented in all the frailty measurement tools considered in this review, including those which used only routinely collected data in tools for the measurement of frailty. Clinical measurement components and clinical assessment components were identified in 23 (40%) and 21 (36%) respectively of the frailty measurement tools reviewed, with some tools including both components. This was consistent with the findings regarding the mode of administration, which demonstrated that 35 (60%) of frailty measurement tools included some form of clinical review.

Although the accumulation of physical health deficits is accepted as an important aspect of frailty, many authors advocate integrated models of frailty that go well beyond the physical and physiological determinants of frailty (16,43,44). Clear arguments have been made for models of frailty to include psychological, emotional and social domains alongside the well-established

physical health domains (16,43,44). These components therefore have a potentially important role to play in tools for the measurement of frailty. In this review, after physical health factors and components involving clinical review, psychological components were found to be the next most common components in the frailty measurement tools identified and were contained in 36 (62%) of the studies reviewed. The next most frequently considered component category was that of social factors, which were included in 23 (40%) of the frailty measurement tools in this review.

It has been suggested earlier in this thesis (section 1.4, page 8), that systems of healthcare should be considered not only as vehicles to deliver interventions to frailty, but also in terms of their potential to influence the course of developing frailty trajectories. This review therefore investigated the role of healthcare use in the frailty measurement tools identified and found that healthcare use featured as a component in 7 (12%) of the frailty measurement tools reviewed.

There is current interest and discussion surrounding the use of routine datasets in the measurement of frailty, particularly the development of methods to use such data to generate a frailty index based upon the cumulative deficit model of frailty (104). Most of the frailty measurement tools considered in this review contained some items of routinely collected data, usually demographic data. However, routinely collected clinical data was identified as a major or exclusive component of the tool in only 2 (3%) of the studies in this review.

The case for including an environmental domain, considering such things as housing conditions, within models of frailty has also been made (48). Environmental factors were the least frequently considered component in the frailty measurement tools identified, which were specifically included in only one of the frailty measurement tools in this review.

This review therefore identifies that there is considerable scope to further develop a multi-dimensional approach to the measurement of frailty in primary care and at transitions of care. Furthermore, this review identifies two specific areas of opportunity: Firstly, to more comprehensively embed psychological and social components into frailty measurement tools in primary care. Secondly, to further research the possible contribution to frailty measurement tools of components relating to healthcare use and environmental factors.

3.5.5 Elements included in the components of the frailty measurement tools

A cumulative list of the elements included within the components of the frailty measurement tools in this review were collated and categorised according to a framework devised empirically by the first reviewer.

Physical health factors were grouped into three categories, namely diseases and diagnoses, functional ability / impairment (e.g. activities of daily living) and symptoms (e.g. shortness of breath). Clinical measurements were also categorised into three groups, anthropometric data (e.g. body mass index), specific tools and tests (e.g. physical activity score for the elderly), and blood tests. Clinical assessments were the only components that did not appear to warrant further sub-categorisation. Psychological factors were grouped into four categories of mental health (e.g. depression), cognitive function (e.g. memory loss), symptoms (e.g. loss of confidence) and descriptive features (e.g. mental well-being). Social factors were described in two categories, namely defined / external factors (e.g. lives alone) and personal / perceptual factors (e.g. feeling of loneliness). Healthcare use was defined according to three categories, namely secondary care use (e.g. hospital admissions in the last year), general use (e.g. special equipment provided) and place of care (e.g. nursing home admission). Routinely collected data was categorised into four groups of diagnostic codes, prescribing data, symptom codes and demographic data. Environmental factors were categorised in two groups, as either specific (e.g. steps to get into home) or general / descriptive (e.g. insufficient comfort).

The purpose of this part of the review was to generate a comprehensive list of elements that have been included in tools for the measurement of frailty in primary care and at transitions of care to use in later research. These elements were therefore not scored for frequency of occurrence within the frailty measurement tools reviewed.

3.5.6 Uses of frailty measurement tools

The three main uses of frailty measurement tools considered in this review were the measurement of frailty status, the prediction of outcomes in frailty and the prediction of frailty in the non-frail. These three functions could be considered to represent a spectrum of opportunities and approaches in the management of frailty ranging from mostly reactive to strongly proactive.

The measurement of current frailty status is an important function, which facilitates the targeting of frailty specific health and care interventions towards those individuals currently experiencing the greatest levels of need. This approach primarily facilitates the effective delivery of reactive interventions designed to deliver effective care to people currently experiencing frailty. This review identifies that existing frailty measurement tools applied in primary care and at transitions of care are predominantly directed towards the measurement of current frailty status, with 56 (97%) of the tools having been used in this way. Tools with the ability to recognise and quantify current frailty status have an important role in supporting the delivery of reactive interventions, which are timely, appropriate and proportionate in the context of an individual's degree of frailty.

Certain adverse outcomes are recognised as being associated with frailty, including death, increasing levels of disability and dependency, and acute unscheduled care episodes (section 1.5.3, page 12). The trajectories towards some of these outcomes contain opportunities at which timely and appropriate interventions can influence the course of events. The use of frailty measurement tools with the ability to predict outcomes in frailty could therefore be valuable in supporting the proactive use of frailty interventions, which can in turn prevent, attenuate or delay the development of some adverse outcomes. Even when such outcomes cannot be avoided, the ability to predict them can still help to facilitate preparation for, and acceptance of, the likely course of events by both individuals concerned and their carers. Frailty measurement tools that can predict outcomes in frailty therefore have the potential to make a valuable contribution towards moving the focus of the management of frailty from a predominantly reactive to a more proactive approach. This review identified that 14 (24%) of the frailty measurement tools considered had been used to predict outcomes in frailty, thus highlighting the need for further development of this approach to the measurement of frailty.

Frailty is a dynamic condition, which can be amenable to interventions designed to reverse or slow its progression (1). Furthermore, frailty usually develops over a period of time and 'pre-frail' states can exist. Interventions to reverse or slow down the progression of frailty whilst the condition is in an early developmental phase therefore have great potential for reducing overall levels of frailty. This would have a positive impact upon both individual quality and experience of life, and upon care need and provision at a population level. The use of frailty measurement tools in primary care which have the ability to predict frailty in the non-frail would therefore facilitate a much more

proactive approach to the management of frailty along the whole trajectory of the condition. However, none of the tools for the measurement of frailty in primary care or at the transitions of care considered in this review had been used in this way. This review has therefore identified that there is currently a gap in this area of frailty measurement.

This review has therefore highlighted the need for the development of frailty measurement tools for primary care which can be used not only to measure frailty status, but which can also be more widely used to predict outcomes in frailty, and in particular, which can be used to predict frailty in the non-frail.

3.5.7 External validation of frailty measurement tools

Comprehensive geriatric assessment is currently the most well established method for the assessment of frailty. External validation using CGA was therefore considered the 'gold standard' for assessing the point in time accuracy of frailty measurement tools in this review. However, carrying out comprehensive geriatric assessment requires considerable time commitment from suitably trained professionals and is therefore a costly process that may not always be practically deliverable in either research or clinical practice. In this review, 16 (28%) of the tools had been validated using some form of comprehensive geriatric assessment, whilst 42 (72%) had not been tested in this way.

Another way of validating tools for the measurement of frailty is to validate them using outcomes associated with frailty. In this study 51 (88%) of the tools had been validated using these outcomes. Ideally validation of a frailty measurement tool using outcomes associated with frailty would take place in addition to, and in follow up to, first line validation of the tool using comprehensive geriatric assessment.

In this review, 14 (24%) of the tools had been validated using both CGA and outcomes related to frailty, 2 (3%) using CGA alone, 37 (64%) using other outcomes alone, and 5 (9%) of the tools had not been validated using either CGA or other outcomes associated with frailty.

The identification of the outcomes associated with frailty that are the most relevant and useful in the external validation of frailty measurement tools warrants further discussion. The ultimate objective of measuring frailty in primary care and at transitions of care is to inform an approach to the management of frailty that will improve the quality and experience of life for individuals living

with frailty. It is therefore important that tools for the measurement of frailty are validated using outcomes that are most relevant to this experience and quality of life.

In this review, death was the outcome associated with frailty most frequently studied and was considered in 35 (60%) of studies. Some advantages of selecting death as an outcome include that it is clearly defined, well recorded and easy to identify. However, although death is an important and indeed inevitable outcome for all people living with frailty, it is in many ways an outcome of limited usefulness in assessing individual frailty and its impact upon an individual's experience and quality of life. I would like to consider the other outcomes identified in this review broadly in two categories: Firstly, those outcomes which focus upon factors relevant to the individuals' experience and quality of life. Secondly, those outcomes that are orientated more towards aspects of healthcare, systems and process, for example episodes of acute care.

Quality of life is arguably the most important outcome in relation to the measurement and management of frailty. However, this outcome was considered for the validation of frailty measurement tools in only 4 (7%) of the studies in this review. Outcomes related to levels of disability and functional decline are also of great importance to an individual's experience and quality of life. These outcomes were selected for use in the validation of frailty measurement tools in 22 (38%) of the studies in this review.

Overall, outcomes orientated towards aspects of healthcare, system and process featured much more strongly than those related to quality of life in the studies in this review. Acute hospital admission was considered in 18 (31%) of studies, admission to nursing home in 9 (16%), emergency department attendance in 5 (9%), and falls and/or fractures in 5 (9%).

There is a strong case developing that an increasingly interventionist and technological approach to the medical management of disease is often not the most appropriate approach to caring for people living with frailty and complex needs. Efforts in the management of frailty should be clearly directed towards achieving individual, person-centred objectives, which relate directly to maximising a person's quality and experience of life. In order to appropriately support and direct this activity, and measure its impact, frailty measurement tools used in primary care should be validated using outcomes that are directly relevant to the key objectives of care. These should focus much more strongly upon patient centred outcomes and outcomes such as quality of life,

disability and functional decline should be used for the validation of all tools for the measurement of frailty in primary care.

This review has therefore identified a gap in the external validation of tools for the measurement of frailty in primary care using both comprehensive geriatric assessment and patient centred outcomes. Quality of life has been a particularly little used outcome and there is also scope for wider use of outcomes related to disability and functional decline. This review highlights the need to address these areas more comprehensively in the future development of tools for the measurement of frailty in primary care.

3.5.8 Assessment of internal validity of frailty measurement tools

Consideration of internal and external validity is a key element of the development of healthcare measurement tools. The external validation of the frailty measurement tools in this review using comprehensive geriatric assessment and outcomes associated with frailty is discussed above. The internal validity of the frailty measurement tools reviewed was considered across the four domains of face validity, criterion validity, construct validity and predictive validity. Only one study presented validity assessment across all four of these domains. Validity assessment was reported for none or one domain in 22 (38%) studies and for 2 or 3 domains in 35 (60%).

Two of the multi-dimensional tools in this study, namely the Tilburg Frailty Indicator (101) and the Groningen Frailty Indicator (148), reported validation against other outcomes that included quality of life measures, and of these two, the most comprehensive reporting of internal validation was for the Tilburg Frailty Indicator. The Groningen Frailty Indicator had been used to measure frailty status, whilst the Tilburg Frailty Indicator had been used both to measure frailty status and to predict outcomes in frailty. Another of the multi-dimensional tools in this group, namely the EASY-care two step tool (127), describes an approach to the measurement of frailty status in which the first step uses a review of primary care records and the second uses clinical assessment.

This review identified that there had not been a consistent approach to internal validity across four key domains of validity in the development and testing of tools for the measurement of frailty in primary care and at transitions of care. It is essential that these aspects are given full consideration in future studies in order to develop acceptable, high quality tools for the measurement of frailty in

such settings. There is a particular need for development in the consideration of face validity and predictive validity for such tools.

3.5.9 Quality Assessment

The quality of studies in this review was assessed using the QUADAS tool (section 3.3.5, page 46). Overall, the quality of the studies was good with respect to the risk of bias in the index test, reference standard, and with flow and timing. Only 5-7% of the studies were considered to be at high risk of bias in each of these areas; around 75% of studies were considered to have low risk of bias for the index test and reference standard, and 62% to be low risk regarding flow and timing. The risk of bias with respect to the index test and the reference standard was considered to be high for a study in which both tests had been carried out by the same clinician, and for a study in which the index test had been tested against a reference standard which had itself been the model for the design of the index test. The risk of bias was considered high for flow and timing where there was a delay between the index and reference test assessments and where the tests included subjective clinical judgements made by a range of clinicians.

The domain in which the quality concerns regarding bias were greatest was that of patient selection, with 52% of included studies considered to be at high risk of bias in this area. The main concerns in this area were due to the inclusion and exclusion criteria of a number of studies. In particular, some studies excluded patients with cognitive impairment or dementia and some studies excluded patients with mobility or other impairments sufficient to prevent them from attending a clinical assessment centre to participate in the study. Another aspect considered to increase bias in some studies was the recruitment strategy used. Strategies that included recruitment via specific community settings delivering care and support to older people or via recommendation by clinicians working in the field, or by simply asking for volunteers, caused particular concern. Another area of concern in some studies was the high number of participants lost to follow up and the fact that those lost to follow up tended to show particular characteristics such as being older and having greater levels of physical and cognitive impairment, thus increasing the risk of bias.

The quality assessment showed that concerns regarding applicability were low in all areas, with no studies found to have high concerns about applicability with respect to the index test and only 5% with high concerns in this domain with respect to patient selection and the reference standard.

The results of the quality assessment in this systematic review suggested that the main challenge regarding quality in the design of studies to develop and test tools for the measurement of frailty lies in the need to minimise bias in patient selection. There are inevitable challenges associated with population selection in this area of study. For example, there is a particular issue with studies involving frailty assessment tools comprised of self-reported questionnaires, as the presence of cognitive impairment inevitably impacts upon the participation of individuals with this condition in studies using this tool design.

Study design should also consider ways to enable inclusion of individuals across the full spectrum of frailty, including advanced frailty, and not exclude participants on the basis of characteristics that are likely to be associated with frailty, such as cognitive and physical impairment and disability. Study design should also consider strategies to improve the retention of individuals living with advancing frailty within study populations during the follow up period, therefore reducing the loss to follow up in this group which can introduce bias into study results.

This review highlighted the need for future studies concerned with the development and testing of tools to measure frailty in primary care and at transitions of care to focus more strongly upon efforts to minimise bias in patient selection.

3.5.10 Research implications

This systematic review highlighted the fact that there is currently no single accepted tool for the measurement of frailty in primary care. However, it identified the following framework through which such an instrument could be developed (Table 3.15).

1) Conceptual basis of tool: This review identified the three main concepts of frailty underpinning current tools for the measurement of frailty in primary care, but did not clearly favour one over the others. However, given the holistic and contextual nature of primary care there is a strong argument that a multi-dimensional model of frailty most accurately and comprehensively reflects the nature of frailty in primary care and would therefore be the most appropriate conceptual basis for a frailty measurement tool in this setting.

2) Mode of administration: This review identified an opportunity to improve upon current tools by taking a stepwise approach to the measurement of frailty that combines the strengths of the different modes of administration and minimises their limitations. An initial measurement stage

could be designed using routinely collected data, giving the advantage of a systematic and comprehensive approach enabling the inclusion of all people who have an electronic healthcare record, not just those presenting to specific healthcare professionals or services. A second, more detailed and targeted stage of measurement, including both clinical and quality of life measurements, could take place for those individuals identified during the first stage.

3) Components of measurement tool: This review highlighted the established role of physical, psychological and social components within this multi-dimensional approach to the measurement of frailty, whilst at the same time emphasising the need to more comprehensively embed the latter two components. It also identified a need for further research into the possible role for components relating to healthcare use and environmental factors in a tool to measure frailty in primary care.

4) Uses of measurement tool: This review also demonstrated the need for the development of frailty measurement tools for primary care that can be used not only to measure frailty status, but also to predict outcomes in individuals with frailty and to predict frailty in the non-frail.

5) External validation of the tool: This review highlighted the need to further develop the external validation of tools for the measurement of frailty in primary care, using both Comprehensive Geriatric Assessment and patient centred outcomes, particularly quality of life and disability and functional decline.

6) Internal validation of the tool: The need for a consistent and rigorous approach to internal validity in the development and testing of tools for the measurement of frailty in primary care and at transitions of care was identified. There was a particular need for improvement in assessment of face validity and predictive validity for such tools.

7) Quality of development of tool: Finally, the need for future studies to focus more strongly upon efforts to minimise bias in patient selection was clearly demonstrated in this review.

Table 3.15: Recommended framework for the development of a new tool for the measurement of frailty in primary care, drawn from results of this systematic review:

Aspect of Frailty Measurement Tool	Recommendation from results of Systematic Review
Conceptual basis of tool	Multi-dimensional
Mode of administration	Stage One – Routinely collected data Stage Two – Clinical review (including quality of life)
Components of measurement tool	Confirmed for inclusion but requiring further definition • Physical factors • Clinical measurements and assessments • Psychological factors • Social factors Requiring further research and consideration for inclusion • Healthcare use • Environmental factors
Uses of measurement tool	To measure frailty status AND To predict outcomes in frailty AND To predict frailty in the non-frail
External validation of tool	To be completed using Comprehensive Geriatric Assessment AND Outcomes associated with frailty, specifically including • quality of life • functional ability
Internal validity of tool	To consider all the following: • Criterion validity • Construct validity • Predictive validity • Face validity with special focus on the latter two aspects
Quality of development of tool	Particular focus upon study design to minimise the risk of bias in the selection of participants when developing and testing the new tool

3.5.11 Strengths and limitations of this review

This review had a number of strengths. It took a broad and comprehensive approach to identifying tools used for the measurement of frailty in primary care and at transitions of care. The studies included in this review were identified through a clearly described search strategy and using clearly defined inclusion and exclusion criteria. Data was extracted from the studies identified using a structured data extraction protocol designed to minimise bias. Furthermore, this review investigated both the structure and function of the frailty measurement tools identified and considered other important features, such as internal and external validation of the measurement tools and the quality of the studies reviewed. The vast majority of the studies identified in this review had been published in the last ten years and were therefore fully reflective of contemporary views regarding the concepts and consequences of frailty.

One of the main limitations in this review was the difficulty in identifying relevant studies concerning the measurement of frailty at 'transitions of care'. The first challenge in this respect concerned search terms to identify studies carried out at 'transitions of care'. There is no MeSH search term for 'transitions of care' and using a free text search for relevant representative key words or phrases identified unmanageably large numbers of studies. After consideration and discussion between the two reviewers, it was decided that since the review aimed to identify studies at the transition between primary care and other levels of care, then such studies would also contain reference to primary care. Therefore, the decision was taken that given the limitations described the search strategy would not include specific search terms for 'transitions of care'.

The second challenge in identifying studies of the measurement of frailty at 'transitions of care' suitable for inclusion in the study was the relationship between the inclusion criteria in relation to studies at 'transitions of care' and the exclusion criteria in relation to studies limited to a specified disease, condition or predefined aspect of frailty. In other words, most studies identified at transitions of care were set in the emergency department and focused specifically upon groups of people with specific disease, conditions or predefined aspects of frailty rather than considering general populations of older people, and were therefore excluded from the review.

A further limitation of this review was that the initial search strategy set an inclusion criterion of a lower age limit of 65 years for study populations. This was intended to reflect the fact that frailty is predominantly a condition of older age. However, six papers were identified in the original literature search that included age limits for the population at the start of the studies of less than 65 years but

greater than or equal to 50 years. These studies were considered to be important in this field and so after a discussion between the two reviewers a decision was made to include them in the review, despite the impact of this upon the fidelity of implementation of the original inclusion criteria for the review.

Finally, this review was limited to English language publications. The majority of the published literature on tools for the measurement of frailty in primary care identified in this review reports on studies conducted in Europe and North America. If such tools are considered for use in other settings, it is important to consider that they may not necessarily translate readily to other populations and societies, particularly if the tools include social, environmental and contextual components. However, the geographical focus in Europe and North America of the studies identified may be to some extent an artefact resulting from the inclusion criteria for publication in the English language in the article selection for this review. Expanding the scope of this review to include non-English language publications would therefore help to establish whether published evidence exists regarding the use of frailty measurement tools in primary care in other parts of the world but which was not identified due to the language restriction in the search strategy, or whether there is a gap in the evidence regarding the use of frailty measurement tools in primary care outside Europe and North America.

3.6 Conclusions

This systematic review identified the current evidence on the frailty tools that apply to primary care and identified a framework for the development of a tool for the measurement of frailty in primary care and at transitions of care (table 3.15, page 79). A frailty measurement tool should be based on a single model of frailty which covers emergence to frailty transitions and includes components representing physical health factors, clinical measurements, clinical assessments, psychological factors, social factors, healthcare use and environmental factors. The range of elements to be included within these components should be further explored using consensus studies. The tool should be administered in two stages, the first based on routinely collected data and the second upon individual review, and should be suitable for the prediction of the onset of frailty, the measurement of frailty status and the prediction of outcomes in frailty. These aspects of frailty are closely related conceptually and the same elements are therefore likely to be relevant to all of

them. However, their individual importance might vary at different points along the frailty trajectories. The tool should be validated using CGA and outcomes associated with frailty, specifically including quality of life and functional ability. It should also be assessed for criterion, construct, predictive and face validity, with particular emphasis on the latter two aspects. The study design during development of the tool should pay particular attention to minimising the risk of population selection bias.

Chapter 4: The measurement of frailty in a primary care population using an electronic Frailty Index

4.1 Introduction: Frailty and comorbidity

The complex relationship between frailty, comorbidity of disease and disability is recognised. Frailty is understood to be related to, but distinct from, disability and comorbidity (2). Extensive overlap between frailty, comorbidity and disability has been demonstrated (5) and there is a trend of increasing frailty for people with greater numbers of comorbidities (2). However, at the same time many people with two or more long-term conditions do not have frailty (2) and some people with frailty have only one or no long–term conditions (4). It has been shown that although frailty and disability are closely related, they are each independent of the number of long-term conditions and frailty is also independent of other comorbidity (6). Furthermore, frailty can be a cause of disability in some cases and a consequence of disability in others, and increasing disability has been demonstrated with increasing age, even when no explanatory diseases or other risk factors are present (6,156) .

Comorbidity and frailty concepts are therefore implicitly linked and yet there is very little evidence on how they emerge together and how they develop over time in relation to each other. There is a range of evidence on how individual diseases might interact with frailty and examples include cardiovascular disease, chronic kidney disease and dementia (52,157-159). For example, it has been found that there is a significant association between frailty and incident heart failure in older adults (52) and that people with chronic kidney disease have a high risk of frailty (159). Furthermore, the evidence of a strong association between frailty and cognitive impairment and dementia has raised the question whether dementia should be included in the frailty definition (157) and led to the suggestion that frailty might drive disease expression (158). However, currently no single unifying pathway has been defined to link progression from comorbidity through disability and on to established frailty, or to describe how frailty might drive disease expression. Furthermore, in cases of advanced single condition disease, for example cardiac failure, it can be very difficult to distinguish the signs and symptoms of frailty from those of the advanced disease (27) and frailty can therefore sometimes ‘hide behind’ comorbidity and disability (3).

Disease prevention and the optimal management of long-term conditions can play an important role in reducing or avoiding disability in older age. However, optimal approaches to the management of long-term conditions may differ for people with advancing frailty (12) and there are unresolved tensions between the management of individual long-term conditions and the holistic management of frailty. Furthermore, the relationship between frailty and multimorbidity is also likely to be influenced by other domains in the multi-dimensional model of frailty, such as social networks and environmental factors. Effective care for the increasing number of older people with multimorbidity (12) and frailty (6) requires a more comprehensive and dynamic understanding of the relationship between multimorbidity and frailty, from the emergence of frailty through progression to end stage frailty. Possible hypotheses in understanding the relationship between long-term conditions and frailty include that:

i) Long-term conditions are a trigger for the emergence of frailty.

ii) Different long-term conditions contribute to frailty severity.

iii) Combinations of long-term conditions may contribute to frailty emergence and progression.

iv) Long-term conditions can act as markers for the emergence of frailty or other key stages in the progression of frailty.

Exploring the nature of the relationships between index long-term conditions and frailty, alone and in combination, will therefore inform the debate concerning the important relationship between frailty and comorbidity. This in turn has the potential to translate into clinical service developments and improvements.

Osteoarthritis and cardiovascular disease are important diseases of ageing. They are two of the most frequently occurring long-term conditions in older people and often occur together in the same individuals. These conditions can be considered as important index conditions with respect to comorbidity and frailty not only because of the nature of the diseases, but also because of their impact and interactions with factors across a range of domains represented in a multi-dimensional model of frailty. The presence of cardiovascular disease often results in multiple healthcare interactions over a prolonged period of time, representing both planned and acute care. Furthermore, cardiovascular disease states can be influenced by social and environmental factors and can have psychological impact upon people living with the condition. In the case of osteoarthritis, in addition to physical pathological features, the condition is characterised by

features such as chronic multi-site pain, loss of functional ability and psychological consequences. Through such characteristics osteoarthritis also has strong links to important frailty concepts, including social isolation and psychological status.

There is evidence for individual relationships between cardiovascular disease and frailty and between osteoarthritis and frailty. A diagnosis of cardiovascular disease has been shown to be associated with an increased likelihood of frailty, defined using a phenotype model of frailty, compared to people without the condition, even after adjusting for age and gender (27,54). Furthermore, in people giving no history of cardiovascular disease, non-invasive measures of cardiovascular disease are also associated with frailty (54). Frailty has also been shown to be independently associated with a risk of heart failure in adults (52). People with osteoarthritis have also been shown to have both a greater prevalence and a greater risk of the frailty phenotype than people without this condition (27,53). Despite the evidence regarding the individual relationships between these common conditions and frailty, evidence extending this investigation to include comorbid interactions between them is lacking.

Increased understanding of the emergence and progression of frailty in a population which has been defined by the example of cardiovascular and osteoarthritis disease states and comorbidity could therefore have important implications for the design of interventions to influence frailty trajectories, particularly considering that the general population includes many people with this frequently occurring combination of long-term conditions.

The 'Comorbidity Cohort (2C) study: Cardiovascular disease severity and comorbid osteoarthritis in primary care' (160) was set up to investigate the comorbid interaction and impact of these two common long term conditions on individual physical health status and quality of life over a 12-month time period. This study data therefore offered an ideal opportunity for focused investigation of the relationships between cardiovascular and osteoarthritis disease states and severity, and their comorbid interactions, and frailty, through retrospective analysis of the study data.

4.2 Background: Measurement of frailty in a primary care comorbidity cohort

4.2.1 Study framework

The second phase of this project was designed to build upon the results of phase one through analytical testing of some of the concepts arising from the findings of the systematic review.

4.2.2 Frailty measurement in primary care using routinely collected data

The systematic review identified the advantages of frailty measurement tools which use routinely collected data, particularly in that they can be applied comprehensively, consistently and at relatively low cost. However, technical and information governance challenges frequently remain in attempts to link secondary care and social care data to primary care data, and thus most current focus in this area concerns tools which use routinely collected primary care data alone. The question also arose as to whether routinely collected primary care data alone can fulfil a multi-dimensional approach to frailty measurement. The second phase of the study was designed to start addressing this question by using a frailty measurement tool based on routinely collected primary care data (100) to:

i) Characterise frailty in a primary care population (160) according to socio-demographic and comorbidity features, and

ii) Investigate how frailty changed over time in this population.

4.2.3 The electronic Frailty Index

The frailty measurement tool used in this study was an electronic Frailty Index (eFI) calculated from routine primary care data, recently developed by Clegg et al (100). The eFI is based upon a cumulative deficit model of frailty. The eFI was developed using a standard procedure for creating a frailty index and used relevant Read codes within primary care databases to create categories of deficits (38). Development took place using the ResearchOne database, which contained four million anonymised primary care records (161). The frailty index for any individual is the number of deficits, in the case of the eFI determined through the Read coded data in the person's electronic primary care record, as a proportion of the total number of possible deficits.

The development and validation study reported by Clegg included 454,051 people aged over 65 years, for whom the mean eFI was 0.13, the 99th centile was 0.41 and the maximum eFI was 0.70 (100). Predictive validity was investigated by calculating 1-year and 5-year hazard ratios (HRs) for mortality, which were significantly increased for those with mild (1 year HR 2.31, 5 year HR 2.03),

moderate (1 year HR 3.97, 5 year HR 3.28) and severe frailty (1 year HR 5.99, 5 year HR 7.13), compared to people without frailty (100).

The first publication regarding the development and validation of this tool occurred after the completion of the systematic review described in Chapter 3 of this thesis, hence the eFI was not included in the systematic review. However, the eFI clearly addressed one of the key findings of the systematic review, namely the recommendation that the first stage of a frailty measurement tool for primary care should be based on routinely collected data. It was therefore an ideal tool for use in the second phase of this project. A spread-sheet containing details of the Read codes and deficits used in the derivation of the eFI were provided for use in this study in a personal communication from Dr Andrew Clegg in November 2014.

4.2.4 The Comorbidity Cohort (2C) Study

This study was a post-hoc analysis of data from the 'Comorbidity Cohort (2C) study: Cardiovascular disease severity and comorbid osteoarthritis in primary care' (160), which was set up to investigate the comorbid interaction and impact of these two common long-term conditions upon individual physical health status and quality of life over a 12-month time period.

The denominator population for the 2C study was drawn from ten general practices in North Staffordshire, Stoke on Trent and Cheshire. These practices were not randomly selected but the composition of their population was representative of the wider primary care population. The denominator population was recruited to four main cohort groups:

1) No record of either cardiovascular disease or osteoarthritis (reference group)
2) Record of cardiovascular disease without osteoarthritis
3) Record of osteoarthritis without cardiovascular disease
4) Record of cardiovascular disease and osteoarthritis (comorbid group)

The cardiovascular disease group was further subdivided using a previously defined order of disease severity, in which hypertension, ischaemic heart disease and heart failure were used as indicators of ascending disease severity, with allocation to a cohort based upon the most severe cardiovascular disease category present (162). For example, if an individual had consulted for both hypertension and heart failure they would be allocated into the heart failure cohort (160).

In this study the eFI was used to test hypotheses that were driven by the need to understand in general populations the following questions:

1) Is increasing CVD severity associated with an increase likelihood of frailty compared to non-CVD and non-OA population?

2) Is OA associated with an increased likelihood of frailty compared with non-CVD and non-OA population?

3) Is the increasing CVD severity and OA associated with an increased likelihood of frailty compared with non-CVD and non-OA population?

4) Is the increasing CVD severity and OA associated with an increasing frailty change compared with non-CVD and non-OA population?

The 2C study therefore provided an appropriate dataset to answer these important questions in older populations with the common chronic disease examples of cardiovascular disease and osteoarthritis for the 5-year time period of that study.

4.2.5 Summary

This study aimed to investigate clinical questions regarding frailty prevalence in a primary care population and methodological questions regarding validation properties of the eFI. It was intended to characterise frailty as measured by an eFI calculated from routinely collected primary care data according to socio-demographic and cardiovascular and osteoarthritis disease status characteristics of a primary care population, and to investigate how this changed over time.

The study used primary care Read coded consultation data from the 2C study (160) along with a newly developed eFI (100) to investigate two hypotheses to further characterise frailty within the context of a specific comorbidity disease set: (i) increasing comorbidity severity is associated with an increased likelihood of frailty and (ii) increasing comorbidity severity is associated with an increased rate of change in frailty over a 2-year time-period.

4.3 Aims and objectives

4.3.1 Aims

The overall aim of this study was to characterise frailty and frailty change over time in a population cohort aged 40 years and over, selected with reference to two key chronic diseases, namely cardiovascular disease and osteoarthritis (160).

4.3.2 Objectives

The objectives of this study were:

1. To investigate how well the electronic frailty index based on routine primary care data identifies frailty in a population selected with respect to two key chronic diseases.
2. To investigate how the construct of the electronic frailty index based on routine primary care data varies with age-demographic and clinical data.
3. To investigate how the electronic frailty index based on routine primary care data changes in this population over a 24-month time-period.

The hypotheses to be tested by this study were as follows:

1) H_0: There is no association between comorbidity severity and frailty as measured by the eFI in this primary care cohort.

   H_1: There is an association between comorbidity severity and frailty as measured by the eFI in this primary care cohort.

2) H_0: There is no association between comorbidity severity and the rate of change in frailty as measured by the eFI over a 2-year time period in this primary care cohort.

   H_1: There is an association between comorbidity severity and the rate of change in frailty as measured by the eFI over a 2-year time period in this primary care cohort.

4.4 Methods

4.4.1 Study design

This study was a post-hoc analysis of data from the 2C study. This data was used to design the investigations in two ways. The cohort study covered a 5-year time period between 2007-2012 and the routinely collected data for first three years formed the basis of defining population frailty and the subsequent 2 years (2010-12) as a measure of change.

4.4.2 Study setting

The study population for the 2C study was drawn from ten general practices in a research network in North Staffordshire, Stoke on Trent and Cheshire. These practices are part of a local research network, the Primary Care Musculoskeletal Research Consortium. These practices, supported by the Primary Care Research West Midlands North (PCR WMN) network, cover a wide range of socio-economic groups. The practices have actively participated in routine collection of clinical data

using computer records for the purposes of epidemiological study. Clinical information relating to all morbidity and drug therapies is recorded using standard classifications of Read codes and BNF (British National Formulary) respectively. Ethics permission for the 2C study was given by the Cheshire Research Ethics Committee (REC ref no: 09/H1017/40) (Appendix VIII, page 248).

4.4.3 Study population and sample size

In the 2C study, adults aged over 40 years were sampled to construct 8 cohort groups, in relation to cardiovascular and osteoarthritis comorbidity, giving a total denominator population of n=9793 (160). An anonymised clinical data archive was constructed containing coded consultation data, diagnoses, prescriptions and referrals for five years in total for the full denominator population (160). The denominator population from which the study population was drawn for this study was all those aged 40 years and over who were included in the denominator population for the 2C study. Therefore, for this study the population n=9793. The population in this study was a purposive sample because it was a cohort defined by age and disease characteristics.

4.4.4 Data access, management and quality

The 2C Study dataset was held in the Institute for Primary Care and Health Sciences department at Keele University and this study was carried out in the Health Services Research Unit (HSRU), which is part of the Institute for Science and Technology in Medicine at Keele University. An external data request was therefore completed through the formal application process and was issued under the existing ethics permission. The data was stored in the secure network drive at Keele University, in a personal password protected folder within the HSRU folder.

The quality of data in electronic patient records in primary care has been shown to vary (163,164). However, the practices involved in this study were part of the General Practice Research Network at the Primary Care Sciences department at Keele University, an audited research network in which specific training mechanisms have been developed and implemented aimed at improving and maintaining high data quality (165). The primary care consultation data in this study was drawn from practices involved in this quality assurance process and was therefore assumed to be good quality.

4.4.5 Frailty measurement tool

The frailty measurement tool used in this study was an electronic Frailty Index calculated from routine primary care data, recently developed by Clegg (100) and used in this study with his permission. The frailty index for any individual was the number of deficits determined through the Read coded data in the person's electronic primary care record as a proportion of the total number of possible deficits. It was derived using 2143 codes grouped into 35 deficits. These Read codes were applied to the consultation datasets to calculate the eFIs as described in Appendix I (page 234). The 35 deficits to which the Read codes contribute are listed in Table 4.1, where they have been broadly classified as 'diseases', 'symptoms' or 'states.'

Table 4.1: Deficits characterised within the eFI and the categories to which they belong

Categories of Deficits	**Individual Deficits**	
Diseases (n=19)	Anaemia	Osteoporosis
	Arthritis	Parkinsonism & tremor
	Atrial fibrillation	Peptic ulcer
	Cerebrovascular disease	Peripheral vascular disease
	Chronic kidney disease	Respiratory disease
	Diabetes	Skin ulcer
	Heart failure	Thyroid disease
	Heart valve disease	Urinary system disease
	Hypertension	Fragility fracture
	Ischemic heart disease	
Symptoms (n=12)	Dizziness	Memory and cognitive
	Dyspnoea	problems
	Falls	Mobility and transfer problems
	Foot problems	Sleep disturbance
	Hearing impairment	Urinary incontinence
	Visual impairment	Weight loss & anorexia
	Hypotension / syncope	
States (n=4)	Housebound	Social vulnerability
	Requirement for care	Activity limitation

4.4.6 Variables and outcomes

The variables and outcomes investigated in this study and their measurement or derivation are summarised in Table 4.2.

Table 4.2: Variables under investigation in this study

	Factor	Classification	Measurement / derivation
Key variable	Electronic Frailty Index (eFI)	Outcome	Calculated from primary care consultation data using codes provided by Clegg.
Socio-demographic variables	Age	Explanatory factor	Primary care electronic patient records, provided in 2C demographic dataset.
	Gender	Explanatory factor	Primary care electronic patient records, provided in 2C demographic dataset.
	Deprivation status	Explanatory factor	Index of multiple deprivation from official national statistics, provided in 2C demographic dataset.
Clinical variable	Disease status group	Explanatory factor	Identified through primary care electronic patient records, provided in 2C demographic dataset.

The eFI was a dependent variable (outcome) in this phase of the study. Age, gender and deprivation were independent variables and potential confounders when examining the individual factors in relation to the outcome of interest and adjustment was therefore made for these variables in the analysis. The disease status group was an independent variable and a potential confounder by indication (167). This is because the population was selected with reference to these disease status characteristics and the disease status also contributed to the eFI outcome. Adjustment was made for this in later analysis.

4.4.7 Data preparation

The methods used to prepare the denominator population demographic data and consultation data for analysis and to calculate the eFI scores are described in Appendix I (page 234).

4.4.8 Data analysis

All data analysis in this study was carried out using IBM SPSS version 21 software (168). The main analytic approaches were (i) descriptive statistics, (ii) unadjusted associations and (iii) two stages of adjusted associations, as described below.

4.4.8.1 Frailty score in the denominator population

The mean, standard deviation, maximum and minimum eFI values were described for the denominator population as a whole at 3, 4 and 5 years.

4.4.8.2 Socio-demographic, disease status and frailty score

This stage of the analysis was designed to investigate how the eFI varied with age-demographic and clinical data in the denominator population.

Firstly the individual eFIs for each person in the denominator population were calculated for the entire 5-year time period and the mean eFI and standard deviation were calculated for the age categories, gender, deprivation status and disease status group, and the subgroups within these variables. The mean eFIs for the subgroups within these variables were then compared to the reference subgroup within each variable (reference group for age was 40-49 years, for gender was men, for deprivation status was the most affluent group and for the disease cohort groups was without cardiovascular disease or osteoarthritis). Linear regression was used to compare each subgroup in turn with the reference group, for example, comparing the 80-89 year age group to the 40-49 year age group. In this approach the independent variables were age, gender, deprivation and disease status and the dependent variable, i.e. the outcome, was the eFI. Regressions were applied in unadjusted and adjusted models.

This approach was used firstly to give the unadjusted difference (and 95% confidence interval) between each subgroup and the reference group for each variable. Linear regression was also then used to compare the groups in two different adjusted models. The first adjusted model included adjustment for age, gender and deprivation status and the second adjusted model

included adjustment for age, gender, deprivation status and the addition of the disease status group when trying to estimate age, gender and deprivation associations.

Study disease status groups had the potential to act as confounders by indication because the eFI included these conditions (167). The hypothesis under investigation in the second adjusted model was therefore that adjusting for these conditions would abolish or reverse any association with frailty, whilst the null hypothesis was that the adjustment would not make a difference.

4.4.8.3 Socio-demographic and disease status and change in frailty score

This stage of the analysis investigated how the eFI score changed over the final two-year period in the denominator population and how this varied by age-demographic and disease status.

Firstly the individual eFIs for each person in the denominator population were calculated for the first three years of the 5-year time period and the mean eFI (for the first 3 years) and standard deviation described for the variables of age, gender, deprivation status and disease status group, and the subgroups within these variables.

The 'baseline' against which change in eFI was measured was chosen to be at 3 years because of the nature of this data set. The data comprised coded consultation data and therefore only included coded problem titles that had presented during consultations in the chosen period and did not 'carry forward' active coded problems on the patient record. For example, a patient with diabetes should have the condition coded on their record as an active problem at time point zero, but until the patient had a consultation relating to their diabetes and therefore generating a coded consultation entry, it would not contribute to their eFI in this consultation dataset. Taking the baseline eFI score as that for the first three years of consultation data provided a sufficient time frame for a person's existing conditions to present in this way and to contribute appropriately to the baseline measure of frailty. It also aligned with the time point for the baseline patient-reported survey in the next chapter of this thesis.

These 3-year eFI scores were then used in conjunction with the total 5-year eFI scores to calculate from this paired data the mean change in eFI over the 2-year period from the end of the first three years to the end of the full 5-year period, and the standard deviation. This mean change in the eFI for the 2-year period between three years and five years was described for the variables of age, gender, deprivation status and disease status group, and the subgroups within these variables.

The mean change in the eFIs over 2 years for the subgroups within these variables were then compared to the reference subgroup within each variable, which was defined as the subgroup with the lowest mean change in eFI. Linear regression was used to compare each subgroup in turn with the reference group, with the change in eFI as the dependent variable and each of the other group variables in turn as the independent variable.

This approach was used firstly to give the unadjusted difference of eFI (and 95% confidence interval) between each subgroup and the reference group for each variable. Linear regression was also used to compare the groups in two different adjusted models. The first adjusted model included adjustment for age, gender, deprivation status and disease status group and the second adjusted model included adjustment for age, gender, deprivation status, disease status group and eFI at three years. This second adjusted model was designed to investigate whether the change in eFI over 2 years was influenced by the eFI at the start of the 2-year period. For example, ceiling effects might occur in the rate of change of the eFI in relation to the baseline eFI, if the eFI was approaching a maximum possible value at baseline (169).

4.4.8.4 Categorising frailty severity and frailty progression over 2 years

This stage of the analysis considered the minimum clinically important difference in eFI, which equates to one whole deficit, and how eFI scores might be categorised into levels of frailty severity. The eFI scores at 3, 4 and 5 years were therefore re-coded into the following severity categories:

- no deficits = not frail
- 1-2 deficits = mild frailty
- 3-4 deficits = moderate frailty
- $\geq$ 5 deficits = severe frailty

These category definitions were intended to allow an understanding of the patterns of severity and progression of frailty in this study, but not to represent an absolute measure or value for frailty or to be applicable to other populations. Cross-tabulation was used to investigate how individuals progressed through these frailty categories over the two years following the first 3-years of the data.

4.5 Results

4.5.1 Denominator population consultation data

The steps described in Appendix I (page 234) created a single file of consultation data for the denominator population, containing 954,071 coded consultations for 9,793 individuals (Table 4.3).

Table 4.3: Table to show steps in merging files for consultation data

Source data file	Total consultations	Uncoded consultations	Coded consultations
File 1	755,970	332,562	423,408
File 2	332,340	0	332,340
File 3	299,346	101,023	198,323
Total	1,387,656	433,585	954,071
Total number of individuals = 9,793			

In total, 598 (27.9%) of the 2143 codes used to construct the eFI appeared within the 954,071 coded consultations over the 5-year time period in the denominator population dataset.

4.5.2 Cumulative frailty over 5 years

As shown in Table 4.4, the mean eFI for the denominator population (n=9793) for the full 5-year period was 0.072 (SD 0.062), minimum eFI was 0, maximum eFI was 0.457 and 99th centile was 0.286. The 99th centile was described in order to enable comparison to published data for the eFI (170). The mean score reflects a total number of 2.5 deficits from the 35 and the maximum score reflects 16 deficits from the 35.

Table 4.4: Descriptive statistics for population eFI at 5 years

Time period	Number	Mean eFI (SD)	Maximum eFI	99th centile eFI
5 years	9793	0.072 (0.062)	0.457	0.286

In this study, the total number of deficits from which the eFI was constructed was 35. Therefore one deficit was equivalent to an eFI increment of 0.029. The frequency distribution for the cumulative number of deficits at 5 years across the denominator population is shown in Table 4.5 and Figure 4.1.

Figure 4.1: Chart to show frequency of cumulative number of deficits over 5 years

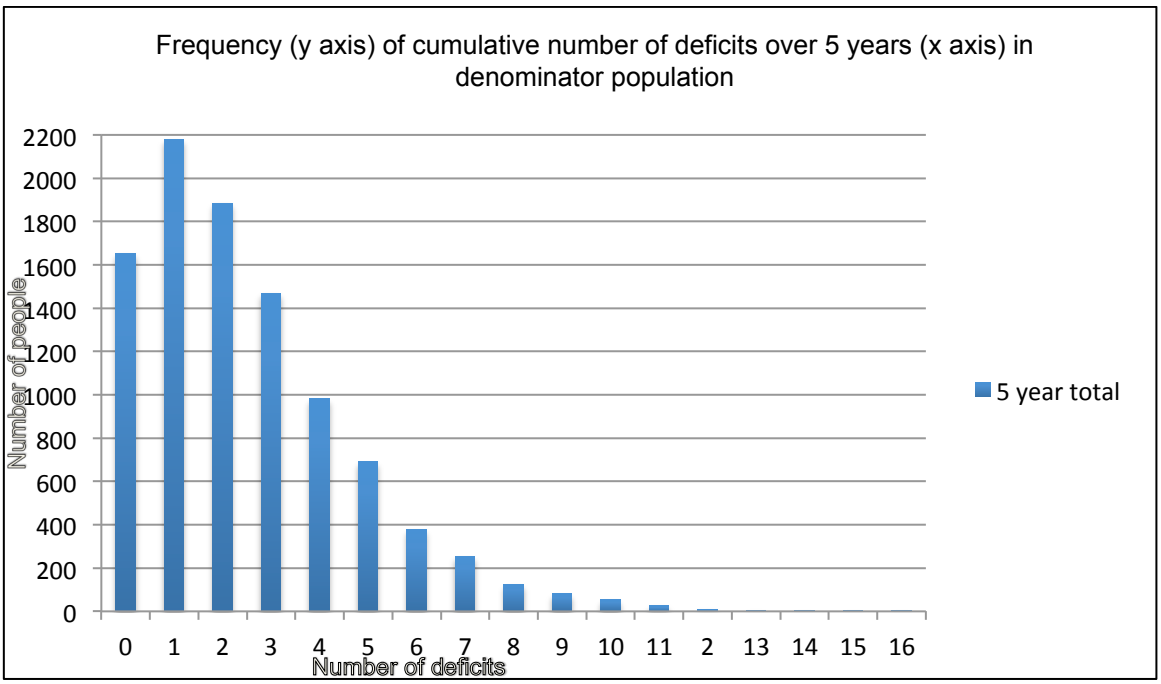


Table 4.5: Table to show distribution of eFI (cumulative number of deficits) at 5 years

eFI (No. of deficits)	Frequency (%) 5 years
0 (0)	1651 (16.9)
0.029 (1)	2181 (22.3)
0.057 (2)	1884 (19.2)
0.086 (3)	1469 (15.0)
0.114 (4)	982 (10.0)
0.143 (5)	690 (7.0)
0.171 (6)	377 (3.8)
0.200 (7)	253 (2.6)
0.229 (8)	126 (1.3)
0.257 (9)	81 (0.8)
0.286 (10)	53 (0.5)
0.314 (11)	26 (0.3)
0.343 (12)	10 (0.1)
0.371 (13)	4 (<0.1)
0.400 (14)	3 (<0.1)
0.429 (15)	2 (<0.1)
0.457 (16)	1 (<0.1)
Total	9793 (100)

4.5.3 Socio-demographic and disease status and cumulative frailty

Table 4.6 shows the mean eFI score at the end of the full 5-year period for the denominator population by socio-demographic characteristics and disease status group. For each group within each variable, the eFI score was compared to the respective reference group for that variable, using linear regression. This was done for both the unadjusted difference and for two different adjusted models, the first of which adjusted for age, gender and deprivation status, and the second of which also included adjustment for disease status group.

Table 4.6: Socio-demographic characteristics, disease status and total mean eFI scores at 5 years

Variables	Categories	Number N = 9793 (%)	Mean eFI at 5 years (SD)	Unadjusted eFI difference* (95% CI)	Adjusted eFI difference	
					Adjusted[1] (95% CI)	Adjusted[2] (95% CI)
Age (years)	40-49[†]	1745 (17.8)	0.028 (0.034)	0	0	0
	50-59	2221 (22.7)	0.048 (0.045)	0.020 (0.016-0.023)	0.020 (0.017-0.023)	0.005 (0.002-0.008)
	60-69	2654 (27.1)	0.073 (0.053)	0.045 (0.042-0.048)	0.045 (0.042-0.049)	0.017 (0.014-0.020)
	70-79	2157 (22.0)	0.104 (0.065)	0.076 (0.073-0.080)	0.077 (0.073-0.080)	0.039 (0.036-0.042)
	80-89	943 (9.6)	0.127 (0.072)	0.098 (0.094-0.103)	0.098 (0.094-0.102)	0.056 (0.052-0.060)
	90-99	72 (0.7)	0.118 (0.064)	0.090 (0.078-0.103)	0.090 (0.077-0.102)	0.044 (0.033-0.055)
Gender	Male[†]	4775 (48.8)	0.066 (0.058)	0	0	0
	Female	5018 (51.2)	0.077 (0.066)	0.010 (0.008-0.013)	0.003 (0.001-0.005)	0.008 (0.006-0.010)
Deprivation Status	Category 1 (most affluent)[†]	2376 (24.3)	0.062 (0.059)	0	0	0
	Category 2	2442 (24.9)	0.070 (0.060)	0.006 (0.003-0.010)	0.004 (0.001-0.007)	0.004 (0.002-0.007)
	Category 3	2453 (25.0)	0.074 (0.062)	0.011 (0.007-0.014)	0.009 (0.006-0.012)	0.007 (0.004-0.009)
	Category 4 (most deprived)	2485 (25.4)	0.080 (0.066)	0.016 (0.013-0.020)	0.018 (0.015-0.021)	0.015 (0.012-0.017)
Disease Status Group**	-CVD -OA[†]	2529 (25.8)	0.023 (0.032)	0	0	n/a
	+HT OA-	1334 (13.6)	0.068 (0.046)	0.045 (0.042-0.049)	0.033 (0.030-0.036)	n/a
	+IHD OA-	2095 (21.4)	0.098 (0.059)	0.075 (0.072-0.078)	0.059 (0.056-0.062)	n/a
	+HF OA-	276 (2.8)	0.138 (0.070)	0.115 (0.109-0.122)	0.090 (0.084-0.096)	n/a
	+OA CVD-	1336 (13.6)	0.052 (0.046)	0.029 (0.026-0.032)	0.019 (0.016-0.022)	n/a
	+HT +OA	1662 (17.0)	0.096 (0.057)	0.073 (0.070-0.076)	0.053 (0.050-0.057)	n/a
	+IHD +OA	492 (5.0)	0.139 (0.069)	0.116 (0.111-0.121)	0.090 (0.086-0.095)	n/a
	+HF +OA	69 (0.7)	0.178 (0.076)	0.155 (0.143-0.167)	0.122 (0.110-0.133)	n/a

[†]Reference group
*Difference in eFI score for each group compared to their respective reference group
[1]Adjusted model includes age, gender and deprivation status.
[2]Adjusted model includes age, gender, deprivation status and disease status group
**CVD=cardiovascular disease and includes HT=hypertension, IHD=ischaemic heart disease, HF=heart failure. OA=osteoarthritis

Age: The unadjusted differences show a progressive and statistically significant increase in total mean eFI for the 5 years for each 10-year age band, up to the age of 89 years. Compared to the reference group aged 40-49 years, the eFI score increased from unadjusted difference for age group 50-59 years of 0.020 (95% CI 0.016-0.023) up to an unadjusted difference for age group 80-89 years of 0.098 (95% CI 0.094-0.103). After adjustment for gender, deprivation status and disease status group, these differences between the age bands were reduced but remained statistically significant, 0.005 (95% CI 0.002-0.008) for the 50-59 year age group and 0.056 (95% CI 0.052-0.060) for the 80-89 year age group.

Gender: There was a small but statistically significant difference between the mean eFI at 5 years for women compared to for men (0.010, 95% CI 0.008-0.013) and this difference was reduced but was still significant (0.008, 95% CI 0.006-0.010) after adjustment for age, deprivation status and disease status group.

Deprivation status: The eFI at 5-years increased with increasing levels of deprivation. There was a small but significant increase in the mean eFI at 5 years for the second (0.006, 95% CI 0.003-0.010) and third (0.011, 95% CI 0.007-0.014) most deprived quartiles compared to the least deprived quartile. These differences were reduced in strength but remained statistically significant after adjustment for age, gender and disease status (0.004, 95% CI 0.002-0.007 and 0.007, 95% CI 0.004-0.009 respectively). The mean eFI at 5 years for the most deprived quartile was higher than those for the middle two quartiles (0.016, 95% CI 0.013-0.020). This difference did not reach statistical significance in the unadjusted model but was significant after adjustment for age, gender and disease status (0.015, 95% CI 0.012-0.017).

Comorbidity groups: The eFI was significantly higher at 5 years for all index disease and comorbidity groups tested when compared to the reference group with none of these conditions. Furthermore, there were significant differences in the mean eFI at 5 years between the different disease status groups, singly or in combination.

For index disease groups, there was a progressive hierarchical increase in unadjusted difference in eFI at 5 years between reference group and osteoarthritis (0.029, 95% CI 0.026-0.032), hypertension (0.045, 95% CI 0.042-0.049), ischaemic heart disease (0.075, 95% CI 0.072-0.078) and heart failure (0.115, 95% CI 0.109-0.122). The combination of hypertension with osteoarthritis was associated with an unadjusted increase in eFI at 5 years compared to the reference group of 0.073, 95% CI 0.070-0.076. This was of a similar magnitude to the sum of the increases associated with the two individual conditions, and also to that for ischaemic heart disease alone. The combination of ischaemic heart disease with osteoarthritis was associated with an unadjusted increase in eFI compared to the reference group of 0.116, 95% CI 0.111-0.121. The increase for this combination of comorbidities was higher than the sum of the increases associated with the two individual conditions, and similar to that associated with heart failure alone. The combination of heart failure with osteoarthritis was associated with an increase in eFI compared to the reference group of 0.155, 95% CI 0.143-0.167, which was higher than the sum of the increase associated with these two individual conditions.

After adjustment for age, gender and deprivation status, all of these differences between index and comorbidity groups were reduced but remained statistically significant: osteoarthritis 0.019, 95% CI 0.016-0.022; hypertension 0.033, 95% CI 0.030-0.036; ischaemic heart disease 0.059, 95% CI 0.056-0.062; heart failure 0.090, 95% CI 0.084-0.096; hypertension with osteoarthritis 0.053, 95% CI 0.050-0.057; ischaemic heart disease with osteoarthritis 0.090, 95% CI 0.086-0.095; heart failure and osteoarthritis 0.122, 95% CI 0.110-0.133.

Comparing the association between different study groups and the frailty score, hypertension associated mean score was approximately twice that of osteoarthritis, ischaemic heart disease three times that of osteoarthritis and heart failure more than four times that of osteoarthritis. The association between heart failure alone and frailty score was the equivalent to ischaemic heart disease with osteoarthritis, whilst that of ischaemic heart disease alone was equivalent to that of hypertension with osteoarthritis. The association between heart disease comorbid with osteoarthritis and frailty score was more than twice that of hypertension comorbid with osteoarthritis.

4.5.4 Change in cumulative frailty over 2 years

The mean eFI for the denominator population (n=9793) for the full 5-year period was 0.072 (SD 0.062) and for the first 3-year period it was 0.053 (SD 0.049), as shown in Table 4.7. The maximum eFI values were 0.457 at 5 years and 0.400 at 3 years, and the 99th centile values for the two time periods were 0.286 at 5 years and 0.200 at 3 years. The overall difference between these means, i.e. the mean change over 2 years for the population as a whole was 0.019 (0.027). This was equivalent to a change from a mean of 1.86 to 2.51 deficits per person.

Table 4.7: Mean eFI scores at 3 and 5 years

eFI time point	Number	Mean (SD)	Maximum	99th centile
eFI at 3 years	9793	0.053 (0.049)	0.400	0.200
eFI at 5 years	9793	0.072 (0.063)	0.457	0.286

The distribution of the cumulative number of deficits and eFI scores at 3 and 5 years are shown in Table 4.8 and Figure 4.2.

Figure 4.2: Frequency of cumulative number of deficits over 3 and 5 years

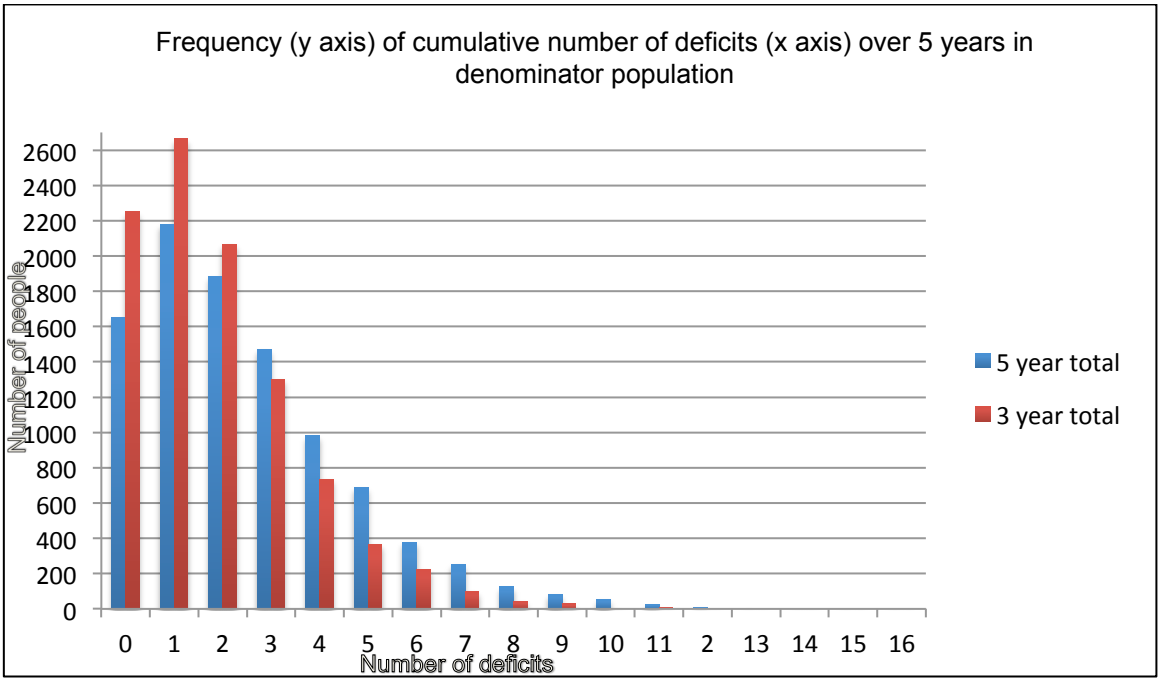


Table 4.8: Distribution of eFI (number of deficits) at 3 and 5 years

eFI (No. of deficits)	Frequency (%) at 3 years	Frequency (%)5 years
0 (0)	2250 (23.0)	1651 (16.9)
0.029 (1)	2663 (27.2)	2181 (22.3)
0.057 (2)	2066 (21.1)	1884 (19.2)
0.086 (3)	1301 (13.3)	1469 (15.0)
0.114 (4)	736 (7.5)	982 (10.0)
0.143 (5)	366 (3.7)	690 (7.0)
0.171 (6)	226 (2.3)	377 (3.8)
0.200 (7)	99 (1.0)	253 (2.6)
0.229 (8)	43 (0.4)	126 (1.3)
0.257 (9)	28 (0.3)	81 (0.8)
0.286 (10)	5 (0.1)	53 (0.5)
0.314 (11)	6 (0.1)	26 (0.3)
0.343 (12)	3 (<0.1)	10 (0.1)
0.371 (13)	-	4 (<0.1)
0.400 (14)	1 (<0.1)	3 (<0.1)
0.429 (15)	-	2 (<0.1)
0.457 (16)	-	1 (<0.1)
Total	9793 (100)	9793 (100)

4.5.5 Socio-demographic factors, disease status and cumulative 2-year frailty change

Tables 4.9 and 4.10 show the change in mean eFI scores (and standard deviations) over 2 years by socio-demographic characteristics and comorbidity group.

For each group within each variable, the change in eFI score over two years was compared to the respective reference group for that variable, using linear regression. This was done for both the unadjusted difference and for two different adjusted models. The first model adjusted for age, gender, deprivation status and disease status group, and the second model also included an adjustment for the eFI at 3 years. This latter adjustment was intended to investigate whether the rate of change of the eFI depended on the baseline eFI.

Table 4.9: Socio-demographic characteristics, disease status and mean change over 2 years

Variables	Categories	Number n = 9793 (%)	Mean eFI over 5 years (SD)	Mean eFI for first 3 years (SD)	Mean change in eFI over 2 years* (SD)
Age (years)	40-49	1745 (17.8)	0.028 (0.034)	0.021 (0.028)	0.007 (0.016)
	50-59	2221 (22.7)	0.048 (0.045)	0.036 (0.037)	0.012 (0.021)
	60-69	2654 (27.1)	0.073 (0.053)	0.055 (0.043)	0.019 (0.026)
	70-79	2157 (22.0)	0.104 (0.065)	0.077 (0.052)	0.027 (0.032)
	80-89	943 (9.6)	0.127 (0.072)	0.093 (0.058)	0.033 (0.037)
	90-99	72 (0.7)	0.118 (0.064)	0.093 (0.061)	0.026 (0.034)
Gender	Male	4775 (48.8)	0.066 (0.058)	0.049 (0.047)	0.017 (0.026)
	Female	5018 (51.2)	0.077 (0.066)	0.057 (0.052)	0.020 (0.028)
Deprivation Status	Category 1 (most affluent)	2376 (24.3)	0.062 (0.059)	0.047 (0.047)	0.015 (0.025)
	Category 2	2442 (24.9)	0.070 (0.060)	0.051 (0.047)	0.018 (0.027)
	Category 3	2453 (25.0)	0.074 (0.062)	0.055 (0.049)	0.019 (0.029)
	Category 4 (most deprived)	2485 (25.4)	0.080 (0.066)	0.059 (0.053)	0.021 (0.029)
Disease Status Group**	-CVD -OA	2529 (25.8)	0.023 (0.032)	0.014 (0.023)	0.009 (0.019)
	+HT OA-	1334 (13.6)	0.068 (0.046)	0.053 (0.034)	0.016 (0.025)
	+IHD OA-	2095 (21.4)	0.098 (0.059)	0.074 (0.046)	0.024 (0.030)
	+HF OA-	276 (2.8)	0.138 (0.070)	0.106 (0.062)	0.032 (0.036)
	+OA CVD-	1336 (13.6)	0.052 (0.046)	0.035 (0.037)	0.017 (0.024)
	+HT +OA	1662 (17.0)	0.096 (0.057)	0.075 (0.044)	0.022 (0.029)
	+IHD +OA	492 (5.0)	0.139 (0.069)	0.107 (0.057)	0.032 (0.036)
	+HF +OA	69 (0.7)	0.178 (0.076)	0.138 (0.067)	0.040 (0.039)

*Change in eFI score from the score after the first 3 years to the score at the end of 5 years
**CVD=cardiovascular disease and includes HT=hypertension, IHD=ischaemic heart disease, HF=heart failure. OA=osteoarthritis

Table 4.10: Socio-demographic characteristics, disease status and change in mean eFI score over 2 years

Variables	Categories	Number n = 9793 (%)	Mean change in eFi over 2 years* (SD)	Unadjusted 'change in eFI' * (95% CI)	Adjusted 'change in eFI' difference	
					Adjusted[1] (95% CI)	Adjusted[1] (95% CI)
Age (years)	40-49[†]	1745 (17.8)	0.007 (0.016)	0	0	0
	50-59	2221 (22.7)	0.012 (0.021)	0.005 (0.003-0.007)	0.003 (0.001-0.005)	0.003 (0.001-0.005)
	60-69	2654 (27.1)	0.019 (0.026)	0.011 (0.010-0.013)	0.008 (0.006-0.009)	0.007 (0.006-0.009)
	70-79	2157 (22.0)	0.027 (0.032)	0.020 (0.018-0.021)	0.015 (0.013-0.017)	0.014 (0.012-0.016)
	80-89	943 (9.6)	0.033 (0.037)	0.026 (0.024-0.028)	0.020 (0.018-0.023)	0.019 (0.016-0.021)
	90-99	72 (0.7)	0.026 (0.034)	0.019 (0.012-0.025)	0.012 (0.006-0.018)	0.010 (0.004-0.017)
Gender	Male[†]	4775 (48.8)	0.017 (0.026)	0	0	0
	Female	5018 (51.2)	0.020 (0.028)	0.003 (0.002-0.004)	0.001 (0.001-0.003)	0.001 (0.000-0.003)
Deprivation Status	Category 1 (most affluent)[†]	2376 (24.3)	0.015 (0.025)	0	0	0
	Category 2	2442 (24.9)	0.018 (0.027)	0.003 (0.001-0.004)	0.002 (0.001-0.004)	0.002 (0.001-0.004)
	Category 3	2453 (25.0)	0.019 (0.029)	0.003 (0.001-0.005)	0.002 (0.001-0.004)	0.002 (0.001-0.003)
	Category 4 (most deprived)	2485 (25.4)	0.021 (0.029)	0.005 (0.003-0.007)	0.005 (0.003-0.006)	0.004 (0.003-0.006)
Disease Status Group**	-CVD -OA[†]	2529 (25.8)	0.009 (0.019)	0	0	0
	+HT OA-	1334 (13.6)	0.016 (0.025)	0.006 (0.005-0.008)	0.002 (0.000-0.003)	0.002 (0.000-0.003)
	+IHD OA-	2095 (21.4)	0.0240 (0.030)	0.015 (0.013-0.016)	0.008 (0.007-0.010)	0.006 (0.004-0.008)
	+HF OA-	276 (2.8)	0.032 (0.036)	0.023 (0.020-0.026)	0.014 (0.010-0.017)	0.010 (0.006-0.013)
	+OA CVD-	1336 (13.6)	0.017 (0.024)	0.008 (0.006-0.009)	0.004 (0.002-0.006)	0.003 (0.001-0.005)
	+H T +OA	1662 (17.0)	0.022 (0.029)	0.012 (0.011-0.014)	0.005 (0.003-0.007)	0.003 (0.001-0.004)
	+IHD +OA	492 (5.0)	0.032 (0.036)	0.023 (0.020-0.026)	0.014 (0.011-0.016)	0.010 (0.007-0.013)
	+HF +OA	69 (0.7)	0.040 (0.039)	0.031 (0.024-0.037)	0.019 (0.013-0.025)	0.014 (0.007-0.020)

[†]Reference group
*Difference in change in eFI over 2 years for each group compared to their respective reference group
**CVD=cardiovascular disease and includes HT=hypertension, IHD=ischaemic heart disease, HF=heart failure. OA=osteoarthritis
[1]Adjusted model includes age, gender, deprivation status and disease status group.
[2]Adjusted model includes age, gender, deprivation status, disease status and baseline eFI score from the first 3 years

Age: The unadjusted differences showed a small but statistically significant increase in the mean eFI over the 2-year period for each 10-year age band, up to the age of 89 years, from 0.005 (95% CI 0.003-0.007) in the 50-59 year age band up to 0.026 (95% CI 0.024-0.28) in the 80-89 year age band. The change in the eFI over the two years for the age band 90-99 years was not significantly above that for the age band 80-89 years, but the number of people in the highest age group was very much smaller than in any of the other population age bands.

After adjustment for gender, deprivation status and disease status, the differences between age bands up to the age of 89 years were reduced but remained statistically significant from 0.003 (95% CI 0.001-0.005) in the 50-59 year age band up to 0.020 (95% CI 0.018-0.23) in the 80-89 year age band. These differences also persisted after adjustment for starting eFI for the two year time period, i.e. the eFI at 3 years, from 0.003 (95% CI 0.001-0.005) in the 50-59 year age band up to 0.019 (95% CI 0.016-0.21) in the 80-89 year age band. These results demonstrate that the eFI increased more rapidly over the two year time period with increasing age bands and that within the range of this dataset this difference in rate of change did not depend upon the starting eFI.

Gender: The unadjusted increase in eFI over the 2-year period was very slightly higher for females than for males, 0.003, 95% CI 0.002-0.004. However, after adjustment for age, deprivation status, disease status group and eFI at 3 years, this difference was insignificant (0.001, 95% CI 0.000-0.003). In other words there was no significant difference in the rate of increase in eFI over two years comparing females to males.

Deprivation: Regarding deprivation status, the increase in eFI over the 2-year period was slightly greater for all other quartiles when compared to the least deprived quartiles but there were no significant differences between the second to fourth quartiles (0.003, 95% CI 0.001-0.004 for next least deprived; 0.003, 95% CI 0.001-0.005 for second most deprived; 0.005, 95% CI 0.003-0.007 for most deprived). These very small but statistically significant differences in the rate of increase of eFI over two years between all other quartiles compared to the least deprived quartile persisted after adjustment for age, deprivation status, disease status group and eFI at 3 years (0.002, 95% CI 0.001-0.004 for next least deprived; 0.002, 95% CI 0.001-0.003 for second most deprived;

0.004, 95% CI 0.003-0.006 for most deprived). In other words, the rate of increase in eFI over 2-years in the least deprived quartile was lower than that for all more deprived quartiles.

Disease status group: The unadjusted change in eFI between 3 years and 5 years was significantly higher for all cardiovascular and osteoarthritis disease status groups tested when compared to the reference group with none of these conditions. Furthermore, there were significant differences in the change in eFI between 3 years and 5 years between the different disease status combinations tested. For the individual disease status groups, the unadjusted difference compared to the reference group for the change in eFI between 3 years and 5 years was similar for the groups with hypertension (0.006, 95% CI 0.005-0.008) or osteoarthritis (0.008, 95% CI 0.006-0.009). The unadjusted increase compared to the reference group was higher for ischaemic heart disease (0.015, 95% CI 0.013-0.016) and further increased for heart failure (0.023, 95% CI 0.020-0.026). The combination of hypertension with osteoarthritis was associated with an increase in change in eFI between 3 years and 5 years compared to reference of 0.012, 95% CI 0.011-0.014, which was of a similar magnitude to the sum of the increases associated with the two individual conditions, and also to that for ischaemic heart disease alone. The combination of ischaemic heart disease with osteoarthritis was associated with an increase in eFI compared to the reference of 0.023, 95% CI 0.020-0.026. The increase for this combination was similar to the sum of the increases associated with the two individual conditions, and also to that associated with heart failure alone. The combination of heart failure with osteoarthritis was associated with an increase in change in eFI between 3 years and 5 years compared to the reference group of 0.021, 95% CI 0.024-0.037, which was similar to the sum of the increase associated with these two individual conditions.

The increase in eFI score between three and five years for ischaemic heart disease was approximately twice that for hypertension or osteoarthritis, and similar to that for osteoarthritis with hypertension. The increase for heart failure eFI score was approximately three times that for hypertension or osteoarthritis and similar to that for ischaemic heart disease with osteoarthritis.

After adjustment for age, gender and deprivation status all of these differences were reduced. The difference between hypertension and the reference group became non-significant (0.002, 95% CI

0.000-0.003). The differences between the other groups all remained significant and the patterns of the relationships between them persisted; osteoarthritis 0.004, 95% CI 0.002-0.006; ischaemic heart disease 0.008, 95% CI 0.007-0.010; heart failure 0.014, 95% CI 0.010-0.017; hypertension with osteoarthritis 0.005, 95% CI 0.003-0.007; ischaemic heart disease with osteoarthritis 0.014, 95% CI 0.011-0.016; heart failure and osteoarthritis 0.019, 95% CI 0.013-0.025.

After adjustment for age, gender, deprivation status and eFI at 3 years, all of these differences were further reduced. The difference between hypertension and the reference group was insignificant (0.002, 95% CI 0.000-0.003) and those between osteoarthritis alone (0.003, 95% CI 0.001-0.005) and osteoarthritis with hypertension in combination (0.003, 95% CI 0.001-0.004) became marginally significant. The differences between the other groups all remained significant and the patterns of the relationships between them persisted: ischaemic heart disease 0.006, 95% CI 0.004-0.008; heart failure 0.010, 95% CI 0.006-0.013; ischaemic heart disease with osteoarthritis 0.010, 95% CI 0.007-0.013; heart failure and osteoarthritis 0.014, 95% CI 0.007-0.020.

4.5.6 Frailty severity and progression of frailty over 2 years

Frailty severity categories were assigned according to the number of deficits. People with no deficits (eFI=0) were defined as non-frail, those with 1-2 deficits (0< eFI <0.06) as having mild frailty, those with 3-4 (0.06< eFI <0.13) deficits as having moderate frailty and those with 5 or more deficits (eFI > 0.13) as having severe frailty.

Tables 4.11 and 4.12 show the distribution of the cumulative number of deficits and the frailty categories at 3, 4 and 5 years respectively. Table 4.13 and 4.14 show the progression to higher frailty categories from 3 to 4 years and from 3 to 5 years respectively.

Table 4.11: Cumulative numbers of deficits at 3, 4 and 5 years

eFI (No. of deficits)	3 years Frequency (%)	4 years Frequency (%)	5 years Frequency (%)	% change over 2 years
0 (0)	2250 (23.0)	1912 (19.5)	1651 (16.9)	-6.1
0.029 (1)	2663 (27.2)	2443 (24.9)	2181 (22.3)	-4.9
0.057 (2)	2066 (21.1)	1998 (20.4)	1884 (19.2)	-1.9
0.086 (3)	1301 (13.3)	1394 (14.2)	1469 (15.0)	+1.7
0.114 (4)	736 (7.5)	868 (8.9)	982 (10.0)	+2.5
0.143 (5)	366 (3.7)	531 (5.4)	690 (7.0)	+3.3
0.171 (6)	226 (2.3)	298 (3.0)	377 (3.8)	+1.5
0.200 (7)	99 (1.0)	169 (1.7)	253 (2.6)	_+1.6
0.229 (8)	43 (0.4)	85 (0.9)	126 (1.3)	+0.7
0.257 (9)	28 (0.3)	51 (0.5)	81 (0.8)	+0.5
0.286 (10)	5 (0.1)	21 (0.2)	53 (0.5)	+0.4
0.314 (11)	6 (0.1)	10 (0.1)	26 (0.3)	+0.2
0.343 (12)	3 (<0.1)	9 (0.1)	10 (0.1)	0
0.371 (13)	-	2 (<0.1)	4 (<0.1)	0
0.400 (14)	1 (<0.1)	1 (<0.1)	3 (<0.1)	0
0.429 (15)	-	-	2 (<0.1)	0
0.457 (16)	-	1 (<0.1)	1 (<0.1)	0
Total	9793 (100)	9793 (100)	9793 (100)	

Table 4.12: Frailty severity categories at 3, 4 and 5 years

Frailty category (no. of deficits)	Frequency (%) at 3 yrs	Frequency (%) at 4 yrs	Frequency (%) at 5 yrs	% change over 2 years
None (0)	2250 (23.0)	1912 (19.5)	1651 (16.9)	-6.1
Mild (1-2)	4729 (48.3)	4441 (45.3)	4065 (41.5)	-6.8
Moderate (3-4)	2037 (20.8)	2262 (23.1)	2451 (25.0)	+4.2
Severe (>5)	777 (7.9)	1178 (12.0)	1626 (16.6)	+8.7
Totals	9793 (100)	9793 (100)	9793 (100)	

Table 4.13: Progression of frailty severity categories from 3 to 4 years

Frailty category at 3 years	Frequency (%)	Frailty category at 4 years Frequency (% of 3 year category)			
		None	Mild	Moderate	Severe
None	2250 (23.0)	1912 (85)	326 (14.5)	11 (0.5)	1 (<0.1)
Mild	4729 (48.3)	-	4115 (87)	588 (12.4)	26 (0.5)
Moderate	2037 (20.8)	-	-	1663 (81.6)	374 (18.4)
Severe	777 (7.9)	-	-	-	777 (100)
Total	9793 (100)	1912 (19.5)	4441 (45.3)	2262 (23.1)	1178 (12.0)

Table 4.14: Progression of frailty severity categories from 3 to 5 years

Frailty category at 3 years	Frequency (%)	Frailty category at 5 years Frequency (% of 3 year category)			
		None	Mild	Moderate	Severe
None	2250 (23.0)	1651 (73.4)	545 (24.2)	48 (2.1)	6 (0.3)
Mild	4729 (48.3)	-	3520 (74.4)	1083 (22.9)	126 (2.7)
Moderate	2037 (20.8)	-	-	1320 (64.8)	717 (35.2)
Severe	777 (7.9)	-	-	-	777 (100)
Total	9793 (100)	1651 (16.9)	4065 (41.5)	2451 (25.0)	1626 (16.6)

Of the 9793 people in the denominator population, 2250 (23%) had no coded deficits at the 3-year time point and were therefore defined as non-frail at that point. Twelve months later (at the four year time point) 326 (14.5%) of these had progressed to mild frailty, 11 (0.5%) to moderate frailty and 1 (<0.1%) to severe frailty. Whilst two years later (at the five year time point) 545 (24.2%) of these had progressed to mild frailty, 48 (2.1%) to moderate frailty and 6 (0.3%) to severe frailty.

4729 (48.3%) had 1-2 coded deficits at the 3-year time point and were therefore defined as having mild frailty at that point. Twelve months later (at the four year time point) 588 (12.4%) of these had progressed to moderate frailty and 26 (0.5%) to severe frailty. Whilst two years later (at the five year time point), 1083 (22.9%) of these had progressed to moderate frailty and 126 (2.7%) to severe frailty.

There were 2037 (20.8%) people who had 3-4 coded deficits at the 3-year time point and were therefore defined as having moderate frailty at that point. Twelve months later (at the four year time point) 374 (18.4%) of these had progressed to severe frailty. Whilst two years later (at the five year time point), 717 (35.2%) of these had progressed to severe frailty.

There were 777 (7.9%) people who had 5 or more coded deficits at the 3-year time point and were therefore defined as having severe frailty at that point. The total number of people with severe frailty had increased to 1178 (12.0% of total population) at the 4-year time point and 1626 (16.6% of total population) at the 5-year time point.

4.6 Discussion

4.6.1 Associations between socio-demographic characteristics, disease status and frailty

The eFI development and validation study reported by Clegg included 454,051 people aged over 65 years, for whom the mean eFI was 0.13, the 99th centile was 0.41 and the maximum eFI was 0.70 (100). The levels of frailty in this study were lower, with the mean eFI over the 5 years 0.072, the 99th centile 0.285 and the maximum eFI 0.46. There were two main reasons why the eFI values in this study were expected to be lower than in the published study. Firstly, the population age range in this study was 40 years and over, compared to the published study in which the population aged over 65 years. Frailty increases with age and therefore a younger study population would be expected to have lower mean eFI. Secondly, the eFIs in the published study were calculated from the Read coded data in the entire electronic patient records for the individuals in that study population, whereas the eFIs in this study were calculated only from the Read coded data in the 5 year consultation dataset and did not include any coded data in the electronic patient record prior to that period. All the individuals in this study therefore had their eFI scores calculated from their consultation activity during the same five-year period, regardless of their previous consultation history. The eFI works on the principle of 'cumulative deficits' and the approach in this study would therefore inevitably have resulted in lower overall eFI scores than in the published study.

However, the selection of the denominator population in this study by disease status would have tended to increase the eFI in this study compared to the published study, which used a general primary care population. The 2529 people in the reference group in this study had neither cardiovascular disease nor osteoarthritis. However, 5041 people in this study were in index disease groups that would have conferred at least one deficit contributing to the eFI and 2223 people were in disease status groups that would have conferred at least two deficits to contribute to the eFI. This selection process would therefore have resulted in a minimum of 9487 deficits across the

population of 9793, or a mean of 0.97 deficits per person, equating to a minimum mean eFI of 0.028. This compared to an actual mean eFI of 0.072 for the study denominator population, or on average about 2.5 deficits per person, implying that not all the frailty measured in this population using the eFI was a result of the selection process for the denominator population.

Age: One of the criteria for selection of deficits for inclusion in the construct of the eFI was that their prevalence increases with age (38,100). The eFI was therefore expected to increase with age in any population. The finding in this study that the eFI increased with age therefore supported the construct validity of using the eFI calculated from primary care consultation data to measure frailty in this population.

Gender: In this study the eFI for females was higher than that for males, even after adjustment for age, deprivation status and disease status group, implying that females tend to have higher levels of frailty than males. One counter explanation for this could be that females tend to consult in primary care more than males. However, although crude primary care consultation rates are lower in men than women (171) it has been shown that the magnitude of this gender difference varies across the life course and there is no 'excess' female consulting in later life (171). Furthermore, differences in consultation rates between men and women largely disappear when comparing men and women receiving medication for similar underlying morbidities (171). This implies that the gender differences in eFI observed in this study were not simply associated with gender differences in consulting behaviour and supports the hypothesis that frailty is higher in females than males. This finding was therefore consistent with published evidence that frailty is higher in females than males (172,173) and therefore supported the construct validity of using the eFI calculated from primary care consultation data to measure frailty in this population.

Deprivation: In this study, frailty as measured by the eFI increased with increasing levels of deprivation. Published evidence shows that frailty increases with socioeconomic deprivation (174). The findings of this study were consistent with known evidence about frailty and therefore supported the construct validity of using the eFI calculated from primary care consultation data to measure frailty in this population.

Disease status group: The disease status groups that formed the basis of the cohort selection in this study were all included as coded deficits within the construct of the eFI. It would therefore be expected that all the comorbidity groups would have a higher eFI than the reference group. If there were no other differences between the groups, the magnitude of this difference would have been of the order of that representing one deficit (0.029) for disease status groups containing a single condition, and two deficits (0.058) for comorbidity groups containing the combinations of two conditions. The findings of this study that frailty increased as the number of comorbidities increased were therefore consistent with expected results and supported the construct validity of using the eFI calculated from primary care consultation data to measure frailty in this population.

The magnitude of the difference in eFI between the group with hypertension and the reference group was of a magnitude representing more than one deficit, whilst the difference between the group with osteoarthritis and the reference group represented about one deficit. This implies that people with hypertension but without arthritis were more likely to have other coded conditions related to frailty than people with osteoarthritis but without cardiovascular morbidity.

During the selection of the comorbidity cohorts, cardiovascular severity was assessed using a defined order of disease severity, in which hypertension, ischaemic heart disease and heart failure were used as indicators of increasing disease severity, with allocation to a cohort based upon the most severe cardiovascular disease category present. In other words, for example, if an individual had consulted for hypertension and heart failure they would be allocated into the heart failure cohort (160,162). Individuals with higher cardiovascular disease severity could be expected to have other related cardiovascular codes, for example people with ischaemic heart disease might often also have hypertension and people with heart failure might often also have both ischaemic heart disease and hypertension. Increasing cardiovascular severity status would therefore be expected to be associated with increasing eFI and there was indeed a progressive hierarchical increase in eFI with cardiovascular severity status in the single disease status groups. This finding also supported the construct validity of using the eFI to measure frailty in this population.

Comparing the contribution to frailty of different disease status groups, hypertension made a contribution approximately twice that of osteoarthritis, ischaemic heart disease three times that of osteoarthritis and heart failure more than four times that of osteoarthritis. Furthermore, the

increases in eFI for the combinations of osteoarthritis with heart failure and osteoarthritis with ischaemic heart disease were higher than the sums of the increases associated with each pair of individual conditions.

This study therefore demonstrated that different cardiovascular and osteoarthritis comorbidities, alone and in combination, were associated with different patterns of frailty, as measured by the eFI, and that these differences were not simply due to the additive effects of single deficits directly associated with the diagnostic codes for each condition. These finding therefore raise interesting further questions regarding clusters of comorbidities and associated symptoms, and the associations between these and severity of frailty.

There is increasing recognition that the systematic approach to the management of individual long-term conditions in primary care, whilst resulting in improved outcomes in many areas can also present difficulties for increasing numbers of older people with multiple long-term conditions (12). These individuals are often prescribed multiple different medications by a system of care that effectively treats them as a collection of single diseases rather than recognising them as a single individual with multiple conditions and the potential impact of this multiple drug prescribing in older people has been highlighted (175).

The construct of the eFI includes codes for diseases/conditions, symptoms (e.g. breathlessness) and states (e.g. housebound). The relationship between frailty as measured by the eFI and different comorbidities is therefore likely to vary by condition, as demonstrated in this study. This is because both the condition and the symptoms associated with the condition and/or its treatment, can make separate contributions to the eFI, and these are likely to occur in different patterns and therefore to have differing impacts upon frailty for different long-term conditions, alone or in combination. For example, hypertension contributes one deficit to the eFI but is usually asymptomatic, whereas heart failure, which also contributes one deficit, can often be associated with symptoms such shortness of breath and dizziness, which might be a consequence of the either the heart failure itself or treatments for the condition and which also each contribute a deficit to the eFI. Furthermore, for example, treatment for heart failure with diuretics can be associated with incontinence, which is another deficit, particularly in the presence of the further deficit of poor mobility.

In other words, the deficits that make up the eFI are not independent and in some cases the deficits overlap, with some codes contributing to more than one deficit. Exploring the patterns of frailty deficits associated with different index disease groups and comorbidity combinations, in this case cardiovascular comorbidities and osteoarthritis, could have important implications for the management of long-term conditions in the context of frailty, and for the management of frailty in the context of comorbidity.

4.6.2 Association between socio-demographic characteristics, disease status and frailty change

This study demonstrated that the rate of increase of eFI over the 2-year period increased in older age groups. This is important because it implies that the higher levels of frailty in older age groups are not just a result of a longer life and a potentially linear accumulation of deficits across that life span. Instead there is evidence to support the more rapid accumulation of deficits in older age, corresponding to acceleration in the development of frailty in people of an older age. This finding resonates with clinical experience that some people in the oldest age groups seem to 'suddenly' become frail and has potentially important implications for the management of frailty.

Although females were found to have higher levels of frailty than males, there was no gender difference in the change in frailty over this two-year period. However, with respect to deprivation status, the more affluent groups had both lower levels of frailty and lower rates of change in frailty over this two-year period, with higher levels and higher rates of increase in the more deprived groups. These findings have important potential implications for the organisation and delivery of care for people with frailty, particularly with respect to proactive interventions intended to influence frailty trajectories. These results suggest that targeting such interventions to populations with higher levels of socioeconomic deprivation is likely to have a greater public health impact than directing them towards more affluent populations.

Comparing the disease status groups, ischaemic heart disease and heart failure had greater increases in frailty over the two-year period than hypertension and osteoarthritis. In other words, increasing cardiovascular disease severity was associated with increased rate of change of frailty. Exploring the patterns of additional deficits contributing to the change in frailty for different disease status groups over this two-year period could have potential to inform the management of frailty

and comorbidity. For example, the best approach to managing frailty progression if the change in eFI was primarily the result of the accumulation of additional condition deficits might differ to the management approach if the change in eFI was primarily due to additional deficits defined by symptom codes.

For all socio-demographic variables other than gender, groups with higher levels of frailty also had greater increases in frailty over the two-year time period studied. There was therefore no evidence of 'ceiling' effects in the development of frailty in this study, rather there appeared to be acceleration in the development of frailty in groups with higher levels of frailty compared to those with lower levels of frailty.

4.6.3 Profile and progression of frailty over 2 years

The progression of frailty across frailty severity categories in the denominator population showed that the majority of people progressed gradually in stages through the categories from non-frail to mild, moderate and severe frailty over the two year time period. However, a small percentage of people progressed more rapidly through the stages of frailty, transitioning from non-frail or mild frailty to severe frailty within the one or two year time scales investigated. This demonstrated that the progression of frailty was not necessarily linear and that it varied between individuals.

4.6.4 Clinical and research implications

4.6.4.1 The construct of the eFI as a measurement of frailty in primary care

The patterns of frailty in relation to the socio-demographic variables of age, gender and deprivation described in this population by the eFI were consistent with previous evidence in this area (172-174). Furthermore, the eFI described patterns of frailty in respect to the number and severity of the index cardiovascular and osteoarthritis disease status groups that were consistent with the frailty construct. This study therefore validated the construct of the eFI for use in the measurement of frailty in this primary care population. This study also demonstrated that the differences in frailty between the disease status groups as measured by the eFI were both statistically and clinically significant. Furthermore the eFI was shown to be sensitive to change in frailty over a two year time period in this primary care population.

However, this study also identified the need for further research to investigate the validity of this approach for use in routine primary care clinical practice, specifically considering:

i) Content validity in relation to a multi-dimensional model of frailty, in other words, to map the current content of the eFI against a multi-dimensional model of frailty in order to determine whether all domains are adequately represented in the eFI, and if not how these gaps could be addressed.

ii) Criterion validity compared to comprehensive geriatric assessment, in other words to investigate the strength of the association between frailty severity as measured by the eFI and frailty severity as determined by Comprehensive Geriatric Assessment.

iii) Predictive validity in respect of holistic outcomes related to frailty, in particular the ability of the eFI to predict quality of life outcomes for people with frailty.

iv) Face validity with multidisciplinary primary care teams, to determine how relevant and appropriate these clinicians consider this approach to be for the measurement of frailty in their routine clinical practice.

In addition, given that the deficits that make up the eFi are not independent, further research is needed to explore the patterns of frailty deficits associated with different index comorbidities and the implications of this for this approach to frailty measurement.

Finally, significant conceptual challenges remain in using a cumulative deficit approach to frailty measurement constructed from the Read Codes from the individual's entire 'lifetime' electronic primary care record. Over time, such a measure can only ever stay the same or increase, and is never able to decrease, because codes will only ever be added to, and never removed from, the electronic primary care record. Therefore there is dissonance between the underlying construct of this frailty measurement tool and the well-described concept that an individual's degree of frailty can fluctuate and in some cases may improve as well as progress (1).

4.6.4.2 Frailty trajectories

Better understanding of frailty trajectories, which is a plot of individual's frailty over time that may progress slowly or rapidly, has the potential to offer greater opportunities for timely clinical intervention, both to respond to the needs of people at different stages of frailty and to influence the progression of the underlying frailty. Frailty transitions across healthcare interfaces are important because they have been identified as opportunities at which the progression of frailty might be prevented, reversed or delayed (3,11,44). This study has shown that important differences exist between individuals in the rate of progression of frailty, in other words between individual frailty

trajectories. However, at this stage the main implications of these findings are as the basis for further research, rather than in immediate clinical applications.

This study has started to characterise the socio-demographic and clinical features of those people whose frailty progressed more rapidly. However, further research is needed and would make an important contribution towards the understanding of frailty trajectories. Examining the patterns through which the deficits or clusters of deficits contributing to the overall frailty emerged in individuals with differing frailty trajectories would further inform this understanding. This would help identify, for example, whether increasing frailty at certain points is more likely to be associated with increasing burden of disease or whether due to increasing symptoms, which may be associated with pre-existing conditions. This could help to predict the emergence and rate of progression of frailty, to better characterise the relationship between frailty and comorbidity, and most importantly to help better identification of critical tipping points and maximal opportunities for intervention along frailty trajectories.

4.6.5 Strengths and limitations of the study

4.6.5.1 Use of the 2C study dataset

The use of the 2C study dataset to investigate the measurement of frailty using the eFI had a number of strengths but was also the major limitation of this study. The strengths and limitations of this approach are discussed in full in chapter six (section 6.3, page 176).

4.6.5.2 Application of the eFI

There were both strengths and limitations associated with the way in which the eFI was applied in this study. The eFI was developed as a tool to obtain a measure of frailty generated from an individual's entire electronic primary care record. However, in this study the tool was applied to a five year 'window' of coded consultation data and not to the entire primary care record.

One limitation of this approach was that an eFI generated in this study from the five years of consultation data would systematically 'under-estimate' frailty when compared to an eFI generated from the entire electronic patient record. However, even though the absolute values of the eFI obtained in this study would therefore have 'under-represented' frailty, these systematic differences

would have applied to all individuals in the study. Therefore comparisons of relative frailty between socio-demographic and disease status characteristics could still be made.

Care was needed in interpreting the rate of change in frailty over the 5 year time period. Baseline frailty at the start of the time period had to be recognised as 'unknown' and not zero. Assuming this baseline to be zero could have led to an apparent rapid change in frailty in the early part of the five year period, when in fact the contributing consultation activity could have related to clinical features identifiable within the electronic primary care record prior to the start of the study period and not newly developed within it. This would be particularly relevant to consultation activity associated with pre-exiting long-term conditions. The study design addressed this limitation by calculating the eFI at the end of the first three years of the study, during which time the majority of active and relevant pre-existing conditions could have been expected to present in primary care, and using this as the baseline against which to measure change in frailty over the following two years.

4.6.5.3 Construct of the eFI

The construct of the eFI was shown to be statistically sensitive to measuring increasing frailty in this population during the study period. However, there was a conceptual limitation associated with the use of the eFI as a frailty measurement tool for the investigation of frailty trajectories. Although transitions in frailty are most frequently towards increasing frailty, it is acknowledged that improvements can also occur (1,29). However, the eFI is based upon a cumulative deficit model that uses the entire electronic primary care record and can therefore only measure stable or increasing frailty and cannot reflect improvements in the condition. Whilst many diseases contributing to frailty are long term conditions or conditions with life-long consequences, some states and symptoms may be transient, raising the question as to whether they should always thereafter contribute to an individual eFI score. Although the design in this study, using five years of consultation data as the basis for describing frailty, prevented 'historic' or 'inactive' conditions from contributing to the eFI score, this measurement approach was still unable to detect improvements in frailty during the study period. Understanding the factors that can exert a positive influence and be associated with improvement in frailty is as important as understanding factors associated with deterioration of the condition. The inability of the eFI to detect and measure improvement in frailty therefore limited the contribution that could be made by this study to the further understanding of frailty trajectories.

4.7 Conclusions

This study demonstrated that frailty in this population, as measured by the eFI, increased with age and with increasing levels of deprivation. Frailty was also higher in females than in males. In this population, frailty increased with the number of index cardiovascular and osteoarthritis conditions and with increasing cardiovascular comorbidity severity. These differences were not only statistically significant but also represented potentially clinically significant differences. This conclusion was reached because when the fractional differences in eFI were translated back into equivalent numbers of clinical deficits, they were of an order of magnitude that represented whole additional deficits and not just small fractions of deficits.

This study also demonstrated that the eFI as a measure of frailty in this population was sensitive to change over the two year time period. It also showed that the rate of change in frailty in this population, as measured by the change in the eFI over a 2-year period, i) was not uniform and varied between individuals, ii) within the range of this study, no ceiling effects were observed. The rate of change of frailty increased with age and with increasing levels of deprivation, although there was no difference in the rate at which frailty changed in females compared to in males. In this population, the rate of change in frailty increased with the number of index cardiovascular and osteoarthritis comorbidities, as well as with increasing cardiovascular comorbidity severity. In other words, with the exception of female gender, the socio-demographic and comorbidity characteristics associated with increased levels of frailty were also associated with increased rates of change in frailty.

In conclusion, the findings of this study were:

1) The initial hypothesis that there was an association between comorbidity severity and frailty, as measured by the eFI, and in this primary care cohort was confirmed.
2) The initial hypothesis that there was an association between comorbidity severity and an increased change in frailty, as measured by the change in the eFI over a 2-year period, in this primary care population was confirmed.
3) The construct of the eFI as a measure of frailty in this primary care population was validated to some extent.

Chapter 5: An investigation of the relationship between frailty and quality of life in primary care

5.1 Introduction: Frailty and quality of life

The third phase of this study built on the conclusions and recommendations of the second phase by further investigating:

i) The content and predictive validity of the eFI as a tool to measure frailty in primary care.

ii) How other factors relevant to a multi-dimensional model of frailty but which are not included in the eFI relate to frailty.

iii) The relationship between frailty and quality of life.

iv) Frailty trajectories and their relationship with quality of life.

The importance of quality of life as an outcome in frailty has been discussed (section 1.5.3, page 12 and section 2.3.4, page 28). Focusing upon person-centred quality of life outcomes is key to an integrated and holistic approach to frailty (13,27,176). The ability of the eFI to predict quality of life outcomes is important if this tool is to find clinical application in support of the delivery of integrated person-centred care. During its development, the eFI had been validated against morbidity and mortality outcomes and against health related events associated with frailty such as nursing home admission (100). However, the relationship between the eFI and quality of life had not yet been investigated. The third phase of this study therefore used the opportunity presented by 2C survey population to investigate the relationship between eFI and quality of life and to test the predictive ability of the eFI for quality of life. It also addressed additional questions regarding eFI content and construct validation.

5.2 Background: Frailty and quality of life in a primary care population

5.2.1 Study framework

This third phase of the project built upon the findings of the first two phases. It was designed to test the content and predictive validity of the eFI as a measure of frailty in primary care, and to investigate the relationship between frailty and quality of life in a primary care population.

5.2.2 Findings from the systematic review

5.2.2.1 Construct of frailty measurement tools

Given the holistic and contextual nature of primary care, a strong case has been made for a multi-dimensional approach to the measurement of frailty in primary care (3,16,28,43-6,48). The systematic review in the first phase of this project demonstrated that within this approach there is a need to embed psychological and social domains more comprehensively alongside physical health domains in the measurement of frailty.

This study was designed to address this question by applying a frailty measurement tool based on routinely collected primary care data (100) to a data set of coded consultations (160) and then testing whether the association and predictive ability of this tool in relation to quality of life, a key outcome associated with frailty, could be improved by adding the following factors into the measurement tool:

a) Enhancing the input into the social domain with questionnaire data.
b) Enhancing the input into the psychological domain with questionnaire data.
c) Adding an input domain related to levels of fatigue, a strong phenotypic feature of frailty.
d) Adding an input domain related to level of primary care healthcare use.

5.2.2.2 Outcomes in frailty

Quality of life and functional capability have been highlighted as important outcomes in relation to the measurement and management of frailty (13,16,27,46,48). However, these outcomes had been relatively little used in the external validation of the frailty measurement tools identified in the systematic review and this was identified as a key gap.

5.2.3 Findings from the denominator population study

The denominator study demonstrated that frailty in this population, as measured by the eFI, increased with age, with increasing levels of deprivation and with increasing cardiovascular comorbidity severity. The study also demonstrated that the eFI as a measure of frailty in this population was sensitive to change over the two year time period and that the rate of change in frailty in this population was not uniform. The study therefore validated the construct of the eFI as a measure of frailty in this primary care population, but also recommended further validation studies

to investigate other properties of the eFI in this context. Further studies were also recommended to characterise frailty trajectories in more detail.

5.2.4 The Electronic Frailty Index

The frailty measurement tool used in this study was the eFI (section 4.2.3, page 86)(100).

5.2.5 The Comorbidity Cohort (2C) Dataset

The Comorbidity Cohort (2C) study (160) dataset was used in this study. There were three phases to the data collection in the 2C study. The first phase (survey population) was a postal questionnaire that was sent to the entire denominator population cohort at baseline (2010). This questionnaire obtained self-reported information on physical and mental health, well-being, functional abilities and social networks using validated or previously used questionnaires. Those people who responded to the baseline survey were sent the same questionnaire at follow up 12 months later. The second phase (consultation dataset) constructed an anonymised clinical consultation data archive for a five year period (from three years before through to two years after the first survey point) for the entire denominator population. The third phase (linkage population) linked the survey data to primary care consultation data for those people who responded to the survey and gave their written consent for this linkage to take place (160).

5.2.6 Outcomes and explanatory factors

The particular outcome of interest in this study was quality of life, as measured by the EQ-5D score (182). In this study the eFI was considered as an independent variable and its relationship with the dependent variable (outcome) of quality of life was explored. The objective was to investigate the ability of the eFI to predict quality of life and to investigate whether including additional explanatory factors representing other domains in the multi-dimensional model of frailty along with the eFI would improve this prediction. Additional explanatory factors were therefore selected in order to represent a range of the components of frailty measurement identified in the systematic review, and their relationships with frailty and quality of life explored. The explanatory factors included in the investigation were:

- Levels of anxiety and depression as an indicator of psychological status.
- Social network data, representing the social environment.
- A healthcare use measure derived from primary care consultation data.

- A measure of fatigue.

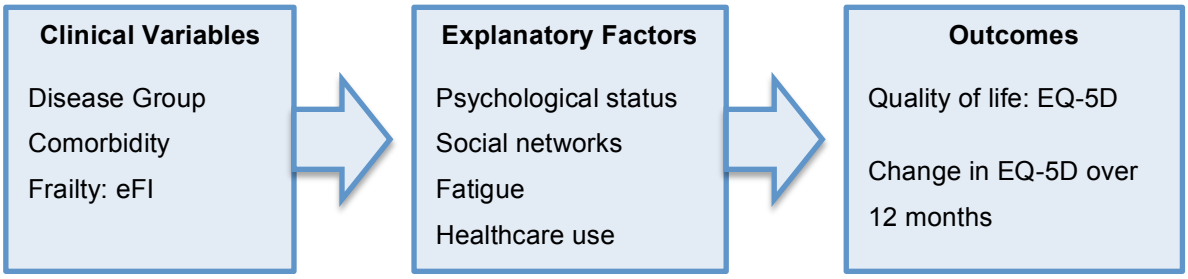
Fatigue is a key phenotypic feature of frailty and investigating the relationship between the eFI and fatigue scores would also therefore investigate the construct validity of the eFI as a measure of frailty in this primary care population.

5.3 Aims and objectives

5.3.1 Aims

The overall aim of this study was to investigate the relationship between frailty and quality of life in a population cohort aged 40 years and over (160). Specifically, the study aimed to investigate the relationship in this population between an eFI calculated from routinely collected primary care data (100) and i) other variables, namely psychological status, social networks, levels of fatigue and healthcare use, ii) the outcome of quality of life. The relationship between the clinical variables, explanatory factors and outcomes in this study are illustrated schematically in Figure 5.1.

Figure 5.1 Schematic illustration of clinical variables, explanatory factors and outcomes.



5.3.2 Objectives

The detailed objectives in this study were:

a) To investigate the association between frailty, comorbidity severity, psychological status, social network measure, levels of fatigue, healthcare use and baseline quality of life.

b) To investigate the association between frailty, comorbidity severity, psychological status, social network measure, levels of fatigue, healthcare use and change in quality of life measured over a 12-month time-period.

The summary objectives in this study were:

1) To investigate whether the electronic frailty index calculated from routine primary care data predicts quality of life.

2) To investigate whether the electronic frailty index predictive validity can be improved by the addition of other domains.

5.3.3 Hypotheses

The hypotheses to be tested by this study were as follows:

1) H_0: There is no association between frailty status (measured by eFI) and quality of life in this comorbidity cohort.

   H_1: There is an association between frailty status (measured by eFI) and quality of life in this comorbidity cohort.

2) H_0: The strength of any association between frailty status (measured by eFI) in this comorbidity cohort and quality of life is not increased if questionnaire data on social networks and/or psychological status and/or levels of fatigue, and/or a measure of healthcare usage is added into the model.

   H_1: The strength of any association between frailty status (measured by eFI) in this comorbidity cohort and quality of life is increased if questionnaire data on social networks and/or psychological status and/or levels of fatigue, and/or a measure of healthcare usage is added into the model.

3) H_0: Change in quality of life over a 12 month period cannot be predicted by frailty status (measured by eFI) at baseline in this comorbidity cohort.

   H_1: Change in quality of life over a 12 month period can be predicted by frailty status (measured by eFI) at baseline in this comorbidity cohort.

4) H_0: The ability of frailty status (measured by eFI) in this comorbidity cohort at baseline to predict changes in quality of life over the following 12 month period is not increased if data on social networks and/or psychological status and/or levels of fatigue and/or healthcare usage is added into the model.

   H_1: The ability of frailty status (measured by eFI) in this comorbidity cohort at baseline to predict changes in quality of life over the following 12 month period is increased if data on social networks and/or psychological status and/or levels of fatigue and/or healthcare usage is added into the model.

5.4 Methods

The study design, study setting, denominator population, arrangements for data access and management, data quality and the frailty measurement tool used were as described in sections 4.4.1-5 (pages 89-91).

5.4.1 Sample size

In the 2C study, the individuals in the denominator population were invited to complete a baseline postal health questionnaire and an identical 12-month follow-up questionnaire (section 5.2.5, page 123). The study sample in this study was all people aged over 40 years in the 2C study who completed both questionnaires and gave consent for the survey data to be linked to their primary care consultation data (160). In the 2C study 5426 people responded to the baseline survey, of whom 3984 consented to data linkage, and 3484 of the baseline responders also responded to the 12-month survey, of whom 2878 consented to data linkage. The sample size for this study was therefore 2878.

The minimum sample size for this study was determined by the multiple regression section of this analysis, which required a ratio of at least 15 cases per independent variable (177). In this study there were 12 independent variables and the minimum sample size required was therefore 12 x 15, that is 180. The sample size of 2878 was therefore above the minimum sample size required and adequate for the proposed analysis.

5.4.2 Variables and outcomes

The variables and outcomes described in section 4.4.6 (page 92) were all used in this study. However, this study also investigated:

i) The eFI as an exposure as well as an outcome

ii) Additional explanatory factors,

iii) Quality of life as an outcome variable.

The measurement or derivation of these additional variables are summarised in Table 5.1.

Table 5.1: Additional variables under investigation in this study

	Factor	Classification	Measurement / derivation
Key variable	Electronic Frailty Index (eFI)	Outcome & exposure	Derived from primary care consultation data using codes provided by Clegg[R]
Other explanatory factors	Psychological status	Exposure	Measured by Hospital Anxiety and Depression Score (HADS) in survey data.
	Levels of fatigue	Exposure	Measured by FACIT fatigue score in survey data.
	Social networks	Exposure	Derived from social network survey data.
	Healthcare use	Exposure	Derived from primary care consultation data.
Outcome	Quality of life	Outcome	Measured by EQ-5D score in survey data.

The eFI was both an outcome (dependent variable) and an exposure (independent variable) at different stages of these analyses. Psychological status, levels of fatigue, social network status and healthcare use were all exposures (independent variables) in this study, whilst quality of life was an outcome (dependent variable).

5.4.3 Data Preparation

The methods used to prepare the survey population demographic data and consultation data and to calculate the eFIs are described in Appendix II (page 238).

5.4.3.1 Survey data

Whilst the following survey data were measured both at baseline and 12-months follow up, only the EQ-5D data was used to measure change. The other data were used only as baseline measures.

Level of anxiety and depression (HADS)

The Hospital Anxiety Depression Score (HADS) was first developed in 1983 as an instrument to

detect anxiety and depression in presence of physical illness (178). Since then it has been very widely used and review of the validity of the instrument has found it to perform well in assessing both caseness and symptoms of severity of anxiety and depression in somatic, psychiatric and primary care patients and in the general population (183).

The survey questions from which the HADS were generated are detailed in Appendix III (page 240). The levels of anxiety and depression as measured by HADS were provided in two forms in the survey dataset. Firstly, as absolute scores and secondly reclassified as a) not anxious/depressed b) borderline anxious/depressed and c) probable anxious/depressed. The categorical data rather than the absolute scores were used in this study because this would facilitate the interpretation of the clinical relevance of the results.

Level of fatigue (FACIT-f score)

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-f) score is a patient reported outcome measure, which was first developed in 1998 to measure fatigue in oncology patients (179). It is brief and easy to understand with 13 questions covering four different dimensions of fatigue: physical fatigue (feeling tired), functional fatigue (having trouble finishing things), emotional fatigue (frustration) and social consequences of fatigue (limiting social activity) (179). It has been extensively validated (179,184) and widely used, including with older people (185).

The survey questions relating to the FACIT-f score are detailed in Appendix IV (page 243). The level of fatigue as measured by the FACIT-f score was presented as a continuous variable in the survey dataset and was recoded into quartiles, with category 1 being the least fatigued and category 4 being the most fatigued.

Social network data

The research questions of interest in this study were: (i) how do social network features relate to current frailty and (ii) do social network features help to predict future quality of life? The three social network features explored in this study were:

1. Extent of personal social contacts
2. Level of emotional support

3. Degree of social participation

These three concepts were tested separately to explore their individual relationships with frailty and quality of life. The social network questions in the survey data and the way in which they were used to derive the social network measures is described in Appendix V (page 244).

Quality of life (EQ-5D)

The EQ-5D score is a standardised non disease-specific instrument for measuring health related quality of life. It is a self-report questionnaire with a five dimensional structure (EQ-5D) (186). Respondents complete questions covering five different areas, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and also calibrate their feeling of wellbeing on a scale of 1-100 using a thermometer scale (186). The EQ-5D was first developed in Scandinavia and the UK but has been translated into most major languages and is very widely and internationally used by clinical researchers (182).

The survey questions relating to the EQ-5D scores are detailed in Appendix VI (page 246). The quality of life as measured by the EQ-5D scores was presented as a continuous variable in the survey dataset and was used in this format.

5.4.3.2 Measuring 'Healthcare use'

The ‘healthcare use’ measure was a new variable calculated from the consultation data. The method for this derivation is described in Appendix VII (page 247).

5.4.4 Data analysis

All data analyses in this study were carried out using SPSS version 21 software (168).

5.4.4.1 Comparing the socio-demographic, comorbidity and frailty characteristics of the surveyed population with those of the denominator population

The first stage of the analysis in this phase of the study described the study population and how it compared with respect to age-demographic data, clinical data and frailty, as measured by the eFI, to the denominator population from which the study sample was drawn.

The socio-demographic and comorbidity characteristics of the surveyed population were compared to those of the denominator population by considering the proportions of each population in the subgroups for each of the categorical variables of age, gender, deprivation status and comorbidity.

The frailty characteristics of the surveyed population were compared to those of the denominator population by considering the mean eFIs and standard deviations for each of these populations at the 3, 4 and 5-year time points. The 5-year eFIs were used in order to enable a comparison to be made between frailty levels for the denominator and surveyed populations over the full 5-year time period. The use of the 3-year eFIs enabled a comparison to be made between the frailty levels of the study population and those of the denominator population at the point at which people decided whether or not to respond to the initial survey invitation. Similarly, the use of the 4-year eFIs enabled a comparison to be made between the frailty levels of the surveyed and denominator populations at the point at which people decided whether or not to respond to the follow up survey invitation.

5.4.4.2 Investigating change in quality of life over 12 months by socio-demographic and comorbidity characteristics.

This stage of the analysis was designed to investigate whether quality of life varied by socio-demographic and comorbidity characteristics. These findings would then be used to inform the adjustments required in the regression models in section 5.4.4.3. Using paired data, quality of life at baseline and mean change over the following 12 months were estimated by socio-demographic and comorbidity characteristics.

5.4.4.3 Investigating the relationship between survey variables, frailty and quality of life, and how this changes over time

This stage of the analysis used the linked survey data and consultation data for the survey responding and consenting population. It explored the relationship between the variables of psychological status, levels of fatigue, social network characteristics and healthcare use and the outcomes of electronic frailty index and quality of life scores for the study population, both at baseline and at 12 month follow up. The extent of missing data for each variable at baseline, and each outcome at baseline and at 12 month follow up in this dataset was also assessed.

The two outcomes considered were frailty as measured by eFI and quality of life as measured by EQ-5D. These were therefore the dependent variables. The eFIs were calculated using the primary care consultation data for the study population at baseline (3 years into the 5 year study period) and at 12-month follow-up (4 years into the 5 year study period), corresponding to the two time

points for which questionnaire data was available for the study population. The EQ-5D scores were available in the survey datasets for each time point.

The independent variables for which each of these outcomes were considered were:

- Anxiety measured by HADS
- Depression measured by HADS
- Level of fatigue measured by FACIT score
- Level of social participation derived from baseline survey
- Emotional support which is presence or absence of a close confidant from baseline survey
- Level of social contacts derived from baseline survey
- Healthcare use score from consultation data

The means and standard deviations for eFI and EQ-5D at both baseline and at 12 month follow up were first estimated for each category within each independent variable. The mean change and standard deviation in each outcome over 12 months was then calculated for each category within each variable.

Linear regression was used to calculate the unadjusted differences between the means (and 95% confidence intervals) in relation to the reference category for each variable, for both dependent variables for each of the independent variable categories. The reference categories for each of the variables were as follows: for anxiety it was ‘not anxious’, for depression it was ‘not depressed’, for fatigue it was the least fatigued quartile, for social participation and social contact it was ‘none’, for close confidant it was ‘yes’ and for healthcare use it was the quartile with the lowest use.

As a result of the findings from 5.4.4.2 (page 130) a second calculation was then carried out for both dependent variables, using a model that adjusted for age, gender, deprivation status and disease status group.

The regression analysis was carried out for the study population using the baseline survey data with the corresponding 3-year eFIs and quality of life scores as dependent variables. This allowed the relationship between psychological status, fatigue, social networks and healthcare use, and frailty and quality of life to be investigated in the study population at baseline. Analyses were also carried out for the change in eFI and quality of life scores over the following 12 months, in order to investigate whether change in frailty or quality of life over this period varied by psychological status, fatigue, social networks and healthcare contacts.

5.4.4.4 Investigating the relationship between eFI and quality of life

The relationship between eFI and quality of life scores in the study population at baseline and 12-month follow-up survey data was investigated using firstly, correlation and secondly, linear regression. Although the eFI data was non-normal, the large sample size allowed the use of the Pearson's correlation.

5.4.4.5 Investigating eFI as a predictive factor for quality of life

This stage of the analysis used multiple regression analysis to identify the relationship between different independent variables at baseline and quality of life at baseline and at 12 month follow up. It investigated the relationship between eFI at baseline and quality of life at baseline and 12-month follow-up, and whether the introduction of additional variables increased the strength of the relationship between the eFI and quality of life.

The dependent variables in the multiple regression analyses were therefore quality of life at baseline and 12-month follow-up, whilst the independent variables were:

- eFI at baseline
- Age
- Gender
- Deprivation status
- Disease status group
- Anxiety
- Depression
- Fatigue
- Social participation
- Social contacts
- Emotional support
- Healthcare use

No adjustments were made for multiple testing.

Two key assumptions for multiple regression methods relate to sample size and co-linearity.

a) Sample size: The sample size calculation is described in section 5.4.1 on page 126.

b) Collinearity: Collinearity or multi-collinearity exists when two or more independent variables within a regression model are highly correlated (177). If two variables are highly correlated then one of the highly inter-correlated independent variables should be removed from the model (177). This is because two highly correlated independent variables would explain much of the same variation in the dependent variable, thus the addition of the second or removal of the first of the two such variables would have little effect on the model in terms of explaining remaining variability, thus obscuring its true relationship to the outcome variable (187).

Testing the multicollinearity assumption for the multiple regression model:

The multicollinearity assumption was first tested using correlations. It is advised that if two variables show a bivariate correlation of greater than 0.7, then the removal from the model of one of the highly inter-correlated independent variables should be considered (177). A correlation matrix was therefore constructed for the independent variables, in order to confirmed that none of the correlation coefficients exceeded 0.7.

In addition to checking for correlation between the independent variables in the model, the multicollinearity assumptions were also tested using the collinearity variance inflation factor and/or the collinearity tolerance. The variance inflation factor (VIF) assesses the extent of multicollinearity by measuring how much of the variance of an estimated regression coefficient is increased because of collinearity. The higher the VIF the greater the risk of collinearity; a VIF of 10 is usually chosen as a cut off point below which collinearity need not be a cause for concern. The collinearity tolerance is the reciprocal of the VIF, therefore lower values of collinearity tolerance indicate greater collinearity, and 0.1 is usually considered to be the cut off point above which collinearity need not be a cause for concern (177,187).

In this study none of the variables had bivariate correlation above 0.7, collinearity tolerance less than 0.1 or collinearity variance inflation factor greatr than 10. Therefore none of the variables were excluded from the multiple regression analysis on the ground of collinearity.

The multiple regression method used allowed the independent variables to be entered into the model in an order based on clinical and theoretical grounds related to the underlying frailty

concepts and model under investigation, compared to stepwise regression, which adds or removes variables on a purely statistical basis. Variables or sets of variables are entered in steps, with each variable assessed for the additional contribution it makes to the prediction of the dependent variable after controlling for the previous variables. In the final model, the overall model is assessed for the ability to predict the dependent variable and the relative contribution of each block of variables is also assessed (177). These methods allowed potential steps in the model building to be identified based upon clinical and theoretical rationale and then tested mathematically, rather than selecting steps purely based upon statistical characteristics.

The analyses were intended to investigate the clinical question of how well eFI at baseline could predict quality of life at 12-months, after controlling for socio-demographic variables (age, gender and deprivation status) and whether this prediction could be improved by adding in variables representing psychological status, fatigue, social networks and healthcare use. The disease status group variable was not included in this stage of the analysis because of its conceptual and concrete relationship with the eFI, in other words, because all diseases used to define the disease status groups had Read Codes associated with eFI deficits and therefore these conditions were already represented in the model through the eFI variable.

The independent variables were therefore entered into the regression model in the following blocks:

1. Age, gender, deprivation status
2. eFI at baseline
3. Anxiety, depression, fatigue, social participation, social contacts, emotional support, healthcare use

The total variance of quality of life at baseline and at 12 months follow-up explained by the eFI at baseline, after controlling for age, gender and deprivation status was described. The further contribution of anxiety, depression, fatigue, social participation, social contacts, emotional support and healthcare use to the total variance of quality of life at baseline and 12-months follow-up time-points was also described.

5.5 Results

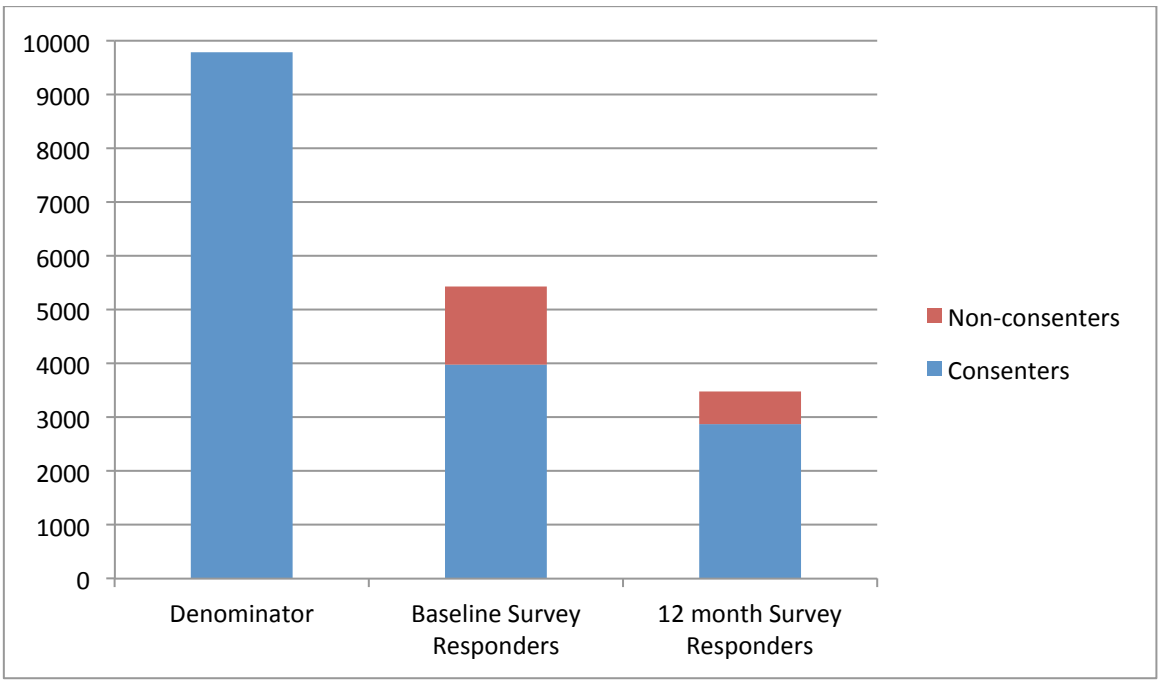
5.5.1 Study population numbers

The number of people in the study population and how this was derived from the denominator population is described in Table 5.2 and Figure 5.2

Table 5.2: Numbers in the different population groups within the 2C study

	Total	Consenters to linkage of survey data	Non-consenters to linkage of survey data
Denominator Population	9793		
Survey population			
Baseline responders	5426	3984	1442
12 month responders	3484	2878	606
Study Population	2878		

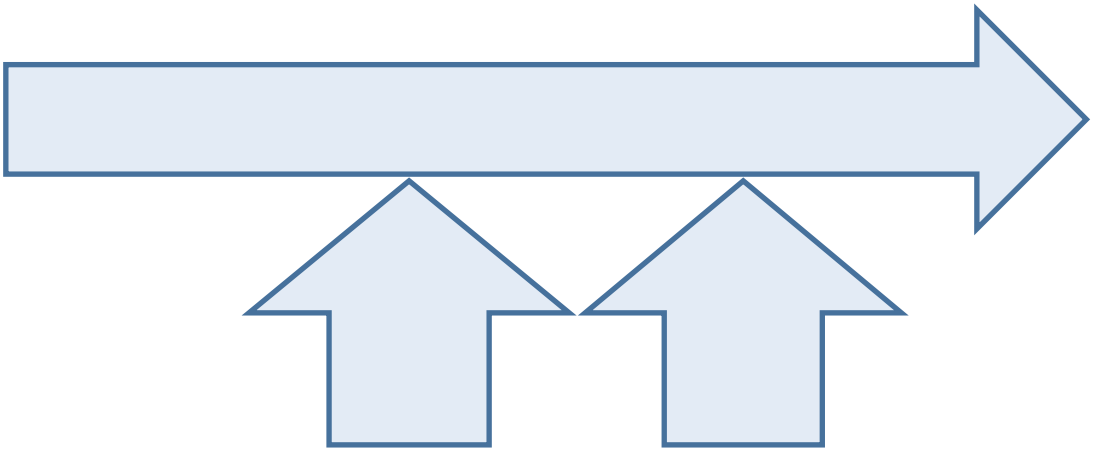
Figure 5.2: Numbers in the different population groups within the 2C study



The denominator population for the 2C study was 9793, and that was also therefore the number for the denominator population in this study. In the surveys, 2878 people responded to both the baseline and 12 month follow up surveys and consented for the survey data to be linked to the primary care consultation data.

A summary of the data available for the denominator and study populations is shown in Figure 5.3.

Figure 5.3: Summary of the data available for the denominator and study populations.



5.5.2 Frailty in the denominator population

These results are described in section 4.5.2-4 (pages 96-102).

5.5.3 Comparing the survey population with the denominator population

Mean eFIs, and standard deviations, for the study population and the denominator population at 3, 4 and 5 years are shown in Table 5.3

Table 5.3: Mean eFIs and Standard Deviations at 3,4 and 5 years.

	Denominator population	Surveyed population
3 year eFI (SD)	0.053 (0.049)	0.055 (0.048)
4 year eFI (SD)	0.062 (0.056)	0.064 (0.054)
5 year eFI (SD)	0.072 (0.062)	0.074 (0.061)

The mean eFI for the study population was slightly higher than that for the denominator population at all the time points considered. A formal statistical comparison was not possible because although the survey population is a subset of the denominator population, the two datasets were not linked for reasons of anonymity.

The people in the study population disease status reference group, with neither osteoarthritis nor cardiovascular disease, had the potential to have no deficits at three years. However, people in all the other disease status groups would, by definition due to the method of selection, all have at least one deficit. Therefore the maximum number of people with no deficits at three years could not exceed the number of people in the study disease status reference group. The number of people in the study population with no deficits at 3 years was 584 and the number of people in the disease status reference group was 595. These findings therefore validated the analytical approach taken.

Table 5.4: Mean eFI scores at 5, 4 and 3 years for the denominator population and surveyed population by socio-demographic disease status characteristics

Variables	Categories	Denominator population				Surveyed Population			
		Number n = 9793 (%)	Mean eFI (SD)			Number n = 2878 (%)	Mean eFI (SD)		
			5 years	4 years	3 years		5 years	4 years	3 years
Age (years)	40-49	1745 (17.8)	0.028 (0.034)	0.025 (0.032)	0.021 (0.028)	200 (6.9)	0.023 (0.032)	0.019 (0.029)	0.016 (0.025)
	50-59	2221 (22.7)	0.048 (0.045)	0.042 (0.041)	0.036 (0.037)	520 (18.1)	0.042 (0.042)	0.036 (0.038)	0.031 (0.034)
	60-69	2654 (27.1)	0.073 (0.053)	0.063 (0.048)	0.055 (0.043)	924 (32.1)	0.065 (0.050)	0.057 (0.045)	0.049 (0.040)
	70-79	2157 (22.0)	0.104 (0.065)	0.090 (0.059)	0.077 (0.052)	820 (28.5)	0.094 (0.062)	0.080 (0.056)	0.069 (0.049)
	80-89	943 (9.6)	0.127 (0.072)	0.111 (0.065)	0.093 (0.058)	389 (13.5)	0.120 (0.069)	0.103 (0.060)	0.089 (0.053)
	90-99	72 (0.7)	0.118 (0.064)	0.107 (0.061)	0.093 (0.061)	25 (0.9)	0.114 (0.066)	0.102 (0.058)	0.088 (0.056)
Gender	Male	4775 (48.8)	0.066 (0.058)	0.058 (0.052)	0.049 (0.047)	1428 (49.6)	0.073 (0.059)	0.062 (0.053)	0.054 (0.047)
	Female	5018 (51.2)	0.077 (0.066)	0.067 (0.059)	0.057 (0.052)	1450 (50.4)	0.075 (0.063)	0.065 (0.056)	0.056 (0.049)
Deprivation Status	Category 1(most affluent)	2376 (24.3)	0.062 (0.059)	0.054 (0.053)	0.047 (0.047)	817 (28.5)	0.064 (0.057)	0.055 (0.051)	0.048 (0.046)
	Category 2	2442 (24.9)	0.070 (0.060)	0.060 (0.053)	0.051 (0.047)	786 (27.5)	0.072 (0.059)	0.062 (0.052)	0.053 (0.047)
	Category 3	2453 (25.0)	0.074 (0.062)	0.064 (0.055)	0.055 (0.049)	700 (24.5)	0.076 (0.058)	0.065 (0.052)	0.057 (0.046)
	Category 4(most deprived)	2485 (25.4)	0.080 (0.066)	0.070 (0.056)	0.059 (0.053)	559 (19.5)	0.087 (0.067)	0.075 (0.056)	0.065 (0.052)
Disease Status Group*	-CVD -OA	2529 (25.8)	0.023 (0.032)	0.019 (0.028)	0.014 (0.023)	595 (20.7)	0.023 (0.031)	0.018 (0.026)	0.013 (0.021)
	+HT -OA	1334 (13.6)	0.068 (0.046)	0.060 (0.040)	0.053 (0.034)	374 (13.0)	0.071 (0.045)	0.062 (0.040)	0.055 (0.032)
	+IHD –OA	2095 (21.4)	0.098 (0.059)	0.085 (0.053)	0.074 (0.046)	639 (22.2)	0.098 (0.055)	0.084 (0.048)	0.072 (0.042)
	+HF –OA	276 (2.8)	0.138 (0.070)	0.122 (0.065)	0.106 (0.062)	64 (2.2)	0.144 (0.070)	0.127 (0.064)	0.114 (0.060)
	+OA -CVD	1336 (13.6)	0.052 (0.046)	0.044 (0.042)	0.035 (0.037)	462 (16.1)	0.051 (0.046)	0.042 (0.041)	0.034 (0.037)
	+HT +OA	1662 (17.0)	0.096 (0.057)	0.085 (0.051)	0.075 (0.044)	555 (19.3)	0.091 (0.056)	0.080 (0.050)	0.070 (0.043)
	+IHD +OA	492 (5.0)	0.139 (0.069)	0.123 (0.063)	0.107 (0.057)	168 (5.8)	0.141 (0.066)	0.123 (0.060)	0.109 (0.054)
	+HF +OA	69 (0.7)	0.178 (0.076)	0.156 (0.074)	0.138 (0.067)	21 (0.7)	0.186 (0.064)	0.161 (0.067)	0.146 (0.065)

*CVD=cardiovascular disease and includes HT=hypertension, IHD=ischaemic heart disease, HF=heart failure, OA=osteoarthritis

Table 5.4 shows a comparison between the socio-demographic characteristics, disease status groups and eFIs calculated at 3, 4 and 5 years for the denominator population (n=9793) and those of the surveyed population (n=2878).

Age: Compared to the denominator population, a smaller proportion of people in the surveyed population were in the youngest two age bands (6.9% compared to 17.8% in the 40-49 year age band and 18.1% compared to 22.7% in the 50-59 year age bands). However, a greater proportion of people were in all the age bands between 60 and 89 years (32.1% compared to 27.1% in the 60-69 year age band, 28.5% compared to 22.0% in the 70-79 year age band and 13.5% compared to 9.6% in the 80-89 year age band).

Gender: The proportions of males and females were very similar for both populations (denominator population 48.8% males and 51.2% females and surveyed population 49,6% and 50.4% respectively).

Deprivation: People from the most deprived quartile of the denominator population were proportionately under-represented in the surveyed population (19.5% compared to 25.4%). However, people from the two least deprived quartiles of the denominator population were proportionately over represented in the study population (28.5% compared to 24.3% for the most affluent quartile and 27.5% compared to 24.9% for the second least deprived quartile). The proportions of people in the second most deprived quartile were very similar in both population groups (24.5% in study population compared to 25.0% in the denominator population).

Disease status: The disease status group characteristics of the surveyed population were broadly similar to those of the denominator population. However, compared to the denominator population, a smaller proportion of people in the surveyed population were in the reference group with neither osteoarthritis nor cardiovascular comorbidities (20.7% study population compared to 25.8% denominator population) and a greater proportion of people were in the osteoarthritis (16.1% study population compared to 13.6% denominator population) and osteoarthritis with hypertension (19.3% study population compared to 17.0% denominator population) groups. The proportions of

people in the other groups were very similar in both populations: hypertension 13.6% in denominator and 13.0% in surveyed population; ischaemic heart disease 21.4% in denominator and 22.2% in surveyed population; heart failure 2.8% in denominator and 2.2% in surveyed population; ischaemic heart disease with osteoarthritis 5.0% in denominator and 5.8% in surveyed population and heart failure with osteoarthritis 0.7% in both populations.

Overall, when compared to the denominator population, the surveyed population were slightly older and more affluent, with a lower proportion of people in the disease status reference group and slightly higher proportions of people with osteoarthritis and osteoarthritis with hypertension. These age and disease status differences in the population profile would be likely to increase overall levels of frailty in the study population compared to the denominator population, whilst this difference in deprivation profile of the population would be likely to reduce the overall frailty levels.

In summary, in the study population compared to the denominator population, there was some selection bias in favour of people aged over 60 years and people with lower levels of deprivation. With respect to disease status, there was some selection bias away from people with neither cardiovascular comorbidity nor osteoarthritis, and towards those with osteoarthritis alone or in combination with hypertension. Overall, the study population was slightly older and with greater levels of cardiovascular and osteoarthritis comorbidity, and therefore slightly more frail than the denominator population at both baseline and follow-up time points.

5.5.4 Investigating associations between socio-demographic and comorbidity characteristics and quality of life and change in quality of life.

The quality of life scores and the way in which they changed over two years by socio-demographic and disease status characteristics are described in Table 5.5. Quality of life decreased with increasing age, 0.796 (SD 0.271) in the 40-49 years age group compared to 0.545 (SD 0.265) in those aged >90 years. It also decreased with increasing deprivation, 0.734 (SD 0.249) in least deprived group compared to 0.601 (SD 0.318) in the most deprived group, and with comorbidity severity, 0.826 (SD 0.200) in the reference group compared to 0.442 (SD 0.325) in the group with osteoarthritis and heart failure.

Table 5.5: Mean quality of life scores at baseline and 12 month follow up, and the change over this 12 month period, by socio-demographic characteristics disease status group in the study population

Variables	Categories	Number n = 2878 (%)	Mean EQ-5D score at baseline (SD)	Mean eFI EQ-5D score at 12 month follow up (SD)	Mean change in EQ-5D score over 12 months (SD)
Age (years)	40-49	197 (6.8)	0.796 (0.271)	0.791 (0.283)	-0.006 (0.156)
	50-59	513 (17.8)	0.737 (0.281)	0.728 (0.280)	-0.006 (0.208)
	60-69	908 (31.5)	0.703 (0.276)	0.677 (0.290)	-0.026 (0.212)
	70-79	803 (27.9)	0.657 (0.276)	0.634 (0.280)	-0.021 (0.213)
	80-89	364 (12.6)	0.604 (0.278)	0.601 (0.272)	-0.015 (0.206)
	90-99	24 (0.8)	0.545 (0.265)	0.520 (0.273)	-0.032 (0.230)
Gender	Male	1391 (48.3)	0.705 (0.275)	0.695 (0.280)	-0.010 (0.203)
	Female	1418 (49.3)	0.672 (0.286)	0.647 (0.292)	-0.026 (0.211)
Deprivation Status	Category 1 (most affluent)	795 (27.6)	0.734 (0.249)	0.719 (0.257)	-0.013 (0.187)
	Category 2	772 (26.8)	0.710 (0.264)	0.686 (0.282)	-0.022 (0.201)
	Category 3	680 (23.6)	0.686 (0.290)	0.670 (0.286)	-0.018 (0.205)
	Category 4 (most deprived)	546 (19.0)	0.601 (0.318)	0.581 (0.316)	-0.020 (0.244)
Disease Status Group*	-CVD -OA	588 (20.4)	0.826 (0.200)	0.815 (0.203)	-0.011 (0.161)
	+HT –OA	368 (12.8)	0.785 (0.215)	0.752 (0.230)	-0.033 (0.178)
	+IHD –OA	620 (21.5)	0.694 (0.279)	0.677 (0.269)	-0.019 (0.202)
	+HF –OA	62 (2.2)	0.576 (0.221)	0.488 (0.298)	-0.082 (0.249)
	+OA -CVD	446 (15.5)	0.635 (0.282)	0.623 (0.287)	-0.008 (0.247)
	+HT +OA	543 (18.9)	0.582 (0.304)	0.571 (0.312)	-0.008 (0.225)
	+IHD +OA	163 (5.7)	0.523 (0.303)	0.495 (0.334)	-0.031 (0.233)
	+HF +OA	19 (0.7)	0.442 (0.325)	0.452 (0.275)	-0.032 (0.218)
*CVD=cardiovascular disease and includes HT=hypertension, IHD=ischaemic heart disease, HF=heart failure, OA=osteoarthritis					

These results also demonstrated that quality of life decreased over a 12-month period for all groups within all variables. However, the rate of deterioration in quality of life varied with the socio-demographic and disease group characteristics in the surveyed population. By age, this change was least for age groups under 60 years old, -0.006 (SD 0.156), and greatest for those aged > 90 years, -0.032 (SD 0.230). By deprivation, the change was least in the most affluent group, -0.013 (SD 0.187) and greater and similar for all other deprivation categories, -0.018 (SD0.205) to -0.022 (SD 0.201), and by disease status group it was least in the reference, OA and hypertension groups, -0.008 (SD 0.247) and highest in the heart failure group, -0.082 (SD 0.249).

These results showed that quality of life, and change in quality of life, varied by socio-demographic and disease status characteristics in the study population. These factors could act as potential confounders in the association between frailty and quality of life and adjustments were therefore made in the analysis that followed in section 5.5.5.

5.5.5 Investigating the relationship between other explanatory factors, frailty and quality of life

The available dataset was assessed by considering the number of missing values for each of the variables and outcomes at both baseline and 12-month follow-up (Table 5.6).

Table 5.6: Missing values for variables in the surveyed population.

Variable/outcome	Source	Baseline		12 month follow up	
		N (/2878)	Missing (%)	N (/2878)	Missing (%)
Anxiety	Survey	2799	79 (2.7)	2810	68 (2.4)
Depression	Survey	2797	81 (2.8)	2809	69 (2.4)
Fatigue	Survey	2806	72 (2.5)	2816	62 (2.2)
Social contact	Survey	2846	32 (1.1)	2834	44 (1.5)
Social participation	Survey	2824	54 (1.9)	2816	62 (2.2)
Emotional support	Survey	2780	98 (3.4)	2749	129 (4.5)
Healthcare contacts	Consultation data	2878	0	2878	0
eFI	Consultation data	2878	0	2878	0
Quality of life	Survey	2809	69 (2.4)	2823	55 (1.9)

The healthcare use measure and eFI variables were calculated from the consultation data for the surveyed population. Consultation data was available for all individuals and therefore there were no

missing values for these variables. The psychological status (anxiety and depression), fatigue, social network (social contacts, social participation, emotional support) and quality of life variables were obtained through survey data, provided through self-reported postal questionnaires. The number of missing values per variable ranged from 1.1%-3.4% at baseline and from 1.5%-4.5% at 12-month follow-up. At both survey points, the variable with the fewest missing values was social contact and the variable with the most missing values was emotional support. Excluding the emotional support variable, at baseline all other variables had <3% missing values and at 12-month follow-up this figure was <2.5%. Levels of missing data below 5% are generally considered minimal and should not introduce bias therefore imputing missing data was not required (188).

Summary descriptive statistics for eFI and quality of life in the study population at baseline and 12 month follow up are shown in Table 5.7.

Table 5.7: Mean (and standard deviation) eFI and quality of life at baseline and 12 month follow up

Survey point	eFI		Quality of life	
	n	Mean (SD)	n	Mean (SD)
Baseline (3 yrs)	2878	0.055 (0.048)	2809	0.688 (0.281)
12 month follow up (4 years)	2878	0.064 (0.054)	2823	0.671 (0.287)

Table 5.8 shows the eFI at 3 years (mean and standard deviation) by the three other explanatory factors (HAD, social network status and fatigue) and two linear regression models showing the differences (and 95% confidence intervals) between the groups within each category compared to the reference group for each variable. The first model was unadjusted and the second then adjusted for age, gender, deprivation status and disease status group. Table 5.9 shows the same estimations with respect to the change in eFI during the 12 month follow up period.

Table 5.10 shows the quality of life score at baseline (mean and standard deviation) by the three other explanatory factors and two linear regression models showing the differences (and 95% confidence intervals) between the groups within each category compared to the reference group for each variable. The first model was unadjusted and then the second adjusted for age, gender, deprivation status and disease status group. Table 5.11 shows the same calculations with respect to the change in quality of life scores during the 12-month follow up period.

Table 5.8: Other explanatory factors and baseline eFI at 3 years

Variables	Categories	Number (%)	Mean baseline eFI (SD)	*Unadjusted difference in eFI (95% CI)	**Adjusted difference in eFI (95% CI)
Anxiety	Not anxious	1888 (65.6)	0.050 (0.045)	0	0
	Borderline anxious	531 (18.5)	0.064 (0.051)	0.014 (0.010 to 0.019)	0.012 (0.008 to 0.016)
	Probable anxious	380 (13.2)	0.065 (0.056)	0.015 (0.010 to 0.020)	0.013 (0.009 to 0.018)
Depression	Not depressed	2212 (76.9)	0.049 (0.044)	0	0
	Borderline depressed	385 (13.4)	0.073 (0.056)	0.023 (0.018 to 0.028)	0.014 (0.010 to 0.019)
	Probable depressed	200 (6.9)	0.076 (0.057)	0.026 (0.019 to 0.033)	0.018 (0.012 to 0.024)
Fatigue category	Q1 Least fatigued	642 (22.3)	0.036 (0.035)	0	0
	Q2	683 (23.7)	0.049 (0.044)	0.009 (0.005 to 0.014)	0.006 (0.002 to 0.010)
	Q3	717 (24.9)	0.059 (0.046)	0.020 (0.015 to 0.024)	0.012 (0.008 to 0.016)
	Q4 Most fatigued	764 (25.7)	0.077 (0.056)	0.037 (0.032 to 0.042)	0.025 (0.021 to 0.029)
Social Participation category	None	1885 (65.5)	0.053 (0.047)	0	0
	Low	403 (14)	0.059 (0.050)	0.005 (0.000 to 0.010)	0.001 (-0.004 to 0.005)
	Medium	456 (15.8)	0.058 (0.050)	0.004 (-0.001 to 0.009)	0.001 (-0.004 to 0.005)
	High	80 (2.7)	0.051 (0.054)	-0.002 (-0.013 to 0.009)	-0.004 (-0.013 to 0.005)
Social Contacts category	None	234 (8.1)	0.059 (0.048)	0	0
	Low	926 (32.2)	0.056 (0.048)	-0.003 (-0.010 to 0.004)	0.000 (-0.006 to 0.006)
	Medium	1425 (49.5)	0.053 (0.048)	-0.005 (-0.012 to 0.001)	-0.001 (-0.007 to 0.005)
	High	293 (10.2)	0.057 (0.049)	-0.003 (-0.011 to 0.005)	-0.002 (-0.009 to 0.005)
Close confidant	Yes	2377 (82.6)	0.054 (0.048)	0	0
	No	403 (14)	0.054 (0.044)	0.000 (-0.005 to 0.005)	0.000 (-0.005 to 0.004)
Healthcare use	Q1 Lowest	741 (25.7)	0.027 (0.029)	0	0
	Q2	773 (26.9)	0.044 (0.036)	0.017 (0.013 to 0.021)	0.008 (0.004 to 0.012)
	Q3	666 (23.1)	0.062 (0.042)	0.035 (0.030 to 0.039)	0.021 (0.017 to 0.025)
	Q4 Highest	697 (24.2)	0.090 (0.058)	0.062 (0.058 to 0.066)	0.062 (0.042 to 0.051)

*Difference in eFI at 3 years for each group compared to their respective reference group
**Adjusted model includes age, gender, deprivation status and disease status group.

Table 5.9: Other explanatory factors and change in eFI over 12 months

Variables	Categories	Number (%)	Mean eFI change (SD)	*Unadjusted difference in eFI change (95% CI)	**Adjusted difference in eFI change (95% CI)
Anxiety	Not anxious	1888 (65.6)	0.008 (0.016)	0	0
	Borderline anxious	531 (18.5)	0.011 (0.020)	0.003 (0.001 to 0.004)	0.002 (0.001 to 0.004)
	Probable anxious	380 (13.2)	0.011 (0.018)	0.003 (0.001 to 0.004)	0.003 (0.001 to 0.005)
Depression	Not depressed	2212 (76.9)	0.008 (0.016)	0	0
	Borderline depressed	385 (13.4)	0.012 (0.021)	0.004 (0.002 to 0.006)	0.003 (0.001 to 0.005)
	Probable depressed	200 (6.9)	0.012 (0.019)	0.004 (0.001 to 0.006)	0.003 (0.001 to 0.005)
Fatigue category	Q1 Least fatigued	642 (22.3)	0.006 (0.014)	0	0
	Q2	683 (23.7)	0.007 (0.015)	0.001 (-0.001 to 0.003)	0.000 (-0.001 to 0.002)
	Q3	717 (24.9)	0.011 (0.020)	0.004 (0.002 to 0.006)	0.003 (0.002 to 0.005)
	Q4 Most fatigued	764 (25.7)	0.012 (0.020)	0.006 (0.004 to 0.007)	0.004 (0.003 to 0.006)
Social Participation category	None	1885 (65.5)	0.008 (0.107)	0	0
	Low	403 (14)	0.010 (0.019)	0.002 (0.000 to 0.003)	0.001 (-0.001 to 0.003)
	Medium	456 (15.8)	0.008 (0.016)	0.000 (-0.002 to 0.001)	-0.001 (-0.003 to 0.001)
	High	80 (2.7)	0.012 (0.020)	0.003 (-0.001 to 0.007)	0.003 (-0.001 to 0.007)
Social Contacts category	None	234 (8.1)	0.009 (0.018)	0	0
	Low	926 (32.2)	0.009 (0.018)	0.000 (-0.003 to 0.002)	0.000 (-0.002 to 0.003)
	Medium	1425 (49.5)	0.009 (0.016)	-0.001 (-0.003 to 0.002)	-0.001 (-0.002 to 0.002)
	High	293 (10.2)	0.009 (0.017)	-0.001 (-0.003 to 0.003)	-0.001 (-0.003 to 0.003)
Close confidant	Yes	2377 (82.6)	0.009 (0.017)	0	0
	No	403 (14)	0.008 (0.016)	-0.001 (-0.003 to 0.001)	-0.001 (-0.003 to 0.001)
Healthcare use	Q1 Lowest	741 (25.7)	0.005 (0.013)	0	0
	Q2	773 (26.9)	0.006 (0.014)	0.001 (-0.001 to 0.003)	0.001 (-0.002 to 0.002)
	Q3	666 (23.1)	0.010 (0.019)	0.005 (0.003 to 0.007)	0.003 (0.002 to 0.005)
	Q4 Highest	697 (24.2)	0.015 (0.022)	0.009 (0.007 to 0.011)	0.007 (0.006 to 0.009

*Difference in eFI change over 12 months for each group compared to their respective reference group
**Adjusted model includes age, gender, deprivation status and disease status group.

Table 5.10: Other explanatory factors and baseline EQ-5D score

Variables	Categories	Number (%)	Mean baseline EQ-5D (SD)	*Unadjusted difference in EQ-5D (95% CI)	**Adjusted difference in EQ-5D (95% CI)
Anxiety	Not anxious	1843 (64.0)	0.766 (0.229)	0	0
	Borderline anxious	523 (18.2)	0.611 (0.265)	-0.152 (-0.177 to -0.128)	-0.135 (-0.158 to -0.112)
	Probable anxious	372 (12.9)	0.414 (0.340)	-0.350 (-0.378 to -0.321)	-0.326 (-0.353 to -0.300)
Depression	Not depressed	2165 (75.2)	0.763 (0.216)	0	0
	Borderline depressed	375 (13.0)	0.491 (0.279)	-0.269 (-0.295 to -0.243)	-0.234 (-0.259 to -0.243)
	Probable depressed	197 (6.8)	0.257 (0.344)	-0.505 (-0.540 to -0.470)	-0.462 (-0.495 to -0.429)
Fatigue category	Q1 Least fatigued	627 (21.8)	0.873 (0.152)	0	0
	Q2	668 (23.2)	0.780 (0.188)	-0.069 (-0.092 to -0.046)	-0.058 (-0.080 to -0.035)
	Q3	703 (24.2)	0.649 (0.229)	-0.199 (-0.223 to -0.175)	-0.169 (-0.192 to -0.146)
	Q4 Most fatigued	747 (26.0)	0.420 (0.304)	-0.429 (-0.453 to -0.405)	-0.382 (-0.405 to -0.358)
Social Participation category	None	1845 (64.1)	0.682 (0.289)	0	0
	Low	393 (13.7)	0.696 (0.263)	0.019 (-0.012 to 0.050)	0.033 (0.004 to 0.061)
	Medium	442 (15.4)	0.719 (0.254)	0.040 (0.011 to 0.069)	0.050 (0.023 to 0.078)
	High	78 (2.7)	0.702 (0.308)	0.022 (-0.042 to 0.086)	0.023 (-0.036 to 0.082)
Social Contacts category	None	221 (7.7)	0.688 (0.264)	0	0
	Low	912 (31.7)	0.669 (0.298)	-0.017 (-0.059 to 0.024)	-0.025 (-0.064 to 0.13)
	Medium	1392 (48.4)	0.700 (0.272)	0.014 (-0.026 to 0.054)	0.007 (-0.030 to 0.044)
	High	284 (9.9)	0.693 (0.283)	0.010 (-0.040 to 0.059)	0.015 (-0.031 to 0.061)
Close confidant	Yes	2323 (80.7)	0.693 (0.282)	0	0
	No	393 (13.7)	0.668 (0.277)	-0.026 (-0.056 to 0.004)	-0.023 (-0.051 to 0.005)
Healthcare use	Q1 Lowest	726 (25.2)	0.795 (0.233)	0	0
	Q2	754 (26.2)	0.717 (0.261)	-0.079 (-0.106 to -0.051)	-0.038 (-0.064 to -0.011)
	Q3	651 (22.6)	0.673 (0.257)	-0.122 (-0.151 to -0.094)	-0.053 (-0.081 to -0.025)
	Q4 Highest	677 (23.5)	0.557 (0.317)	-0.239 (-0.267 to -0.210)	-0.147 (-0.176 to -0.119)

*Difference in baseline EQ-5D for each group compared to their respective reference group
**Adjusted model includes age, gender, deprivation status and disease status group.

Table 5.11: Other explanatory factors and change in EQ-5D score over 12 months

Variables	Categories	Number (%)	Mean EQ-5D change (SD)	*Unadjusted difference in EQ-5D change (95% CI)	**Adjusted difference in EQ-5D change (95% CI)
Anxiety	Not anxious	1843 (64.0)	-0.021 (0.185)	0	0
	Borderline anxious	523 (18.2)	-0.012 (0.218)	0.011 (-0.010 to 0.031)	0.012 (-0.008 to 0.033)
	Probable anxious	372 (12.9)	-0.010 (0.287)	0.011 (-0.012 to 0.035)	0.013 (-0.011 to 0.036)
Depression	Not depressed	2165 (75.2)	-0.025 (0.184)	0	0
	Borderline depressed	375 (13.0)	-0.001 (0.256)	0.023 (0.000 to 0.046)	0.024 (0.000 to 0.047)
	Probable depressed	197 (6.8)	0.0262 (0.319)	0.054 (0.024 to 0.085)	0.055 (0.024 to 0.086)
Fatigue category	Q1 Least fatigued	627 (21.8)	-0.007 (0.284)	0	0
	Q2	668 (23.2)	-0.021 (0.206)	0.015 (-0.007 to 0.036)	0.015 (-0.006 to 0.036)
	Q3	703 (24.2)	-0.013 (0.170)	0.006 (-0.015 to 0.028)	0.009 (-0.013 to 0.030)
	Q4 Most fatigued	747 (26.0)	-0.027 (0.149)	0.022 (0.000 to 0.044)	0.024 (0.000 to 0.046)
Social Participation category	None	1845 (64.1)	-0.011 (0.212)	0	0
	Low	393 (13.7)	-0.027 (0.203)	-0.016 (-0.039 to 0.007)	-0.014 (-0.037 to 0.10)
	Medium	442 (15.4)	-0.034 (0.186)	-0.023 (-0.045 to -0.001)	-0.020 (-0.042 to 0.002)
	High	78 (2.7)	-0.030 (0.233)	-0.018 (-0.065 to 0.030)	-0.015 (-0.063 to 0.032)
Social Contacts category	None	221 (7.7)	-0.037 (0.189)	0	0
	Low	912 (31.7)	-0.011 (0.206)	0.026 (-0.005 to 0.057)	0.026 (-0.006 to 0.057)
	Medium	1392 (48.4)	-0.022 (0.208)	0.015 (-0.015 to 0.045)	0.014 (-0.016 to 0.068)
	High	284 (9.9)	-0.005 (0.220)	0.031 (-0.006 to 0.068)	0.030 (-0.007 to 0.068)
Close confidant	Yes	2323 (80.7)	-0.017 (0.206)	0	0
	No	393 (13.7)	-0.010 (0.213)	0.008 (-0.014 to 0.031)	0.005 (-0.018 to 0.027)
Healthcare use	Q1 Lowest	726 (25.2)	-0.011 (0.160)	0	0
	Q2	754 (26.2)	-0.012 (0.207)	-0.001 (-0.022 to 0.020)	-0.001 (-0.023 to 0.021)
	Q3	651 (22.6)	-0.029 (0.217)	-0.018 (-0.040 to 0.004)	-0.018 (-0.041 to 0.005)
	Q4 Highest	677 (23.5)	-0.021 (0.240)	-0.011 (-0.032 to 0.012)	-0.011 (-0.034 to 0.013

**Difference in change in EuroQol over 12 months for each group compared to their respective reference group
[**]Adjusted model includes age, gender, deprivation status and disease status group.

Anxiety:

eFI: The baseline eFI score was significantly higher in the 'borderline anxious' (0.014, 95% CI 0.010-0.019) and 'probable anxious' (0.015, 95% CI 0.010-0.020) categories compared to the 'not anxious' category, although there was no significant difference between the 'borderline anxious' and 'probable anxious' categories. These higher baseline eFI scores comparing anxiety categories to non-anxious category remained significant after adjustment for age, gender, deprivation status and disease status group (0.012, 95% CI 0.008-0.016 for 'borderline anxious' and 0.013, 95% CI 0.009-0.018 for 'probable anxious').

The change in eFI over 12 months was just significantly higher in the 'borderline anxious' (0.003, 95% CI 0.001-0.004) and 'probable anxious' (0.003, 95% CI 0.001-0.004) categories compared to the 'not anxious' category, although there was no significant difference between the 'borderline anxious' and 'probable anxious' categories. These differences in eFI change over 12 months by anxiety category remained just significant after adjustment for age, gender, deprivation status and disease status group (0.002, 95% CI 0.001-0.004 for 'borderline anxious' and 0.003, 95% CI 0.001-0.005 for 'probable anxious').

EQ-5D: There was a sequential deterioration in quality of life with increasing anxiety, with EQ-5D score significantly lower in the 'borderline anxious' (-0.152, 95% CI -0.177 to -0.128) category compared to the 'not anxious' category, and significantly lower again in the 'probable anxious' (-0.350, 95% CI -0.378 to -0.321) category. These differences in EQ-5D score by anxiety category remained significant after adjustment for age, gender, deprivation status and disease status group (-0.135, 95% CI -0.158 to -0.112 for 'borderline anxious' and -0.326, 95% CI -0.353 to -0.300 for 'probable anxious').

There was no significant difference in change in quality of life over 12 months with different levels of anxiety, either before or after adjustment for age, gender, deprivation status and disease status group.

In summary, the presence of anxiety was associated with a significantly higher baseline frailty score, and significantly increased frailty change over 12 months, but frailty and frailty change did not differ between levels of anxiety severity. Higher anxiety level was associated with significantly more reduced quality of life, but there was no association between anxiety and change in quality of life over 12 months.

Depression

eFI: The baseline eFI was significantly higher in the 'borderline depressed' (0.023, 95% CI 0.018-0.028) and 'probable depressed' (0.026, 95% CI 0.019-0.033) categories compared to the 'not depressed' category, although there was no significant difference between the 'borderline depressed' and 'probable depressed' categories. These differences in baseline eFI by depression category remained significant after adjustment for age, gender, deprivation status and disease status group (0.014, 95% CI 0.010-0.019 for 'borderline depressed' and 0.018, 95% CI 0.012-0.024 for 'probable depressed').

The change in eFI over 12 months was just significantly higher in the 'borderline depressed' (0.004, 95% CI 0.002-0.006) and 'probable depressed' (0.004, 95% CI 0.001-0.006) categories compared to the 'not depressed' category, although there was no significant difference between the 'borderline depressed' and 'probable depressed' categories. These differences in change in eFI over 12 months by depression category remained just significant after adjustment for age, gender, deprivation status and disease status group (0.003, 95% CI 0.001-0.005 for 'borderline depressed' and 0.003, 95% CI 0.001-0.005 for 'probable depressed').

EQ-5D: There was a sequential deterioration in quality of life with increasing depressed, with EQ-5D score significantly lower in the 'borderline depressed' (-0.269, 95% CI -0.295 to -0.243) category compared to the 'not depressed' category, and significantly lower again in the 'probable depressed' (-0.505, 95% CI -0.540 to -0.470) category. These differences in EQ-5D score by depression remained significant after adjustment for age, gender, deprivation status and disease status group (-0.234, 95% CI -0.259 to -0.243 for 'borderline depressed' and -0.462, 95% CI -0.495 to -0.429 for 'probable depressed').

The change in quality of life over 12 months was not significantly higher in the 'borderline depressed' (0.023, 95% CI 0.000-0.046) category compared to the 'not depressed' category, but was significantly higher in the 'probable depressed' (0.054, 95% CI 0.024-0.085) categories. These differences in change in quality of life over 12 months by depression category retained their significance (or lack of) after adjustment for age, gender, deprivation status and disease status group (0.024, 95% CI 0.000-0.047 for 'borderline depressed' and 0.055, 95% CI 0.024-0.086 for 'probable depressed').

In summary, the presence of depression was associated with significantly increased baseline frailty, and significantly increased change in frailty over 12 months, but frailty and frailty change did not differentiate by levels of depression severity. Higher levels of depression were associated with significantly reduced quality of life and the highest depression level was also associated with a significantly worsened quality of life over 12 months.

Fatigue

eFI: There was a sequential increase in baseline eFI score with increasing fatigue (by quartile), compared to the reference, least fatigued, group. The unadjusted difference in baseline eFI score for the second quartile was 0.009, 95% CI 0.005-0.014, for the third quartile was 0.020, 95% CI 0.015-0.024 and for the most fatigued quartile was 0.037, 95% CI 0.033-0.042. These differences in baseline eFI score by fatigue category remained significant after adjustment for age, gender, deprivation and disease status (second quartile 0.006, 95% CI 0.002-0.010; third quartile 0.012, 95% CI 0.008-0.016; most fatigued quartile 0.025, 95% CI 0.021-0.029).

There was no significant difference between the change in eFI over 12 months for the second least fatigued quartile compared to the least fatigued quartile, either before or after adjustment for age, gender, deprivation status and disease status group. The change in eFI over 12 months was significantly greater in the two most fatigued quartiles compared to the reference group (third quartile 0.004, 95% CI 0.002-0.006; most fatigued quartile 0.006, 95% CI 0.004-0.007), but there was no significant difference between these two groups. These differences remained significant after adjustment for age, gender, deprivation and disease status (third quartile 0.003, 95% CI 0.002-0.005; most fatigued quartile 0.004, 95% CI 0.003-0.006).

EQ-5D: There was also a sequential deterioration in quality of life with increasing fatigue (by quartile), compared to the reference, least fatigued, group. The unadjusted difference in EQ-5D score for the second quartile was -0.069, 95% CI -0.092 to -0.046; for the third quartile was -0.199, 95% CI -0.223 to -0.175 and for the most fatigued quartile was -0.429, 95% CI -0.453 to -0.405. These differences in EQ-5D score by fatigue category remained significant after adjustment for age, gender, deprivation status and disease status group (second quartile -0.058, 95% CI -0.080 to -0.035; third quartile -0.169, 95% CI -0.192 to -0.146; most fatigued quartile -0.382, 95% CI -0.405 to -0.358).

There was no significant difference in the change in quality of life over 12 months between any of the fatigue severity groups, either before or after adjustment for age, gender, deprivation status and disease status group.

In summary, fatigue was associated with significantly increased frailty and significantly lower quality of life and both increasing frailty and worse quality of life was associated with increasing fatigue levels. The two most fatigued groups also had a significantly greater change in eFI over 12 months compared to the two least fatigued groups.

Social Participation

eFI: There were no significant differences in the baseline eFI scores or the change in eFI over 12 months between any of the categories within the social participation variable when compared to the reference group for that variable, either before or after adjustment for age, gender, deprivation status and disease status group (95% CIs for all differences included zero within their range).

EQ-5D: There was a significant increase in EQ-5D score associated with medium (0.040, 95% CI 0.011-0.069) level of social participation compared to the reference group of no social participation. After adjustment for age, gender, deprivation status and disease status group the difference between the group with low level participation also became significant (0.033, 95% CI 0.004-0.061 for low participation; 0.050, 95% CI 0.023-0.078 for medium participation). There was no significant difference between the EQ-5D score for the category with a high level of social participation compared to the reference group either before or after adjustment (95% CI for both differences included zero within the range).

There were no significant differences in change in quality of life over 12 months between any of the categories within the social participation variable when compared to the reference group for that variable, either before or after adjustment for age, gender, deprivation status and disease status group (95% CIs for all differences included zero within their range).

In summary, differences in social participation were not associated with differences in frailty or frailty change over 12 months. There was a small association between low and medium levels of social participation and higher quality of life, but no difference in change in quality of life over 12 months.

Social contacts

eFI and EQ-5D: There were no significant differences in the baseline eFI score, change in eFI over 12 months, EQ-5D scores at 3 years or EQ-5D change over 12 months, either before or after adjustment for age, gender, deprivation status and disease status group, between any of the categories within the social contact variable when compared to the reference group (95% CIs for all differences included zero within their range).

Emotional support

eFI and EQ-5D: There were no significant differences in the influence of emotional support on baseline eFI, change in eFI over 12 months, baseline EQ-5D scores or EQ-5D change over 12 months, either before or after adjustment for age, gender, deprivation status and disease status group depending (95% CIs for all differences included zero within their range).

Healthcare use

eFI: For the healthcare use measure (which excluded codes contributing to the eFI score) there was a sequential increase in baseline eFI score with increasing healthcare use by quartile compared to the reference group with least healthcare use. The unadjusted difference in baseline eFI score for the second quartile was 0.017, 95% CI 0.013-0.021, for the third quartile was 0.035, 95% CI 0.030-0.039 and for the quartile with most healthcare use was 0.062, 95% CI 0.058-0.066. These differences in baseline eFI score by healthcare use category remained significant after adjustment for age, gender, deprivation status and disease status group (second quartile 0.008, 95% CI 0.004-0.012; third quartile 0.021, 95% CI 0.017-0.025; quartile with most healthcare contacts 0.062, 95% CI 0.042-0.051).

There was no significant difference between the change in eFI score over 12 months for the quartile with the second lowest healthcare use compared to the quartile with least use, either before or after adjustment for age, gender, deprivation status and disease status group. The change in eFI score over 12 months was significantly greater in the two quartiles with most healthcare use compared to the reference group (third quartile 0.005, 95% CI 0.003-0.007; most fatigued quartile 0.009, 95% CI 0.007-0.0011), and the difference between these two groups was significant. These differences remained significant after adjustment for age, gender, deprivation

status and disease status group (third quartile 0.003, 95% CI 0.002-0.005; most fatigued quartile 0.007, 95% CI 0.006-0.009).

EQ-5D: There was a sequential deterioration in quality of life with increasing healthcare contacts (by quartile), compared to the reference group with least healthcare contacts. The unadjusted difference in EQ-5D score for the second quartile was -0.079, 95% CI -0.106 to -0.051; for the third quartile was -0.122, 95% CI -0.151 to -0.094 and for the quartile with highest healthcare contacts was -0.239, 95% CI -0.267 to -0.210. These differences in EQ-5D score by healthcare contacts category remained significant after adjustment for age, gender, deprivation status and disease status group (second quartile -0.038, 95% CI -0.064 to -0.011; third quartile -0.053, 95% CI -0.081 to -0.025; quartile with most healthcare contacts -0.147, 95% CI -0.176 to -0.119).

There was no significant difference in the change in quality of life over 12 months between any of the healthcare use groups, either before or after adjustment for age, gender, deprivation status and disease status group.

In summary, increasing healthcare use in primary care was associated with increasing frailty and increasing frailty change over 12 months. Increasing healthcare contacts were also associated with decreasing quality of life but no difference in change in quality of life over 12 months. This indicated that people with increasing frailty also had increased healthcare contacts that were not directly related to their frailty (i.e. do not have codes which contribute to the eFI)

5.5.6 Investigating the relationship between eFI score and quality of life over 12 months

Correlations between eFI at baseline and quality of life at baseline and at 12 months were:

- Correlation between eFI at 3 years and baseline EQ-5D score (n=2809);

  Pearson Correlation -0.325, $p<0.001$, significant at the 0.01 level (2-tailed)

- Correlation between eFI at 3 years and 12 month EQ-5D score (n=2823);

  Pearson Correlation -0.333, $p<0.001$, significant at the 0.01 level (2-tailed)

Regression analysis of the relationship between eFI at baseline and quality of life at baseline and at 12 months gave the following results:

- The baseline eFI score explained 10.6% of the variance in quality of life at baseline survey; adjusted R square 0.106, standardised beta coefficient -0.325, $p<0.001$.
- The baseline eFI score explained 11.1% of the variance in quality of life at 12 month follow-up survey; adjusted R square 0.111, standardised beta coefficient -0.333, $p<0.001$.

The correlation between eFI score at baseline and quality of life did not change over 12-months.

5.5.7 Investigating eFI score as a predictor of quality of life

5.5.7.1 Correlation matrix

A correlation matrix was constructed to test the relationships between the following variables in the baseline survey data: anxiety, depression, levels of fatigue, social participation category, social contacts category and healthcare contacts category. The presence or absence of a close confidant was binary and therefore correlation testing was not relevant for this variable.

The correlation matrix is shown in Table 5.12. The findings were that the Pearson Correlation between social contacts and social participation, and all other categories, were between -0.200 and +0.120. The Pearson Correlation between healthcare contacts and anxiety was 0.198, between healthcare contacts and depression it was 0.229 and between healthcare contacts and level of fatigue it was -0.316. The Pearson Correlation between level of fatigue and level of anxiety was -0.497, between level of fatigue and level of depression was -0.527. The strongest correlation was between level of anxiety and level of depression +0.556. None of the correlations exceeded 0.7 and therefore none of these variables were excluded from the multiple regression analysis on the ground of collinearity.

Table 5.12: A correlation matrix to test the relationships between the independent variables from the baseline survey

Variables	Correlation data	Social participation	Anxiety	Depression	Fatigue	Healthcare use
Social contacts	Pearson correlation	0.118	-0.035	-0.076	0.059	0.033
	Significance	0.000	0.062	0.000	0.002	0.079
	Number	2824	2799	2797	2806	2877
Social participation	Pearson correlation		-0.049	-0.085	0.035	0.032
	Significance		0.010	0.000	0.064	0.088
	Number		2749	2747	2757	2823
Anxiety	Pearson correlation			0.556	-0.497	0.198
	Significance			0.000	0.000	0.000
	Number			2796	2739	2798
Depression	Pearson correlation				-0.527	0.229
	Significance				0.000	0.000
	Number				2737	2796
Fatigue	Pearson correlation					-0.316
	Significance					0.000
	Number					2805

5.5.7.2 Multiple Regression

Investigating the relationship between baseline eFI score and baseline quality of life:

The relationship between the baseline eFI score and quality of life was tested using multiple regression. The dependent variable was therefore quality of life at baseline.

The independent variables were entered into the regression model in the following blocks:

- age, gender, deprivation status
- eFI at baseline
- anxiety, depression, fatigue, social participation, social contacts, emotional support, healthcare use

Therefore the variables in the output models were as follows:

- Model 1: age, gender, deprivation status.
- Model 2: age, gender, deprivation status, baseline eFI score.
- Model 3: age, gender, deprivation status, baseline eFI score, anxiety, depression, fatigue, social participation, social contacts, emotional support, healthcare use.

Checking the assumptions:

- The strongest correlation between independent variables was between level of anxiety and level of depression +0.556 (none > 0.7).
- The minimum value for collinearity tolerance was 0.604 (none < 0.1).
- The maximum value for the collinearity variance inflation factor was 1.679 (none > 10).

The multicollinearity assumption was not therefore violated in this model. The model summary for this regression analysis is shown in Table 5.13.

Table 5.13: Model summary for the relationship between eFI and baseline quality of life

Model	Adjusted R square	R square change	Significance F change
1	0.058	0.059	p<0.001
2	0.123	0.065	p<0.001
3	0.451	0.328	p<0.001

Model 1 explained 5.9% of the variance in baseline quality of life. The addition of eFI score in Model 2 explained an additional 6.5% of the variance, and overall Model 2 explained 12.3% of the variance in baseline quality of life. The further addition of the psychological status, social network, fatigue and healthcare use variables in Model 3 explained an additional 32.8% of the variance in quality of life, and overall model 3 explained 45.1% of the variance in baseline quality of life. All these findings were statistically significant.

The contributions of each of the independent variables in Model 3 were then evaluated. The results are shown in Table 5.14.

Table 5.14: Coefficients and their significance for the independent variables in Model 3

Variable	Standardised Beta Coefficient	Significance
Age	-0.081	p<0.001
Gender	-0.016	p=0.289
Deprivation status	-0.046	p=0.002
Baseline eFI	-0.091	p<0.001
Fatigue score	0.338	p<0.001
Depression	-0.271	p<0.001
Anxiety	-0.095	p<0.001
Healthcare use	-0.044	p=0.009
Social participation	0.022	p=0.126
Social contacts	-0.016	p=0.272
Emotional support	0.008	p=0.592

The strongest estimate in the model was for the fatigue score (0.338), which was followed then by depression (-0.271), anxiety (-0.095), baseline eFI score (-0.091) and age (-0.081). All these values were significant at the level p<0.001. Deprivation status (-0.046, p=0.002) and healthcare use (-0.044, p=0.009) made lesser but still statistically significant contributions. The variables of gender (-0.016, p=0.289), social participation (0.022, p=0.126), social contacts (-0.016, p=0.272) and emotional support (0.008, p=0.592) were not statistically significant in this model.

As a result of these findings, an alternative to model 3, labelled model 4, was constructed which excluded the social network variables and included only the following variables:

- Model 4: age, gender, deprivation status, baseline eFI score, anxiety, depression, fatigue, healthcare use.

The model summary for this revised regression analysis is shown in Table 5.15.

Table 5.15: Summary of revised model for the relationship between eFI and quality of life at baseline

Model	Adjusted R square	R square change	Significance F change
1	0.058	0.059	p<0.001
2	0.123	0.065	p<0.001
4	0.450	0.327	p<0.001

The contributions of each of the independent variables in Model 4 were then evaluated. The results are shown in Table 5.16.

Table 5.16: Coefficients and their significance for the independent variables in Model 4

Variable	Standardised Beta Coefficient	Significance
Age	-0.078	p<0.001
Gender	-0.014	p=0.340
Deprivation status	-0.047	p=0.001
eFI at 3 years	-0.091	p<0.001
Fatigue score	0.337	p<0.001
Depression	-0.271	p<0.001
Anxiety	-0.095	p<0.001
Healthcare use	-0.044	p=0.008

Model 4, which included the psychological status, fatigue score and healthcare use variables in addition to the socio-demographic variables and baseline eFI score, but excluded the social network variables, explained as much of the variance in baseline EQ-5D as Model 3, which included the social network variables.

In summary, multiple regression was used to assess the relationship between baseline eFI score, psychological status, social network status, fatigue score and healthcare use, after controlling for age, gender and deprivation status, and baseline quality of life. Age, gender and deprivation status were entered at step 1 and explained 5.9% of the variance in quality of life at baseline. The eFI was

entered at step 2 and explained a further 6.5% of the variance. Anxiety, depression, fatigue score and healthcare use measures were entered at step 3 and explained a further 32.7% of the variance in quality of life at baseline. The social network variables, namely social participation, social contacts and emotional support were not included in the final model. The final model explained 45% of the variance in baseline quality of life.

Investigating the relationship between baseline eFI score and quality of life at 12-month follow-up:

In this phase of the analysis the dependent variable had changed was quality of life at 12-month follow up. However, the independent variables were the same as in the previous analysis and were entered into the regression model in the same blocks. Therefore the variables in the models in this section were as follows:

- Model 1a: age, gender, deprivation status.
- Model 2a: age, gender, deprivation status, baseline eFI score.
- Model 3a: age, gender, deprivation status, baseline eFI score, anxiety, depression, fatigue, social participation, social contacts, emotional support, healthcare use over the same three year period used to calculate baseline eFI.

The independent variables were the same as above and therefore the multicollinearity diagnostics were unchanged, confirming that the multicollinearity assumption was not violated in this model. The model summary for this regression analysis is shown in Table 5.17.

Table 5.17: Model summary for the relationship between eFI and quality of life at 12 month follow up

Model	Adjusted R square	R square change	Significance F change
1a	0.062	0.063	p<0.001
2a	0.131	0.070	p<0.001
3a	0.390	0.261	p<0.001

Model 1a explained 6.3% of the variance in quality of life at 12-month follow up. The addition of eFI in Model 2a explained an additional 7.0% of the variance, and overall model 2a explained 13.1% of the variance in quality of life at 12-month follow up. The further addition of the psychological status, social network, fatigue and healthcare use variables in Model 3a explained an additional 26.1% of

the variance in quality of life, and overall model 3 explained 39.0% of the variance in quality of life at 12-month follow up. All these findings were statistically significant.

The contributions of each of the independent variables in Model 3a were then evaluated. The results are shown in Table 5.18.

Table 5.18: Coefficients and their significance for the independent variables in Model 3a

Variable	Standardised Beta Coefficient	Significance
Age	-0.070	p<0.001
Gender	-0.036	p=0.021
Deprivation status	-0.051	p=0.001
eFI at 3 years	-0.036	p<0.001
Fatigue score	0.320	p<0.001
Depression	-0.200	p<0.001
Anxiety	-0.109	p<0.001
Healthcare use	-0.066	P<0.001
Social participation	-0.007	p=0.643
Social contacts	0.005	p=0.760
Emotional support	0.009	p=0.580

The strongest estimate in the model was made by the fatigue score (0.320), which was followed by depression (-0.200), anxiety (-0.109), age (-0.070), healthcare use (-0.066) and baseline eFI (-0.036). All these values were significant at the level p<0.001. Deprivation status (-0.051, p=0.001) and gender (-0.036, p=0.021) had lower estimates but were still statistically significant. The variables of social participation (-0.007, p=0.643), social contacts (0.005, p=0.760) and emotional support (0.009, p=0.580) did not make statistically significant unique contributions to this model.

As a result of these findings, an alternative to model 3a, labelled model 4a, was constructed which excluded the social network variables and included only the following variables:

- Model 4a: age, gender, deprivation status, baseline eFI, anxiety, depression, fatigue, healthcare use over the same three year period used to calculate baseline eFI.

The model summary for this revised regression analysis is shown in Table 5.19.

Table 5.19: Summary of revised model for the relationship between eFI and quality of life at 12 month follow up

Model	Adjusted R square	R square change	Significance F change
1a	0.062	0.063	p<0.001
2a	0.131	0.070	p<0.001
4a	0.391	0.260	p<0.001

The contributions of each independent variable in Model 4a were then evaluated (Table 5.20).

Table 5.20: Coefficients and their significance for the independent variables in Model 4a

Variable	Standardised Beta Coefficient	Significance
Age	-0.071	p<0.001
Gender	-0.038	p=0.012
Deprivation status	-0.050	p=0.001
eFI at 3 years	-0.110	p<0.001
Fatigue score	0.319	p<0.001
Depression	-0.199	p<0.001
Anxiety	-0.103	p<0.001
Healthcare use	-0.066	P<0.001

Model 4a, which included the psychological status, fatigue score and healthcare use variables in addition to the socio-demographic variables and baseline eFI, but excluded the social network variables, explained as much of the variance in EQ-5D at 12-month follow up as Model 3a, which included the social network variables.

In summary, multiple regression was used to assess the relationship between baseline eFI score, psychological status, social network status, fatigue score and healthcare use, after controlling for age, gender and deprivation status, and quality of life at 12 month follow up. Age, gender and deprivation status were entered at step 1 and explained 6.3% of the variance in quality of life at 12 month follow up. The eFI was entered at step 2 and explained a further 7.0% of the variance. Anxiety, depression, fatigue score and healthcare use measures were entered at step 3 and explained a further 26.0% of the variance in quality of life at 12 month follow up. The social network variables, namely social participation, social contacts and emotional support were not included in the final model. The final model explained 39.1% of the variance in quality of life at 12 month follow up.

5.6 Discussion

5.6.1 Comparison of the study population with the denominator population

In the surveyed population compared to the denominator population, there was some selection bias in favour of people aged over 60 years and people with lower levels of deprivation. With respect to comorbidities, there was some selection bias away from people with neither cardiovascular comorbidity nor osteoarthritis, and towards those with osteoarthritis alone or in combination with hypertension. Overall, the surveyed population had slightly, but not significantly, higher frailty than the denominator population over the full time period of the study. In summary, the surveyed population can be considered representative of the denominator population from which it was selected.

5.6.2 The relationship between other explanatory factors, frailty and quality of life

Anxiety and depression

This study showed associations between anxiety and frailty, and depression and frailty. Higher levels of frailty were in people who displayed borderline or probable anxiety or depression than in those who did not have anxiety or depression. There was a difference in frailty between those people with anxiety or depression and those without anxiety or depression. There was no significant difference between levels of frailty across the categories of increasing anxiety or depression. Importantly, Read Codes for neither anxiety nor depression were included in the code set from which the deficits in the eFI score were constructed. The associations identified between anxiety and frailty, and depression and frailty in these analyses were not therefore due to confounding by the way in which the eFI score was constructed with regard to these conditions.

There was also a sequential 'dose related' deterioration in quality of life associated with increasing anxiety and/or depression. However, some association would be expected between the HAD score, used to measure anxiety and depression in this study, and the EQ-5D score because one of the domains in the latter instrument includes questions specifically about anxiety and depression status (Appendix VI, page 246).

The associations demonstrated in this study did not imply or indicate causality. However, the hypotheses that i) frailty could cause anxiety and/or depression, ii) anxiety and/or depression could increase frailty, and iii) combinations of these conditions could have an adverse effect on quality of

life are all plausible. Other factors may also act as mediators in the relationships between anxiety, depression and frailty, and how they in turn relate to quality of life. For example, in older people following hospital admission, lower self-management abilities associate with depression and higher self-management abilities associate with well-being (189). Furthermore, associations between self-management skills, frailty and healthy ageing have also been investigated and a positive association between self-management abilities and healthy ageing demonstrated (190).

These results emphasise the importance of the clinical recognition and management of each one of the conditions of anxiety, depression and frailty in the presence of the others and highlight the need for further research to investigate the nature of the relationships between these conditions and between them and quality of life.

Fatigue

There was an association between fatigue and frailty as measured by the baseline eFI at both time points in these analyses, with increasing fatigue associated with increasing frailty. Fatigue is a classic phenotypic feature of frailty (2,4) and the finding of increased eFI score associated with increased fatigue supported the construct validity of using the eFI as a measure of frailty in this population group.

There was a sequential deterioration in quality of life associated with increasing fatigue. However, some association would be expected between the FACIT-f score and the EQ-5D score because one of the domains in the EQ-5D and two of the questions in the FACIT-f score ask specifically about a person's ability to perform their usual activities (Appendix IV, page 243 and Appendix VI, page 246).

Social networks

There was no significant association between frailty as measured by the baseline eFI score and with any of the social network measures (social contacts, social participation and emotional support) in these analyses. There was no significant association between social contacts or emotional support and quality of life, although there was a weak but inconsistent association between greater levels social participation and higher quality of life.

One explanation for these findings is that they reflected a true lack of association between social network factors and frailty or quality of life in the study population. However, evidence exists that social environment can have an important impact upon health and wellbeing (85) and it has been suggested that this might be particularly important for older people (191). Furthermore, qualitative studies from national bodies have reported that the number of social contacts, along with their quality, nature and the individual's degree of control over them, are important factors for wellbeing of older people with frailty (15,192).

A second possible explanation concerns the method of measurement of social network factors in this study. The survey data in this study regarding psychological status, levels of fatigue and quality of life was all obtained using well-established and validated measurement tools. However, although the survey questions regarding social networks had been derived from previous relevant studies measuring social function and participation (180,181), they did not represent a fully validated social network measurement tool.

Social support is considered a multi-dimensional concept and four dimensions of support have frequently been used as the basis for measurement of social support: emotional support, tangible or instrumental support, informational support and companionship (191,193). However, other authors in this field have focused upon the quality of social experiences (both positive and negative) as the basis for measurement, pointing out that the four dimensions of social support do not appear to be independent (86). The theoretical and methodological challenges of reducing complex data into scaled variables to measure the concept of social support have also been highlighted, pointing out both the need to understand the components and interactions of the concept, and the need for a scale to be constructed through a valid numerical transformation if a reliable measurement tool is to be achieved (85,86).

The social network questions used in this study were constructed from available evidence and designed to reflect as far as possible the recognised dimensions of social support (180,181). However, these social network measures were quantitative and did not consider the qualitative aspects of the social network experiences (86). Furthermore, although the social network questions in the survey were evidence based, these questions were then combined on an empirical basis to create the social network measure used in the analyses (Appendix V, page 244). The measurements were not therefore made using a recognised instrument validated for the

measurement of social networks. The accuracy and reliability of this approach to measurement of the specified features of social networks was therefore uncertain hence the validity of the findings with respect to the relationships between social network status and frailty or quality of life are also uncertain. Further research is required in this important area.

Healthcare use

In this study increased healthcare use was associated with increased frailty as measured by the eFI and reduced quality of life. The healthcare use measure related to activity that did not directly contribute to the eFI, because it excluded contacts with codes that contributed to the deficits in the eFI. The findings therefore showed that in addition to 'frailty related' healthcare activity, people with higher levels of frailty also had greater healthcare use for reasons that, from a coding point of view at least, did not directly relate to their frailty. This association warrants further investigation and could be important for a number of reasons.

Firstly, if validated, this finding raises an important potential role for the eFI in informing the planning and commissioning of services for older people with frailty. The eFI profile of populations, from individual GP practices, localities, CCGs or wider regional and area footprints, should be easy to measure through electronic primary care records and could help to understand and predict healthcare needs of this population group, thus informing service development and commissioning.

Secondly, the association between increased healthcare use and frailty raises potentially important issues regarding the risks and opportunities of care for people with frailty. One consideration is that higher healthcare use might leave people with frailty particularly vulnerable to the adverse consequences of poor systems of care. However, it also offers increased opportunities for positive interventions for people with frailty in effective systems of care.

The association between higher healthcare use and lower quality of life demonstrated in this study is also notable. This association does not imply or demonstrate causality in either direction. In this study, increased healthcare use did not protect against deteriorating quality of life and the hypothesis that increased healthcare use contributed to worsening quality of life cannot be excluded at this stage. However, there is evidence that specific targeted interventions can improve quality of life for older people with frailty, for example nurse-led health promotion and disease prevention programmes (194). The relationship between healthcare use and quality of life requires

further investigation for people with frailty, in order to identify the nature and timing of healthcare interventions required to improve outcomes in this area.

For the variables of anxiety, depression, fatigue and healthcare use, higher levels of frailty were also associated with an increased rate of change in frailty over 12 months. This was consistent with the findings that across socio-demographic variables, groups with higher levels of frailty were also associated with greater change in frailty over two years (section 4.6.2, page 115). However, these differences in frailty change over 12-months were unlikely to have been clinically significant because they were all of an order of magnitude that represented less than one deficit in the eFI.

Within the scope of this study, although levels of frailty increased over the 12 month follow up period, the relationships between psychological status, fatigue, social networks and healthcare use, and frailty and quality of life, did not change over time. Possible explanations for this include, firstly that the relationships between these variables are stable over time and secondly that the relationships change more slowly over time than could be detected during the 12-month follow up period in this study. Differentiating between these two hypotheses could have important implications for clinical interventions intended to maximise quality of life for people with frailty.

5.6.3 The relationship between frailty and quality of life

The quality of life as measured by the EQ-5D (182) score was an appropriate outcome to use in this study because the five domains included in this tool, namely mobility, self care, usual activities, pain and discomfort, and anxiety/depression, are all particularly relevant to the experiences of older people living with frailty.

During the development and validation of the eFI, the focus was on mortality (100) and admission to nursing homes (195), as key outcomes associated with frailty. Developing an understanding of how the eFI relates to the quality and experience of life for people living with frailty is an important next step in defining potential opportunities and limitations for the practical application of this frailty measurement tool to help support person-centred care for people living with frailty.

Investigating the relationship between the eFI at baseline and the quality of life both at baseline and at 12 month follow up demonstrated that i) there was an association between the eFI and

quality of life, and, ii) there was no change in this relationship over the 12 month follow up period. There was a moderate correlation between eFI and quality of life at both baseline and follow up, with increasing eFI associated with decreasing quality of life. Simple linear regression demonstrated that about 11% of the variance in quality of life at both baseline and 12 month follow up could be explained by the eFI value at baseline. The association between eFI and quality of life was therefore statistically significant and of low to moderate magnitude.

Investigating what other factors were associated with quality of life in older people with frailty, and how these factors interacted with the moderate association between eFI and quality of life was therefore the focus of the next stage of this study.

5.6.4 Frailty and other explanatory factors as predictors of quality of life at 12-months

Quality of life for people living with frailty is influenced by a range of factors. To be of practical use in primary care, any model developed to help identify variables that influence quality of life for people living with frailty needs to focus upon those that can be easily and reproducibly measured. Furthermore, a balance needs to be achieved between the potential predictive power of the model and the number and complexity of the variables included. Any model needs to be simple enough to be practically useful, yet have sufficient predictive power to be relevant to clinical case management.

The model generated through the multiple regression analysis in this study predicted 45% of the variance in quality of life at baseline and 39% of the variance in quality of life at 12 month follow up. In each case, around 6% of the variance was explained by age, gender and deprivation status and around a further 7% by the eFI at baseline. A further 32% of the variance in quality of life at baseline and a further 26% of quality of life at 12 month follow up was explained by the addition of fatigue, depression, anxiety and healthcare use variables into the model. Of these variables, fatigue score made the strongest unique contribution, followed by depression, anxiety and finally healthcare use measures. The social network measures used in this study made no significant further contribution to the power of the model and were not therefore included in the final model. However, as discussed above, the lack of association with social network factors in this study might reflect poor validity of the measures used, rather than a true absence of influence. The value of this

model is not so much in the ability to quantitatively predict quality of life scores, but more in helping to understand both the influence of frailty on quality of life and the extent to which the other variables under investigation influence the outcome of quality of life in the presence of frailty.

This model demonstrates that levels of frailty have an influence on quality of life, and therefore implies that strategies to influence levels and trajectories of frailty have the potential to influence quality of life outcomes. However, this model also demonstrates that a number of other factors relevant to a multi-dimensional model of frailty also have a very significant relationship with quality of life in the presence of frailty measured by the eFI. These factors include i) fatigue, which is related to frailty through the construct of the frailty phenotype (2) and also has a direct relationship with quality of life, ii) anxiety and depression, which may be directly or indirectly related to frailty and quality of life (91,92,189), and iii) healthcare use which might also be directly or indirectly related to frailty and quality of life (67,71,190,194). All these factors might therefore have complex and bidirectional relationships with both frailty and quality of life. Importantly, all of these factors are also potentially modifiable to a greater or lesser extent, for example through both specific treatment interventions and/or through lifestyle and behavioural change programmes.

This model helps us to understand the relationship between frailty and quality of life. It also highlights that even if the opportunities to influence the level and progression of frailty are limited, influencing other modifiable factors, including fatigue, psychological status and systems of care might offer considerable potential to improve the quality of life for people living with frailty. This list is not exhaustive and further work is indicated to identify and test the influence of other candidate variables upon quality of life in the presence of frailty. In particular, the systematic review highlighted the relevance of the physical environment in a multi-dimensional model of frailty (48,196) and proposed further research to test the inclusion of an environmental component in a frailty measurement tool for primary care and transitions of care. This is a very important question in relation to the holistic management of frailty and the integration of care not only between health and social care, but also in the context of links with services such as housing, local communities and our wider society.

5.6.5 Clinical and research implications

5.6.5.1 Frailty and psychological status

This study has shown an association between anxiety and depression and frailty, and between these factors and quality of life. These results do not prove causality in this association but nevertheless they have important implications for both clinical applications and research in this area.

From the clinical point of view, they provide evidence to suggest potential value in assessing for anxiety and depression in people with frailty. This is consistent with the framework used for the primary care based management of other more established long-term conditions and supports the proposition that frailty should be conceptualised and managed as a long-term condition. Equally, these results suggest a potential role for assessing for frailty in older people identified with anxiety and depression. From a research perspective, these results indicate the need to further investigate the nature and causality of the association between anxiety, depression and frailty, in order to inform the nature and timing of interventions to improve quality of life for people with frailty.

5.6.5.2 Frailty and fatigue

The strong association demonstrated between frailty and fatigue in this study is consistent with fatigue as a key feature of the well-described frailty phenotype. It therefore has important research implications in supporting the construct validity of the eFI as a measurement tool for frailty. These findings also have important clinical implications in raising a potential role for fatigue severity as a marker of frailty severity and raise additional research questions concerning potential interactions between fatigue and other components within the multidimensional construct of frailty, and the impact of these upon quality of life.

5.6.5.3 Frailty and social networks

This study did not demonstrate any association between the social network measures used and frailty and therefore currently has no direct clinical implications in this area. However, these findings are inconsistent with other evidence that suggests a relationship between social networks and frailty, and therefore raise questions to be addressed through further research. These include the suggestion that a systematic review be carried out to identify the nature and properties of existing tools to measure social network status in people with frailty. Depending upon the findings of the review, further research to develop and validate a tool for this purpose might also be indicated. A

further research question to consider is whether there are any sources of routinely collected data available that might be relevant to social network status, and if so how these might relate to both the construct of the eFI and to quality of life outcomes in frailty.

5.6.5.4 Frailty and healthcare use

This study has shown that frailty is associated with higher general levels of healthcare use and that this is not just due to greater activity for problems recognised to be associated with frailty (indicated by Read codes which are included in the eFI), but also reflects higher numbers of healthcare contacts for other reasons.

These findings have a number of potential clinical implications. Firstly, they imply the possibility that higher healthcare use can act as a marker for frailty, suggesting that clinicians should be alert to identifying and managing the condition in people observed to have higher healthcare use. Secondly, it raises the possibility that through their increased healthcare use, people with frailty might be more at risk of healthcare associated side effects, complications, adverse events and unintended consequences. Clinicians should therefore be alert to this patient safety risk for people with frailty. Thirdly, it could indicate that opportunities might exist in the context of other frequent healthcare contacts to maximise the provision of interventions relevant to frailty, including for example simple interventions such as sign-posting to information and services relevant to supporting self-care. These opportunities might be general, for example provision of relevant information in public areas such as waiting rooms, or specific, for example through opportunistic individual support or advice offered during the consultation.

5.6.5.5 Frailty and quality of life

This study has shown that frailty has moderate predictive validity for quality of life over a 12-month period and that the predictive ability is enhanced in a model that includes additional explanatory factors relevant to a multidimensional model of frailty. The additional explanatory factors that contributed to the prediction in this model were fatigue, depression, anxiety and healthcare use. This has potential application in that these additional explanatory factors are all identifiable in clinical practice and potentially modifiable. The clinical implications of these findings are therefore that in addition to clinical approaches aimed at identifying and managing frailty in order to improve quality of life outcomes, approaches focusing upon the identification and management of anxiety,

depression and fatigue might also have the potential to improve the quality of life outcomes for people with frailty.

From the academic perspective, these findings imply that adopting a multidimensional model of frailty has validity in relation to quality of life outcomes. However, it also raises the question as to whether the addition of any other explanatory factors might improve the predictive power of this model and implies the need for further research in this area.

5.6.5.6 Frailty trajectories and clinically significant progression of frailty

This study found that higher frailty levels were associated with higher rates of frailty change. However, although these findings were statistically significant they might not have been clinically significant over the 12-month period of the study because they represented changes of the order of magnitude of less than one deficit in the eFI. However, the differences identified still have potential clinical implications both for the clinician's understanding of the frailty prognosis and for how this information is communicated to individuals and their carers, particularly in the context of advanced care planning and transitions into end of life care. They also have implications for the design and delivery of services to support people with advancing frailty both for people living in their own homes and for those living in care homes. Further research is indicated to explore frailty trajectories by investigating the timescales over which clinically significant changes in frailty take place and how these rates of change relate to baseline frailty severity and other explanatory factors.

The relationship between frailty and the other explanatory factors and the outcome of quality of life did not change over the time period of this study. This implies that the clinical implications related to the individual explanatory factors described would remain relevant over time. It also implies that a frailty measurement tool constructed on the basis of this model would remain valid over time. However, it could be that the relationships do change over time, but more slowly than could be detected in the 12-month duration of this study. Further research is therefore required to investigate whether the relationships between these various explanatory factors and quality of life for people with frailty remain stable over longer periods of time.

5.6.5.7 Consensus studies in primary care

The systematic review in the first phase of this project identified a gap in relation to the assessment of face validity of frailty measurement tools used in primary care. The research implication is therefore that the findings from this third phase should be taken forward into a consensus study to contribute to the design of a validated approach to the measurement of frailty in primary care and at transitions of care.

Firstly, the consensus study should consider whether the model generated in this study to understand the influence of frailty, in combination with other explanatory factors, upon quality of life is likely to be useful and relevant in clinical practice. Secondly, if this model is considered to be clinically relevant, then the consensus study should go on to consider how the definition of the elements considered within each of the relevant domains and represented by the explanatory factors could be improved, and whether any other additional domains should be tested.

5.6.6 Strengths and limitations of the study

5.6.6.1 Use of the 2C study dataset

The strengths and limitations of using the 2C study dataset in this investigation are discussed in detail in chapter six (section 6.3, page 176).

5.6.6.2 Use of the eFI

The strengths and limitations of the construct of the eFI and the application of the eFI as a measure of frailty in the 2C study population have been described (section 4.6.5, page 118). In this phase of the study the eFI was used both as an exposure and as an outcome. This study therefore used a consistent measure of frailty to start exploring not only how frailty develops and relates in connection to other important cofactors, but also how frailty in turn associates with the key patient centred outcome of quality of life.

5.6.6.3 Measurement of explanatory factors

The explanatory factors under investigation in this study were clearly linked to a multidimensional model for frailty and had been identified as a result of the systematic review. Furthermore, the potential explanatory factors of anxiety, depression and fatigue score were all measured using recognised tools validated for measurement of the characteristic of interest. It was a potential

limitation of the study that all of these measurements were carried out using self-report questionnaires and therefore in addition to the possible selection bias through non-responders, there was also the risk that missing data within returned questionnaires would have an adverse effect on data quality. However, in fact there were only very low levels of missing data in the responses contributing to the measurement of these three factors.

The healthcare use measure was derived from the consultation data, which was considered to be reliable and of good quality. However, it was a potential limitation of the study that this measure was relatively simply based upon a count of all activity recorded in the electronic primary care record. It was not designed to analyse the nature of the observed healthcare use beyond whether the activity did or did not have a code which was recognised within the eFI code set, in other words whether the activity was considered 'frailty related' or not.

This study attempted to investigate the relationship between social networks and frailty and how these two factors related to quality of life. However, although the individual survey questions regarding social networks had been derived from available evidence and tested in previous studies, it was a limitation that the way in which the question responses were combined to produce the measures of social network features used in this study had not been previously validated.

5.6.6.4 Quality of life as an outcome in frailty

Quality of life was chosen as the key outcome measure in relation to frailty in this study, because this aligned conceptually with an approach to frailty management that prioritises person-centred goals and outcomes of care. However, this data was collected through self-report questionnaire and was therefore associated with potential limitations regarding response rates and missing data, although in fact the amount of missing data in the EQ-5D responses was very (section 5.5.5, page 141).

5.7 Conclusions

This study investigated the relation between frailty and various cofactors relevant to a multidimensional model of frailty and explored the relationship between frailty, these factors and quality of life for people with frailty. It also considered these relationships, and frailty change, over time.

The study found that anxiety and depression were associated with higher levels of frailty and lower quality of life. The relationship identified between frailty and anxiety and depression is relevant to the debate concerning the conceptualisation of frailty as a long-term condition and could be seen as evidence to support such an approach. The study also found that higher levels of fatigue were associated with higher levels of frailty, thus supporting the construct validity of the eFI as a measure of frailty in this population. Higher levels of fatigue were also associated with a lower quality of life. Higher levels of healthcare use were also associated with higher levels of frailty, offering potential opportunities to develop tools to support the planning and delivery of healthcare services for this group of people. Furthermore, higher levels of healthcare use were associated with lower quality of life, raising important questions in relation to patient safety and the experience of care. Higher levels of anxiety, depression, fatigue and healthcare use were also associated with an increased rate of change in frailty over time, although these differences did not appear to be clinically significant over this 12-month study period.

In this study, no significant association was found between social network status and frailty, frailty change or quality of life. However, this may have been due to the nature of the measurement approach, indicating the need to identify a validated measurement tool for use in future research in this area.

This study found an association between frailty and quality of life both at baseline and at 12-month follow up. The predictive ability at both baseline and 12-month follow up was improved by including fatigue, anxiety, depression and healthcare use as additional explanatory factors in the model. This has possible clinical implications because frailty, fatigue, anxiety, depression and healthcare use are all factors that can be identified and modified in primary care, thus offering potential opportunities to influence quality of life outcomes for people with frailty. Although overall levels of frailty increased over the 12-month follow up period, the relationships between psychological status, fatigue, social networks and healthcare use, and frailty and quality of life, did not change during this time.

In conclusion, therefore, the findings of this study were as follows:

1) The hypothesis that for this population there was an association between frailty status measured by the eFI and quality of life was confirmed.

2) The hypothesis that the strength of this association between frailty status and quality of life would be increased if questionnaire data on social networks and/or psychological status and/or levels of fatigue, and/or a measure of healthcare usage were added into the model was confirmed for all these explanatory factors except for social networks.
3) The hypothesis that for this population, change in quality of life over a 12-month period could be predicted by frailty status at baseline was confirmed.
4) The hypothesis that the ability of frailty status at baseline to predict changes in quality of life over the following 12 month period would be increased if data on social networks and/or psychological status and/or levels of fatigue and/or healthcare usage were added into the model was confirmed for all explanatory factors except for social networks.
5) The relationship between frailty and levels of fatigue supported the construct validity of the eFI as a measure of frailty in this primary care population.

Chapter 6: Strengths and limitations

This thesis was designed to investigate the measurement of frailty in primary care, in particular, the structure and application of frailty measurement tools and quality of life as an outcome in frailty measurement in these settings. Previous chapters have discussed the individual strengths and limitations of the systematic review, the investigation of frailty measurement and the investigation of the relationship between frailty and quality of life. This chapter revisits the central research questions and considers the strengths and limitations of the overall approaches applied to investigate complexity in frailty in this thesis.

6.1 Models of frailty

The model of frailty identified to be the focus for investigation in this thesis was a multi-dimensional model of frailty (section 1.2.3, page 6 and section 2.1.2, page 18), because this was considered to be the model most relevant to primary care and transitions of care. However, it is a limitation of this approach that there is still no universal agreement regarding a single model of frailty and that the model chosen for this study is one of three leading models for frailty (section 1.2, page 4) described in current literature (2,18,43).

6.2 Study settings

It was a strength of this thesis that frailty measurement in the primary care setting could be clearly investigated. It was possible to identify primary care as the setting for frailty measurement in the systematic review using well-established search terms (section 3.3.2, page 40) and to test the application of frailty measurement in primary care using a primary care consultation dataset (section 4.2, page 86). However, investigating frailty measurement at transitions of care was much more challenging. Firstly, no clear search terms could be identified in the systematic review for the study setting of 'transitions of care' (section 3.5.11, page 80). Secondly, transitions of care were not identifiable within the primary care consultation dataset used in the analytical phases of this study and therefore the application of frailty measurement at transitions of care was not specifically tested. The inability to identify evidence regarding frailty measurement at transitions of care or to

test the application of frailty measurement at transitions of care were therefore significant limitations of current evidence.

6.3 Use of 2C Study dataset

There were a number of strengths in using the 2C study dataset for the quantitative investigations in this thesis, particularly in relation to the robust nature of the data from electronic primary care records. However, the fact that this work was a post-hoc retrospective analysis of the 2C dataset, and therefore bound by the methodological approaches in the original study, presented a number of limitations.

6.3.1 Population selection

The denominator population in the 2C study was a systematically constructed primary care population drawn from the general population in 10 general practices, all of which were members of an established primary care research network with specific training mechanisms to maintain high data quality (165). Furthermore, primary care consultation data for the entire denominator population for the whole five-year period was available and there was no loss to follow up from this population during the study. However, the denominator population was not sampled randomly from the general primary care population. Instead, it was characterised by age (over 40 years) and by disease status with respect to cardiovascular and osteoarthritis comorbidity. This population therefore incorporated a baseline risk of frailty that was likely to differ from that of the general population. However, the construction of the cohort with respect to age and disease status characteristics was relevant to the primary care population group of interest in this research, namely older people with frailty.

The 2C survey population, used for the frailty and quality of life phase of this thesis, was derived from the denominator population via three different stages. In order to be included , individuals in the denominator population were required to have:

i. Responded to the survey invitation at baseline.
ii. Responded to the follow up survey invitation 12 months later.
iii. Consented to the linkage of their survey responses to their primary care consultation data.

Each of these steps had the potential to create selection bias in the survey population. This was particularly important because features associated with frailty might have had a direct impact upon

the likelihood of individuals responding to the survey and therefore directly influence the profile of the final survey population. For example, people with features associated with frailty such as visual impairment, problems with manual dexterity and cognitive impairment might be less likely than those without frailty to complete and return a postal questionnaire, which would result in their being under-represented. Furthermore, this effect might also cause people experiencing increasing frailty over the 12-month period to be more likely to be lost to follow up during the study, even if they responded at baseline, thus creating censorship bias. As a result, the study survey population might tend to have lower levels of frailty than the denominator population. However, this did not occur and the survey population was slightly but not significantly older, less deprived and more frail compared to the denominator population. Within the survey population compared to the denominator population there was some bias away from people with neither cardiovascular disease nor osteoarthritis and towards those with osteoarthritis alone or in combination with hypertension.

The strengths of using the 2C study population in this work were that the denominator population was a systematically constructed primary care population and that the relationships between this population and both the survey population and the general primary care population could be clearly described.

6.3.2 Methodological approaches

Using the 2C study dataset as the basis for the frailty investigations in this thesis presented some important methodological limitations in three main areas:

1. The approach to the classification of cardiovascular comorbidity severity.
2. The accommodation of non-cardiovascular, non-osteoarthritic co-pathologies.
3. Consideration of the influence of cognitive impairment, both as a covariant and upon some of the key outcome measures used in the study.

Firstly, the classification of cardiovascular disease severity in the 2C study uses hypertension, ischaemic heart disease and heart failure as indicators of ascending severity and as such appears to imply a linear, hierarchical and ordinal progression of cardiovascular disease severity. However, this approach has not been validated and may not adequately account for the complexities of the coexistence and natural history of some cardiovascular conditions, for example, heart failure due to cardiomyopathic or valvular pathologies, without either hypertension or ischaemic heart disease.

One potential way to address this limitation might have been analytical consideration of the relationships between clusters of cardiovascular disease deficits within the eFI and the different cardiovascular severity cohort groups.

Secondly, the 2C study dataset did not accommodate non-cardiovascular and non-osetoarthritis co-pathologies. However, these are relevant co-variables and possibly confounders in this frailty study. Although this question was not addressed in this study, there may have been some potential to do so through interrogation of the co-pathology data present in the eFI, for example by taking a co-pathology count from the 'diseases' deficits within the eFI to develop a comorbidity or multimorbidity score and then considering this as a covariant in some of the analyses.

The third, and potentially most significant, methodological gap in the context of this frailty investigation is that the 2C study did not account for cognitive impairment. Cognitive impairment is an important covariant that was not identified in the study and was not therefore considered in the analysis. Furthermore, cognitive impairment also confounds the EQ-5D and HADS, two of the key outcome variables in the 2C study, with the validity of these indices deteriorating as the level of cognitive impairment increases, to the extent that EQ-5D does not tend to be used in primary studies of patients with advanced cognitive impairment. One possible way to address this limitation would have been to look at the interaction between the "memory and cognitive problems" domain of the eFI and the ED-5D and HADS scores and, if present, include these as interaction terms in the regression models. However this would have been a dichotomous rather than scale variable and therefore would still not have fully captured how the variation in cognitive ability influences HADS and EQ-5D.

In summary, the main limitations of the analytical work in this thesis arose from the study design, which involved the retrospective interrogation of the 2C study data through the prism of the eFI and was therefore bound by the imitations of the 2C study dataset. These included limitations in the approach to the severity classification of cardiovascular disease, in the data collected on non-cardiovascular and non-osteoarthritis comorbidities and in the selection of some of the outcome measures for use in a population likely to include individuals with varying degrees of cognitive impairment. The nature of these limitations were typical of those often associated with conducting this type of retrospective analytical study.

There were some potential opportunities to use data contained in the eFI as a possible mechanism for correcting some of the limitations of the 2C study dataset, in particular by using some of the comorbidity and cognitive impairment data from the eFI to compensate. However, these approaches were considered beyond the scope of this thesis.

6.4 Structure of frailty measurement tools

The structure of frailty measurement tools includes the nature of the components included in the tools and the ways in which data is collected for each of these components.

In this thesis, the literature was systematically reviewed to identify the components of current tools to measure frailty in primary care (section 3.5.4, page 69), and used as part of the evidence base to propose a framework for the measurement of frailty in primary care (section 3.5.10, page 77). The quality of life study explored some innovative components with plausible contributions stories in relation to a multi-dimensional model of frailty, without being constrained by the scope of current evidence in this area. However, without a strong existing evidence base, it is possible that the approach risked bias or omission in the selection of the additional components.

The use of routinely collected data for the measurement of frailty is a practical approach with high potential for widespread application in primary care. However, a potential limitation of this approach is whether routinely collected primary care data can deliver the scope of information required for the holistic measurement of the multi-dimensional concept of frailty (section 4.2.2, page 86). Patient self-reported survey methods enable the exploration of components of frailty not captured in routinely collected primary care data. However, this approach depends upon the availability of validated instruments to measure these components and there is a need for further research and development in this area.

6.5 Application of frailty measurement tools

This thesis aimed to identify and/or develop a single frailty measurement tool appropriate for the measurement of frailty in primary care along a continuum from pre-diagnosis, through emergence and to end stage frailty. Such an approach would clearly have practical advantages in clinical practice compared to an approach of ‘different tools for different purposes’.

However, this approach was associated with an implicit assumption that the continuous variable output of the frailty measurement tool would have a cut-off point that could be identified as diagnostic for the condition. Furthermore, it was also associated with an assumption that values below and above this cut-off point would reflect gradations of pre-diagnostic risk and post diagnostic severity respectively. This approach therefore did not differentiate between the measurement of risk factors for frailty, criteria for the diagnosis of frailty and methods for the measurement and monitoring of the established condition, assuming instead that a single collection of components and their interactions would be relevant to the measurement at all different points along frailty trajectories.

The approach taken in this thesis can be illustrated in the context of the conceptualisation of frailty as a long-term condition. Many long-term conditions, including for example diabetes and heart failure, have diagnostic criteria distinct from the parameters used in the measurement and monitoring of progress for the established condition. Furthermore, risk factors for developing the condition are identified as being separate again from the components of both diagnostic and monitoring tools. Further research is therefore needed to validate whether the use of a single tool for both the diagnosis of frailty and the measurement of established frailty is appropriate, and how these relate to pre-diagnosis risk factors, or whether different tools, or different components of tools, are needed to differentiate these applications. The current drive to align the management of frailty with that of the long-term condition model of care requires these questions to be resolved.

6.6 Quality of life as an outcome in frailty

Quality of life is a key outcome for people living with frailty and this thesis investigated how the outcome of quality of life was associated with a multidimensional approach to frailty. However, other outcomes are also important in frailty, including, in particular, other health and social care interactions and the costs of care. The current reality in many healthcare systems, including the NHS, is that care for people with frailty is delivered in the face of limited resources and tight financial pressures. Reconciling a key focus upon individual experiences and quality of life with the need to recognise the strong pressures concerning the use of services and resource allocation is likely to be a continuing challenge in understanding, measuring and managing frailty in primary care and at transitions of care.

6.7 Understanding and interpreting complexity in frailty

The dynamic and complex nature of frailty was discussed (sections 2.1.3, page 20 and 2.3.1, page 26), along with how frailty might relate to other disease states (section 1.3, page 7) and the implications of this for the delivery of integrated pathways of care (section 2.3.2, page 27). The investigations in this thesis were intended to further the understanding and interpretation of some of the key dynamics and complexity of frailty, including how frailty related to socio-demographic and disease status characteristics, the range of components needed to reflect the multidimensional concept of frailty and how the components of frailty could be represented through both routinely collected primary care data and survey data. Although a range of components relevant to a multi-dimensional model of frailty were investigated in this thesis, the nature of the interactions between these components and how they come together to create the overall condition of frailty remain to be disentangled. Therefore, whilst the results presented in this thesis could be used to propose or support the relationships between some of the different components of frailty, they do not provide evidence regarding the mechanisms of these interactions.

There was also an initial investigation into frailty trajectories, both by considering the change in frailty over a 12-month time period and by exploring the relationship between frailty and change in quality of life over time. However, different or longer-term timeframes may provide variation in the relationship between frailty and quality of life, for example, change in quality of life might occur over longer periods of time for people with mild frailty and more rapidly for those with greater frailty severity.

6.8 The gap between theory and practice

The thesis aimed to investigate a number of specific measurement components of the multi-dimensional concept of frailty in primary care and at transitions of care. However, despite increasing evidence to support the recognition and measurement of frailty as a multi-dimensional concept in primary care and at transitions of care, the practical challenges of operationalising this approach mean that additional data are required for application in the complex systems of healthcare delivery. The thesis did not specifically seek to identify mechanisms to support the successful translation of research evidence into clinical practice, or seek to identify and overcome

barriers that might prevent this being achieved successfully. A further programme of research is required in this area.

6.9 Summary

This thesis investigated the measurement of frailty in primary care and at transitions of care, in particular, the structure and application of frailty measurement tools and quality of life as an outcome in frailty measurement in these settings. The thesis approach and methods were clearly described, thus enabling both the strengths and the limitations of the overall approach to the specific research questions to be identified and appraised.

Chapter 7: Discussion

The first part of this chapter will review the key findings of this thesis. The next section will consider the research relevance of the findings, with particular reference to the construct, validation and properties of the electronic Frailty Index as a tool to measure frailty in primary care. The operational relevance of the findings will then be discussed in the context of clinical questions about the application of frailty measurement in primary care and at transitions of care. This will include consideration of the diagnosis, assessment and management of frailty, including the management of frailty as a long-term condition, and how these issues relate to frailty trajectories, transitions of care and outcomes in frailty.

This will be followed by a discussion of the relevance of this thesis in the context of wider frailty issues, policy and approaches. This will begin by exploring the need to change public and professional perceptions about frailty and to develop a common language to discuss the condition. The opportunity to use the eFI to enable a population-based public health approach to frailty and its potential contribution towards supporting integrated person-centred care will also be considered. Associated practical and strategic aspects such as workforce development and the drive towards new models of care will also be discussed. The final section will draw together the conclusions from this thesis.

7.1 Key findings

7.1.1 Systematic review

The systematic review identified the current evidence on frailty tools that apply to primary care and generated a framework for the development of a tool for the measurement of frailty in primary care and at transitions of care. It was proposed that a frailty measurement tool should be based on a single model of frailty relevant throughout frailty trajectories, including at transitions of care, and components representing physical health factors, clinical measurements, clinical assessments, psychological factors, social factors, healthcare use and environmental factors should be considered for inclusion in the tool. Furthermore, it was proposed that data collection across these components should take place in two phases, with the first using routinely collected data and the

second enhancing this with data obtained through individual survey or clinical review. The tool should be suitable for predicting the onset of frailty, the measurement of frailty status and the prediction of outcomes in frailty. It should be validated using CGA (64) and outcomes associated with frailty, specifically including quality of life and functional ability. The tool should also be assessed for criterion, construct, content, predictive and face validity, and the risk of selection bias minimised during development of the tool (84,197).

7.1.2 Measurement of frailty using the electronic Frailty Index

The second phase of this study built upon the findings from the systematic review using the 2C consulting database of nearly 10,000 people aged 40 years and over. It investigated the measurement of frailty using an electronic Frailty Index based on routinely collected data (100) in a primary care population selected by cardiovascular and osteoarthritis disease status, thus providing as excellent opportunity to test key issues related to eFI development. Frailty increased with age and with increasing deprivation and was higher in females than in males. Frailty also increased with the number of index cardiovascular and osteoarthritis conditions and with increasing cardiovascular comorbidity severity. These differences were statistically significant and also represented potentially clinically significant differences because they were of a magnitude equivalent to at least one deficit in the frailty index.

The eFI as a measure of frailty in this population was sensitive to change over a two year time period. The rate of change in frailty over this period increased with age and with increasing levels of deprivation, although there was no difference in the rate of frailty change for females compared to males. The rate of frailty change increased with the number of index cardiovascular and osteoarthritis comorbidities, as well as with increasing cardiovascular comorbidity severity. Therefore, with the exception of female gender, the socio-demographic and disease status characteristics associated with increased frailty were also associated with increased frailty change and there was an association between comorbidity severity and frailty, and comorbidity severity and frailty change.

7.1.3 Relationship between frailty, quality of life and other explanatory factors

The third phase linking the consulting population to those who participated in questionnaire surveys built on the findings of the systematic review and the overall consulting population. It investigated

the relationships between frailty measured by the eFI and quality of life, and between frailty, quality of life and various other explanatory factors relevant to a multidimensional model. The explanatory factors include anxiety, depression, fatigue, social networks and healthcare use.

Anxiety, depression and fatigue were all associated with higher frailty and lower quality of life, as were higher levels of healthcare use. Higher levels of anxiety, depression, fatigue and healthcare use were also associated with an increased rate of change in frailty over time, although these differences did not appear to be clinically significant over the 12-month study period. No significant associations between social network status and frailty, frailty change or quality of life were found. Although overall levels of frailty increased over the 12-month follow up period, the associations between psychological status, fatigue, social networks and healthcare use, and frailty and quality of life did not change during this time.

There was an association between frailty and quality of life both at baseline and at 12-month follow up. The ability of the frailty to predict quality of life at both baseline and at 12-month follow up was improved by including fatigue, anxiety, depression and healthcare use as additional explanatory factors in the model. Adding social network data to the model did not improve the ability of frailty to predict quality of life either at baseline or at 12-month follow up.

7.2 Research relevance of findings

The findings in this thesis highlight opportunities for further investigation in a number of key areas. These include the relationships between the various components of the multidimensional model of frailty (such as social and psychological factors) and potential roles for additional explanatory factors to be included on the model (such as factors relating to the physical environment). They also include research to investigate patterns of healthcare use associated with different degrees of frailty severity and how these relate to frailty change over time. The findings of the thesis therefore have research relevance in relation to the validation of the eFI, the further development of frailty measurement tools in primary care and the investigation of frailty trajectories.

7.2.1 Validation of the eFI

This thesis generated a framework for the development of a tool for the measurement of frailty in primary care and at transitions of care and then tested the validity (84) of a recently developed electronic Frailty Index against this framework.

The first stage of this testing investigated the construct validity(84) of the eFI as a measure of frailty in this primary care population. The eFI was used to characterise frailty in relation to age, gender, deprivation and disease status. The results were consistent with previous evidence, showing that frailty increased with older age (6,156), in females compared to males (172,173), with increasing levels of deprivation (174) and in the presence of cardiovascular disease and osteoarthritis(27,52-54). Analysis of survey data at a later phase in the study also identified a strong association between increasing frailty as measured by the eFI and increasing levels of fatigue, as measured by a validated survey instrument. Fatigue is a strong phenotypic feature of frailty (2,4). Both these phases of testing therefore supported the construct validity of the eFI for the measurement of frailty in this primary care population.

The second stage of testing investigated the predictive validity (84) of the eFI with respect quality of life as an outcome in frailty, which was moderate and providing further validation in the primary care population. This stage of testing also investigated the content validity (84) of the eFI in relation to a multi-dimensional model of frailty that identifies quality of life as a key outcome for frailty, meaning that it investigated whether the eFI had defined and included most components necessary to measure this model of frailty.

The eFI includes deficits relating to dementia and cognitive impairment, which is consistent with current evidence supporting the inclusion of cognitive impairment within the definition of frailty (157). However, it does not include deficits relating to anxiety and depression. A model that included additional self-reported content relating to anxiety and depression was significantly better at predicting the outcome of quality of life than the eFI alone. The inclusion of content relating to levels of fatigue and healthcare use also improved the prediction of quality of life. This implied that there were some gaps in the content of the eFI in these areas in relation to a multi-dimensional model of frailty identifying quality of life as a key outcome.

The addition of content related to social networks did not improve the prediction of quality of life. This might mean that there was no gap in the content of the eFI with respect to social networks and in relation to a multi-dimensional model of frailty identifying quality of life as a key outcome (a ‘true negative’ result). However, it might also mean that there was a problem with either the method used to collect social network data or the way in which that data was combined with the eFI and the other additional factors in the overall model (a ‘false negative’ result). The nature and extent of any

interaction and influence that social networks may have with frailty and quality of life has potentially important clinical and operational implications. There is therefore a need for further research both to identify a validated tool to measure the social network status of people with frailty and to further test the potential value of including content in this area as part of an approach to frailty measurement in primary care and at transitions of care.

The framework for the development of a tool for the measurement of frailty in primary care and at transitions of care generated in the systematic review also identified a need to investigate criterion validity (84) compared to comprehensive geriatric assessment and face validity with primary care teams. However, these validation approaches remain key areas for further research. Furthermore, although this thesis has investigated the properties and validation of the eFI, in order to establish a clinical prediction model, impact analysis and implementation are also required (19,88).

7.2.2 Further development of frailty measurement tools

The underlying principles of frailty measurement were discussed (section 1.6, page 13), as was the application of these concepts to the development of a measurement system for frailty in primary care and at transitions of care (section 2.2, page 21). In addition to their contribution to the validation of the eFI, the results of this study have other relevance to the further development of approaches to frailty measurement, both in direct connection with the eFI and in a wider context.

7.2.2.1 Improving functionality of the eFI

The dynamic nature of frailty and the fact that it is a condition that can fluctuate over time has been discussed (section 2.1.3, page 20) (1,10,11). To have widespread practical applicability, a frailty measurement tool therefore needs to have the ability to detect both clinically significant and bi-directional change in frailty over time. This study found that the eFI had the ability to detect clinically significant change in frailty over time. However, as discussed (section 4.6.4, page 116) it is a limitation of the eFI in its current form that whilst it can measure the progression of frailty, it is not able to detect improvement in the condition. This is because the deficit count at any point in time is derived using all Read Codes in an individual's entire electronic health record and as coded entries are added to but never deleted from the record over time, the eFI can therefore only increase and not decrease.

However, there is theoretical potential to address this limitation through more sophisticated use of the coded data within the primary care record. This is based on the fact that Read Coded 'problem

titles' within electronic health records can and should be assigned different status depending upon the clinical situation, including for example differentiating 'significant' from 'minor' and 'active' from 'past' problem titles. For example, a diagnostic code for diabetes should be identified as 'significant' whereas an upper respiratory tract infection is likely to be 'minor'. Other problem titles, for example a symptomatic code for breathlessness, might only be clinically relevant for a defined period, during which the code should be identified as 'active' and after which this could be changed to 'past'. Deriving the eFI at any point in time from defined subsets of Read Codes, for example those identified as significant and/or active, rather than from the individual's entire history of coded data, could therefore offer the potential for the eFI to measure frailty improvement as well as deterioration.

The potential for such development warrants further investigation because it would offer significantly improved functionality for the eFI, including the potential for it to be used to measure frailty as an outcome as well as an exposure (section 4.6.4, page 116). The challenges in developing such an approach would include the quality and consistency of the recording of problem title status within electronic patient records and possible technical challenges associated with more complex filtering of the coded data.

7.2.2.2 Developing the content of the eFI

The use of routinely collected data, particularly primary care data, in the measurement of frailty is an appealing and powerful concept (100,104,198). However, it is important that limitations of this approach are recognised (section 2.2.6, page 22). In particular there is a risk of bias in favour of including those components of frailty that are well represented in routinely collected primary care data, whilst excluding or under representing those that are absent from or not well coded in these datasets.

One potential approach to addressing this challenge might be to include routinely collected data from other sources, for example secondary care or social care data, in the frailty measurement tool alongside the established contribution of routinely collected primary care data. However, this approach presents a number of potential challenges. Firstly, a number of practical issues would need to be considered, including methods for individual identification and data linkage, issues surrounding data sharing and information governance, and the nature and quality of coding across a range of datasets. Secondly, introducing data from other sources to contribute to the

accumulation of new or existing deficits within the eFI would present both conceptual challenges associated with a broadening definition of deficits and practical research challenges associated with the methodological approach required to identify and validate deficits meeting the criteria for inclusion in a Frailty Index (198).

7.2.2.3 The wider context of frailty measurement

The importance of a multi-dimensional framework for the definition of frailty (46) and its relevance to primary care was discussed (section 2.1.2, page 18). The challenges of developing a frailty measurement system to adequately reflect the complexity of the multiple inputs, associations and individual needs associated with the condition were also discussed (16,43,46,117). Quality of life was identified as a key outcome in frailty and the importance of identifying a range of components for frailty measurement that is broad enough to reflect the full concept of frailty, yet narrow enough to be practically applicable, was also highlighted. The findings showed that other components made important contributions to the prediction of quality of life when included in a model alongside the eFI. This implies that the components represented within the eFI do not cover the full scope of the condition of frailty in primary care as it relates to the outcome of quality of life. It therefore suggests the need to identify and investigate additional factors that might further enhance this approach to frailty measurement.

A number of additional candidate components were considered for inclusion in a model to predict quality of life in the presence of frailty. Further research in this area should therefore seek to identify and test other components that might make a plausible contribution to the model predicting quality of life in the presence of frailty. A comprehensive range of candidate components should be considered in order to represent the full scope of the multi-dimensional condition of frailty and could, for example, include physical environment (48).

There is also a requirement for validated measurement approaches for the individual components of frailty included in measurement tools. The example of the social network component illustrated the difficulty of drawing meaningful conclusions about the role of proposed components in frailty models and measurement systems in the absence of a validated approach to measurement of the individual components. In other words, the example of social network data highlighted the potential challenges of transforming raw data concerning frailty components into validated measurement

scales for each feature (85,86), whilst at the same time emphasising the essential need to do so rigorously for each frailty component considered.

Finally, the thesis raises important questions regarding the conceptual framework through which the different components reflecting the full scope of the multi-dimensional model of frailty could be brought together in a single frailty measurement system. Given the evidence that additional factors can be identified that improve the ability of the eFI to predict quality of life, questions therefore emerge regarding the relationships and interactions between the eFI and these other contributory components, and how these relate to the outcome of quality of life. However, it is also important to reflect that given the current deficit-based definition of the frailty concept and the fact that the absence of frailty is not necessarily the same thing as the presence of total health and wellbeing, it is unlikely that frailty would ever be able to fully predict quality of life and iterative attempts to accommodate ever-closer correlations between measures of frailty and quality of life would be expected to plateau at some point. Therefore, key questions include how the additional components relate to the cumulative deficit model upon which the eFI is based and, in particular, whether they are effectively contributing to the overall model of frailty by acting as additional deficits or whether they relate to the eFI through entirely different constructs, for example as enablers or mediators for the expression of frailty or of individual deficits contained within the eFI. These relationships might also have time dependent characteristics of importance in frailty trajectories. These fundamental questions have potentially important clinical implications, particularly with regard to proactive and holistic approaches to the management of frailty in primary care and at transitions of care, and should therefore be investigated through further research studies.

7.2.3 Frailty trajectories

Frailty is a dynamic, potentially modifiable condition and the rate of frailty change can differ between individuals and in the same individual over time (1,11,29). Improved understanding of frailty trajectories, including how they relate to preferred goals and outcomes of care, is likely to have important implications for frailty interventions. Frailty trajectories are often non-linear and can be characterised by critical tipping points, which may include transitions at any point along the frailty trajectory from the emergence of frailty through to advanced frailty close to the end of life (81). Frailty trajectories may also be influenced by previous life course events (97). Furthermore,

the importance of certain outcomes can differ according to the stage of frailty and frailty trajectories can be associated with emergent outcomes, such as changes in individual goals and priorities for care (13,55,94).

If the characteristics of frailty trajectories were better understood and predicted, there would be increased opportunities to offer timely, appropriate and effective delivery of frailty interventions aligned to person-centred goals of care. Importantly, the ability to predict frailty trajectories would also enable more effective evaluation of the impact of frailty interventions. This is increasingly important in the context of the drive towards proactive self-care and early intervention in frailty, due to the increase in the time lag between the delivery of frailty interventions and the realisation of their impact that is likely to be associated with this approach compared to, for example, the delivery of acute interventions to people with advanced frailty.

Clinically significant changes in frailty severity over a 2 year follow-up time period were found. Different socio-demographic and disease status characteristics, including cardiovascular comorbidity severity, were associated with different rates of frailty change, therefore implying that these different groups might be characterised by differing frailty trajectories. In particular, groups characterised by higher levels of frailty were also generally associated with higher rates of frailty change. This finding might be of particular relevance in identifying and understanding critical tipping points in frailty trajectories, particularly in relation to the progression of advanced frailty towards the end of life.

Further investigation is therefore indicated to characterise in more detail the socio-demographic, disease status and functional features associated with different frailty trajectories. Greater understanding of frailty trajectories, and the factors which influence them, could make a significant contribution to the development of integrated care pathways. Such knowledge would help target the delivery of timely and appropriate frailty interventions and therefore support the ambition to transform current systems of care for people with frailty, which are frequently fragmented and reactive, into much more proactive and integrated models of care.

7.3 Operational relevance of findings

The thesis findings are relevant to both health and care professionals and to individuals living with frailty. They have operational implications for the measurement of frailty in primary care and at

transitions of care, for the understanding of the relationships between frailty and other diseases, states and conditions, and for the management approach that considers frailty as a long-term condition.

7.3.1 Frailty measurement in primary care and at transitions of care

The scale of the impact of frailty in primary care and at transitions of care has been discussed (section 1.5, page 10), along with the potential for improving care through better recognition and measurement of the condition. Frailty instruments have the potential to support more proactive, integrated, holistic and person-centred care (19), through informing clinical decision making, targeting interventions, evaluating impact of interventions and supporting commissioning of services (63). Unsurprisingly, therefore, there has been considerable interest in the eFI since publication of its development and validation (100) and a strong appetite in many areas to apply it in primary care practice.

The Health Ageing Collaborative within the Yorkshire and Humber Academic Health Sciences Network (199) is coordinating work with a range of engagement partners across England to pilot the eFI in practice and to use it to inform the design of services to meet the needs of older people (200). In current applications the eFI is being used to identify frailty in a range of approaches to the development and delivery of services, including: identifying individuals for specific interventions such as medication reviews (Leeds North and Harrogate), proactive care planning (Lincolnshire), falls prevention (Leeds South and East) or support from care coordinators (Leeds West); wider service applications such as the implementation of tiered elderly care services across whole pathways (Airedale, Wharfedale and Craven and West London); public health and commissioning approaches such as the identification of gaps in falls and fracture prevention services (Birmingham) (199,200).

The outcomes under investigation in these pilot studies mainly reflect healthcare use and costs of care, for example numbers of emergency department attendances, unscheduled admissions and prescribing costs. A small number of projects are also considering outcomes related to the use of social care resources and to patient and staff experiences. Very occasionally, quality of life outcomes are also being reported. The eFI is not currently applicable to the measurement of frailty as an outcome to assess the impact of healthcare interventions.

The validation of the eFI described supports the practical application of the eFI as currently reported by the Health Ageing Collaborative (199). Current practical applications are also

consistent with the limitations of the eFI, namely the inability of the eFI to measure improvement in frailty and its limited predictive ability for the outcome of quality of life. Further development in the scope and functionality of frailty measurement approaches using the eFI, or in association with it (section 7.2.2, page 187), could offer the potential for a step-change in the opportunities for its practical application in a range of settings.

7.3.2 Frailty and comorbidity

The relationship between frailty and comorbidity was discussed (section 1.3, page 7 and section 4.1, page 83). Understanding how frailty and comorbidity relate is operationally important because it has implications for clinical interventions, both for the management of other long-term conditions in the presence of frailty and for the management of frailty in the presence of other long-term conditions. Previous attempts to characterise the relationship between frailty, comorbidity and disability have suggested that comorbidity is a precursor to the development of frailty and that frailty in turn leads to disability (2,4). However, more recently an alternative has been proposed in which frailty drives disease expression (158), thus raising important further conceptual and operational questions regarding the mechanisms through which these key concepts are linked.

Using the 2C study population (160) offered the opportunity to build upon previous evidence of associations between cardiovascular disease, osteoarthritis and frailty (52-54) and to investigate whether relative disease severity and comorbidity were associated with increased frailty levels. Frailty was associated with both cardiovascular disease and osteoarthritis and which increased with comorbidity and disease severity. Over half of the frailty measured by the eFI was accounted for by deficits attributable directly to the index disease status and comorbidity groups. These findings therefore emphasised the importance of the close relationship between frailty and comorbidity, whilst at the same time illustrating that frailty is ‘more than comorbidity’ and raising further questions as to what other factors contribute to overall levels of frailty in the presence of key comorbidities. These findings were consistent with the reasons for which the concept of frailty emerged (section 1.1.2, page 1), in other words that in some older people focusing clinical management solely upon long-term conditions does not achieve the desired outcomes (3,6,12).

Through the examples of osteoarthritis and cardiovascular disease, the findings can contribute to the discussion surrounding both conceptual and operational implications of the relationship between comorbidity and frailty. As discussed in section 4.1 (page 83), both cardiovascular disease

and osteoarthritis can reflect not only physical health components of frailty, but also a range of other constructs in the multi-dimensional model of frailty, including for example social isolation and psychological status. This raises the possibility that certain long-term conditions or comorbidity combinations might have wider implications than others in relation to frailty. These conditions might therefore represent critical links between comorbidity and frailty severity, thus offering the potential to act as markers for frailty risk, severity or progression. This perspective offers a potential practical opportunity to target interventions for frailty in the context of index condition and comorbidity status. Equally, it also offers the potential to target interventions for other comorbidities in the context of having identified frailty as the index long-term condition, supporting the increasing view that optimal approaches to the management of long-term conditions may differ in the context of advancing frailty, particularly towards the end of life (12).

7.3.3 Frailty and other explanatory factors

The main operational relevance of understanding explanatory factors in the context of disease and frailty is the potential that they might offer to help identify opportunities for frailty interventions. The steps required to realise this potential are:

1. To describe the associations between potential explanatory factors and both frailty and outcomes of interest in frailty.
2. To explore and understand the mechanisms of these associations, including how they relate to the framework for frailty measurement.
3. To exploit opportunities for intervention arising from these mechanisms.

The thesis outcome of interest in frailty was quality of life and the explanatory factors considered were anxiety, depression, fatigue, social networks and healthcare use. Associations with frailty and quality of life in frailty were identified for all these factors with the exception of social networks (sections 5.6.2, page 161 and 5.6.4, page 166). In simple terms, these findings have clinical implications because frailty, fatigue, anxiety, depression and healthcare use are all factors that can be identified and potentially modified in primary care, thus offering possible opportunities to influence quality of life outcomes for people with frailty. However, an understanding of the mechanisms of these associations is required to realise this opportunity for improvement.

The mechanisms of association may vary considerably for different factors, including associations through biological, behavioural or psychological mechanisms (56,189,190) at variable points in the

life course or frailty trajectory (27). Furthermore, some associations might be direct whereas others might exert their influence through indirect mechanisms, for example, environmental or behavioural factors that increase the risk or severity of other long-term conditions. Finally, some factors might be linked to outcomes through mechanisms offering alternate causal pathways, whilst others might require simultaneous causal strands (55,94).

Whilst the associations between the explanatory factors and frailty and quality of life were investigated, the underlying mechanisms of these associations or their direction and/or causality remain to be dis-entangled. The findings can therefore illustrate potential mechanisms rather than to prove them. However, practically speaking, even in the absence of further evidence about the mechanisms of these associations, some simple operational implications can already be identified and used to support improvements in care, as in the following examples.

Anxiety and depression: There was already known to be a link between anxiety and/or depression and frailty (91,92). A plausible causal pathway can be proposed through which anxiety and depression might have an adverse impact upon quality of life. However, the relationship between anxiety and/or depression and frailty is less easy to interpret, as the hypotheses that frailty might cause anxiety and/or depression and that anxiety and/or depression might drive the expression of frailty both appear equally plausible. Furthermore, it is also plausible that the association is indirect, as, for example, long-term conditions are known to be associated with anxiety and depression and comorbidity is also associated with frailty. However, whatever the direction or directness of the relationship, the combination of frailty with anxiety and/or depression is associated with worse quality of life. This therefore raises a clinical imperative to ensure that anxiety and/or depression are systematically identified and treated in the presence of frailty, and vice versa. Operationally, this has particular relevance and resonance in the context of the management of frailty as a long-term condition, given that there are well-established associations between anxiety and depression and other long-term conditions, as a result of which screening for these conditions is an integral part of the UK primary care framework for the management of long-term conditions.

Healthcare use: People with frailty have higher levels of healthcare use (7,8) and are at greater risk of adverse consequences from these interactions. This can be, for example, through the failure to implement interventions such as CGA that are known to be beneficial in frailty (17), through direct complications of suboptimal care (67) or through other adverse impacts such as the loss of

confidence or autonomy (69,70). Higher healthcare use was associated with higher frailty and lower quality of life. Again this association does not imply directionality or causality and a number of different mechanisms can be proposed to explain these findings (section 5.6.2, page 161). However, the simple operational implication at this stage is to emphasise the clinical imperative to systematically identify frailty and then to consistently maximise the opportunities for positive intervention and minimise the risks of harm presented by the higher levels of healthcare use by this group.

The final consideration is how these explanatory factors relate to the overall framework for frailty measurement in relation to the outcome of quality of life. As discussed (section 7.2.2, page 187) it is conceptually and practically important to understand whether they act as additional deficits in the construct of the frailty index, or whether they relate to frailty in some other way, for example driving or moderating the accumulation or expression of deficits already contained within the frailty index, either directly or indirectly through other mediators. These interactions are not yet described or understood, but will have significant operational implications for frailty interventions.

7.3.4 Frailty as a long-term condition

A case for adopting a long-term condition approach to the management of frailty has been described (32) and was discussed in sections 2.1.1 (page 17). This approach has the advantage of being based in primary care, which on an individual level facilitates a proactive and person-centred approach to care and from a public health perspective enables a population-based approach to the identification and management of the condition. However, there are a number of requirements that must be met in order to enable the operational management of frailty through the framework of a long-term condition, in particular:

- Understanding pre-diagnostic risk factors.
- Establishing agreed diagnostic criteria.
- Availability of evidence based interventions appropriate to different stages of disease progression.
- Availability of validated tools for the measurement and monitoring of the condition.
- Ability to predict outcomes and intervene to influence disease trajectories.

- Ability to identify advanced or end stage disease and enable the transition from disease specific management to end of life care.

In the case of frailty, current knowledge is relatively well established regarding the understanding of pre-diagnostic risk factors and the availability of evidence based interventions for the condition. However, it is at an earlier stage of development in many of the other areas, in particular regarding the identification of clear diagnostic criteria and the availability of validated tools for the measurement and monitoring of the condition.

This thesis provides evidence that can be used to further inform the debate regarding the management of frailty as a long-term condition. This includes the validation of the eFI as a tool for identifying frailty and frailty severity in primary care populations and the findings regarding frailty change, which can help to further the understanding of frailty trajectories. Furthermore, the association identified between frailty and anxiety and depression also supports the alignment of frailty management to the framework of a long-term condition and the identified association between frailty and healthcare use implies that many opportunities exist to offer frailty interventions. However, the findings also highlight the current lack of suitable tools for the comprehensive measurement and, in particular, monitoring of frailty in primary care and at transitions of care and specifically identified the limitations of the eFI in this respect.

Finally, this study also highlights an underlying philosophical tension that arises when considering adopting the approach of managing frailty through the framework of a long-term condition. The concept of frailty emerged because a group of mainly older people were identified for whom focusing clinical management solely upon the management of long-term conditions did not achieve the desired overall outcomes (12). It was recognised that frailty did not fit traditional disease diagnostic criteria and a concept more holistic than the traditional disease entity was required. There is therefore some dissonance in adopting an approach to the clinical management of frailty that attempts to rationalise it as a long-term condition and manage it through the very frameworks that were known not to achieve holistic outcomes for this population.

In summary therefore, there is a real need to determine whether frailty is appropriate and suitable for management through a long-term condition framework or whether a different and more specific model of care for frailty is required. This thesis offers evidence to support the management of frailty as a long-term condition, but also highlights the limitations of this approach and cautions

against allowing it to constraint the wider thinking and innovation required to support the development of increasingly comprehensive frailty concepts and approaches.

7.4 Future approaches to frailty

This thesis has generated evidence to support the development and application of a multi-dimensional model of frailty and an associated frailty measurement system in primary care and at transitions of care. The discussion has reinforced the need for clear agreement regarding the definition and recognition of frailty, as well as a systematic approach to its assessment and management. It has also highlighted the key role of primary care in frailty approaches, given that around 90% of healthcare contacts in the UK take place in this setting (72). This section will now go on to discuss the relevance of this work in the context of the 'real world' need for comprehensive approaches to address key frailty issues for 'individuals and populations' and 'systems and professionals', through both policy and practice.

7.4.1 Changing perceptions

The concept of frailty originally emerged as a positive response to help meet both the individual and collective needs of an ageing population (3). However, current perceptions of frailty, both public and professional, are overwhelmingly negative. This negativity is reflected at every level in current frailty approaches, including the language used to describe the condition, the models used to conceptualise it, the outcomes and objectives associated with frailty management, and the professional and societal stigmatisation of the condition (1,2,15). It is important because these negative perceptions often create reluctance from both the public and professionals to engage on the subject of frailty and thus present barriers to effective recognition and management of the condition.

A comprehensive future system for frailty care needs to radically transform these perceptions and create the momentum needed to enable a fundamental change in approach that will support much wider public and professional understanding of, and engagement with, the concept of frailty. This new paradigm should focus upon the consistent achievement of positive person centred goals and outcomes in frailty in order to maximise individual quality of life. It should also be firmly based upon constructive principles such as promoting resilience and maximising opportunity, rather than

focusing upon more negative outcomes such as reducing vulnerability and avoiding adverse events. Furthermore, the current language of frailty that focuses upon deficits and impairments (1,2,18) should be replaced by an asset-based approach to the condition (201) that promotes empowerment, motivation and capability at all levels.

Further developing the multi-dimensional model and measurement system for frailty described in this study could help to support this aim. The eFI, based upon a cumulative deficit model of frailty, is central to the measurement approach described in this study and the other explanatory factors identified in the model were all associated with increasing levels of frailty and decreasing quality of life. However, the discussion in sections 7.2.2 (page 187) and 7.3.3 (page 194) highlighted the fact that these explanatory factors might not relate to the frailty model simply as additional deficits, but might instead exert their influence by driving or mediating the expression of other deficits within the eFI. Further investigations could therefore be carried out to seek to identify other explanatory factors that might exert their influence by moderating or mitigating the expression of deficits, and thus be associated with decreasing frailty and increasing quality of life. The ability to measure and describe the influence of factors able to help improve quality of life in the presence of frailty could significantly support the aim of generating more positive perceptions of the condition.

7.4.2 Developing a common language

In addition to the challenge of 'creating a more positive image' for frailty, there is also a substantial need to raise awareness and develop a common understanding of the condition that will enable a holistic and person-centred approach to care. The potential of multi-dimensional frailty measurement tools to enable improved understanding between professionals and promote integrated working has been described (16). However, there is also a need for a much wider conversation about frailty, involving professionals at every level across health and care systems, as well as individuals, carers and people supporting older people with frailty throughout our communities. The evidenced based multi-dimensional approach to the measurement of frailty described in this study and the discussion regarding the relationship between this framework and the outcome of quality of life are important concepts relevant to this wider conversation. However, the academic and theoretical reporting of this model would not be relevant or useful to a wider audience.

Therefore, in a separate project and in an attempt to convey a multi-dimensional model of frailty to a much more general audience, I have created an animated model of frailty which I have called the Frailty Fulcrum (202,203). The purpose of this was to create a 'common language' that could be shared between individuals, carers and professionals and would enable frailty to be much more widely discussed. It was also intended to offer an interpretation of frailty that is meaningful, relevant and sustainable for people living with the condition and to offer a consistent framework for holistic assessment and action planning.

The model articulates the multi-dimensional nature of frailty through a series of moving triangles balancing at different points along a fulcrum, with the point of perfect balance representing optimal quality of life and degrees of imbalance representing less good quality of life. It explains how keeping the balance between all the different things going on in our lives becomes more difficult over time and that as we get older the likelihood of relatively small things causing bigger imbalances increases. The model also highlights that these changes can occur more quickly for some people than for others and therefore explains both the association and difference between frailty and ageing. Perhaps most importantly of all, the Frailty Fulcrum animation promotes a positive approach to frailty by pointing out that multi-dimensional opportunities exist to improve quality of life for people living with frailty. The model is therefore intended to empower individuals to exercise choice and control over the care they receive and the ways in which they live their lives.

This experimental approach has been highly successful. The Frailty Fulcrum has been used as a key feature in a multi-professional multi-agency frailty training programme in Nottinghamshire, where it has been very well received by around 400 front line staff from over 40 different organisations across health and social care, voluntary and private sector and other public sector such as housing and the fire service. The Frailty Fulcrum has also been widely shared by NHS England (203) and by the Healthy Ageing Collaborative of the Yorkshire and Humber Academic Health Sciences Network (199).

The strongly positive response to the Frailty Fulcrum suggests that there is a widespread appetite across a more general audience for further information about frailty. It also highlights the importance and value of developing innovative and engaging ways to communicate important frailty concepts, which although extensively and well described in academic literature are currently very little known or understood by a wider audience.

In addition to helping to develop a common language for frailty, the Frailty Fulcrum animation also begins to explore the concept of a more asset-based approach to frailty and implicitly raises the interesting question as to whether future models should seek to quantify the states of resilience as well as deficits, since these also have important influence in the delivery of person-centred care for people living with frailty.

7.4.3 Public health

Researchers, policy makers and health and care providers all recognise the significant and growing impact of frailty, yet public health approaches to the condition are not yet well established (75). There is therefore a pressing need to develop population based public health approaches for frailty (204). Public health promotes collective responsibility for health protection and disease prevention and highlights the need for partnerships between all people and organisations that contribute to population health, including individuals themselves, in order to implement effective evidence based approaches to health protection, health improvement and improving services. In particular, public health recognises the influence of underlying socioeconomic and wider determinants of health and emphasises the need to reduce inequalities, in line with core values of equality and empowerment (204).

This study provides some evidence that could inform the developing public health debate regarding frailty. Firstly, this study has shown that higher rates of frailty and frailty change are associated with particular socio-demographic characteristics, including age and deprivation, and with different disease status groups. This offers potential opportunities for public health approaches to target and reduce these inequalities. Secondly this study has shown that the eFI has the ability to detect both the incidence of new frailty and how established frailty changes over time. It therefore has the potential to offer a population level approach to the understanding and modelling frailty trajectories.

These findings could inform the planning, development and commissioning of relevant services, referring not just to health and social care services but also to wider provision such as supported housing, transport, community and environmental services. This approach could be particularly powerful if two related methods were also developed. Firstly, if the differences in frailty trajectories associated with different index conditions and comorbidity combinations implied by the results of this study could be further defined and the prevalence of these conditions then also included in the modelling of the incidence and progression of frailty severity at a population level, the accuracy of

this frailty modelling might be improved. Secondly, if an approach could be developed through which the eFI could be used to assess the collective 'frailty profiles' of current users of a range of relevant services, then this could be mapped onto the predictive model for population frailty in order to offer a stronger evidence base to help predict the likely nature and scale of requirements for future service provision.

7.4.4 Integrated, person-centred care

The central objective of care for people with frailty should be to improve their quality and experience of life, by supporting them to live their lives in the way that they want and to do the things that matter most to them as individuals. This demands a holistic and person-centred approach to care, with a need to focus upon identifying and appreciating individual goals and priorities of care and in particular upon understanding individual interpretations of quality of life (13). Traditional systems of care have often been fragmented and disease, condition or organisation specific and therefore poorly placed to deliver holistic person-centred care. Instead, integrated systems of care are now required to meet the needs of our ageing population.

It is necessary and important for both individuals and professionals to understand the goals of frailty care and the roles of frailty identification, measurement and management in helping to achieve them. As well as helping people with frailty to achieve their own personal goals of care, the care and support that they are offered should also aim to minimise and appropriately manage their needs at any given stage of frailty and to favourably influence underlying frailty trajectories. This can be achieved through the delivery of proactive care intended to minimise any subsequent or associated need for responsive care and through interventions intended to minimise or even reverse the progression of frailty.

As discussed (section 2.2.5.3, page 22) there is a strong argument for the development of a comprehensive frailty measurement tool to support and enable a unified, integrated and comprehensive approach to frailty care (16), thus avoiding the risk of fragmented and disjointed care that may arise through an approach which adopts 'different tools for different purposes' (30). The challenges of developing a holistic and multi-dimensional model and measurement system for frailty that can be applicable across entire frailty trajectories and throughout systems of care are considerable and it has been stated that 'only the most general model of frailty could retain this flexibility' (30). Current national policy strongly promotes approaches to care which focus upon self-

care and early intervention and are thus intended to reduce demand for secondary and unscheduled care services (31). It is likely that a 'general and flexible' model of frailty would be well placed in this context and indeed it is plausible to suggest that the greater the emphasis on supported self-care and early intervention, the greater the requirement for a holistic and multi-dimensional model for frailty. The investigation of a multi-dimensional model and measurement approach to frailty described in this study is therefore well placed to contribute to this wider debate.

Frailty transitions are important because although they frequently represent critical tipping points that can indicate the start of a rapid cycle of decline (1), they can also offer opportunities at which timely intervention can minimise, prevent or even reverse frailty progression (11). This study has identified the possibility that certain socio-demographic or disease status characteristics might be associated with particular patterns or trajectories of frailty and might therefore act as early indicators of change or markers of severity of the condition. Some combinations of deficits might also have greater functional impact than others and thus be associated with a greater demand for care and support services, or have particular relationships with other explanatory factors that might drive or moderate frailty expression. In other words, certain deficits might have wider implications and impact than others, through their differing relationships with the range of constructs relevant to the multidimensional model of frailty, thus providing insight into the mechanisms by which frailty worsens and offering opportunities for targeted intervention.

Identifying and understanding critical points in advanced frailty trajectories that might indicate the need for transition to an end of life paradigm of care is particularly important. Evidence from a recent audit of end of life care for Doncaster CCG (205) highlighted that end of life care needs were poorly recognised in people with advanced frailty and dementia compared to end of life care needs in those diagnosed with cancer. This finding held even in cases where there were features clearly associated with frailty, such as nursing home admission, recurrent emergency department attendances and unscheduled acute admissions. A training and development need was therefore identified and a programme is now being put in place to support general practitioners and community teams to better recognise transitions into an end of life phase in the presence of advanced frailty and dementia.

The hypothesis that systems of care might induce or contribute to frailty has been proposed and discussed (section 1.4.2, page 10) and the need for further research in this area identified. If this

hypothesis were proven it would have important implications for the measurement and monitoring of the quality and effectiveness of integrated systems of care for older people. Measuring the quality and effectiveness of complete systems of care rather than of individual organisations or services is a challenge well recognised by commissioners and regulators in particular. Although some progress has been made, for example with Care Quality Commission themed inspections for older people's services, this issue is currently inconsistently and often ineffectively addressed. However, if the emergence or progression of frailty was found to be a consequence of poor systems of care and an appropriate frailty measurement tool was available, then local population measures of frailty might have the potential to act as indicators for the quality and effectiveness of local integrated systems of care for older people.

7.4.5 Workforce development

The British Geriatrics Society has emphasised the need to develop education and training packages to make the health and care workforce 'fit for frailty' (63). The delivery of effective care and support for people with frailty across integrated pathways of care requires a diverse and well-trained workforce.

Firstly, there should be a basic level of awareness and understanding of frailty throughout the workforce. Secondly, there is a need for a group of professionals from a range of backgrounds trained to have a more detailed understanding of the condition and the ability to deliver a range of frailty interventions, as well as to refer or signpost individuals to other services as appropriate. Finally, a more specialist group within the workforce is required with more expert knowledge of frailty and the ability to deliver more complex frailty interventions and manage higher levels of clinical risk.

At each of these levels, workforce development can occur either by enhancing the skills of existing staff through training, or through the recruitment of new staff, or both, and examples of each will now be described:

1) The multi-professional multi-agency frailty training programme in Nottinghamshire, referred to above (section 7.4.2, page 199) was funded by Health Education England and offers an excellent example of a system wide approach to improving frailty knowledge and skills within the existing workforce. Furthermore, this programme has also extended to include

colleagues in the voluntary and private sector, as well as other public sector professionals such as fire service personnel.

2) Meanwhile, in Newcastle under Lyme in Staffordshire, the new role of 'elderly care facilitator' has been developed in primary care to create an 'accessible bridge' between older people and a wide range of existing health, care and community resources and services. This role has also improved engagement within and between a range of local professionals, carers, health and care providers and community organisations.
3) Finally, a new 'Frailty and Integrated Care' element has just been launched within the Master Medical Science programme at Keele University. This course will offer education to certificate, diploma or masters level and is intended for the more specialist members of primary care and community services teams.

Holistic clinical judgement by expert generalists has been identified as making a key contribution to comprehensive frailty management (12). However, this component of care cannot be easily systematised and there are challenges in delivering it at the scale and pace required to support the service transformation demanded by current national policies (31), particularly in the face of the current widely acknowledged workforce crisis in general practice. The diversification of the primary care workforce is therefore seen as one potential solution to this, with other practitioners trained either to carry out tasks traditionally delivered by GPs or to take on new roles designed to release GP capacity in other ways, for example through care coordination or supported self care intended to reduce the demand for GP services.

These workforce development initiatives are important not only because they increase the capacity to deliver integrated frailty care, but also because they increase the availability of well trained frontline staff who may be willing and able to contribute to frailty service design, research and development. The capacity to continue an active programme of frailty research studies, such as this one, and innovative service development initiatives, such as that described in Newcastle under Lyme, will make an essential contribution to the future delivery of comprehensive frailty care.

7.4.6 New care models

It is well established that frailty is associated with high levels of healthcare use and correspondingly increased costs of care (22,23,77-79). Indeed, escalating costs of care were an important initial

driver for the development of the concept of frailty (8) (section 1.1.2, page 1). However, the 'total cost' of frailty is much greater and more difficult to estimate that the direct costs associated with the use of health and care resources, with wider impacts including financial, social and emotional costs for individuals, families, carers, communities and societies.

There are current gaps between frailty research, clinical practice and service development, with much of the current innovation occurring through local initiatives rather than through formal research approaches. The quality of the evaluation of both the implementation and the outcomes of such initiatives can be extremely variable and this can present significant challenges when trying to assess the impact and cost effectiveness of service developments, understand associated causal pathways or to determine how successful small scale initiatives can be scaled up.

Current policy is driving a shift towards proactive care and early intervention with the ambition of improving the experience of care, as well as improving clinical and cost effectiveness through reduced need for acute care (31). However, there is very little evidence regarding the cost effectiveness of such approaches (75). The challenges of transforming the model of care in a resource-constrained environment are considerable, particularly when the costs and benefits of such changes might be realised over different timescales and in 'different parts of the system', including costs borne by individuals themselves. Furthermore, in this context 'the system' must be viewed in its widest sense, including public, private and voluntary sector health and care services, wider public services such as police, fire and housing, individuals, families and communities. Therefore there is now a need for integration and innovation of approaches on an unprecedented scale.

NHS England has a strong financial imperative to drive the pace of this large scale transformation and integration, as a result of which local health and care economies have recently been directed to prepare Sustainability and Transformation Plans (STP) (206) describing how they will deliver through to 2021 against the challenging ambitions contained with the NHS Five Year Forward View (FYFV) (31). The STPs must be prepared across geographical rather than organisational footprints and offer clearly integrated plans involving a wide range of partner organisations. Improving the quality and cost effectiveness of care for older people is a major theme within the FYFV and therefore the STPs should be seen as a major opportunity to embed a comprehensive approach to

frailty at the core of new systems of care and to help gain traction in implementing the changes required.

This study investigating the measurement of frailty in primary care and at transitions of care is relevant to this ambitious transformation agenda through the themes discussed above, ranging from promoting a change in public and professional perceptions of frailty and helping to develop a common language for frailty, through to supporting the establishment of a public health approach to the condition and the evolution of integrated person-centred pathways of care, and including contributing to the development of an empowered and motivated workforce capable of delivering comprehensive frailty care.

7.5 Conclusions

This study was set in the context of the now widespread acknowledgement of the concept of frailty and the appreciation of the increasing impact of the condition upon individuals, healthcare systems and society. With the consequent recognition of the need for frailty measurement tools in primary care and at transitions of care, it aimed to investigate the components of frailty measurement tools used in these settings, the application of these components and how these components relate to quality of life.

Current evidence on frailty tools that apply to primary care and transitions of care was used to generate a framework for the development of a tool for the measurement of frailty in these settings. This framework proposed a multidimensional model of frailty, to include routinely collected data from electronic health records, enhanced by additional data obtained from questionnaires or clinical review and with quality of life as a key outcome. An electronic frailty index derived from routinely collected primary care data was tested against this framework in a primary care population selected by cardiovascular and osteoarthritis disease status. Frailty increased with age, deprivation, comorbidity and cardiovascular disease severity, and was higher in females than males. This characterisation of the eFI according to socio-demographic and disease status groups, along with a strong association between frailty and fatigue, validated the construct of the eFI as a measure of frailty in this population.

The eFI had moderate predictive ability for quality of life and this model was improved by including content relating to some additional components of a multi-dimensional model of frailty. Social network data did not contribute to this predictive model; this may have been either a ‘true negative’

result or a reflection of a poor methodological approach to the measurement of this component. Components for anxiety, depression, fatigue and healthcare use all improved the predictive model. Possible mechanisms for these associations with quality of life include that these factors act as additional deficits within the frailty index model, as mediators for frailty or that they drive the expression of existing deficits within the eFI. All the factors investigated in this study were associated with worsening impact upon frailty and deteriorating quality of life. However, it might be possible to identify other cofactors associated with improvement in quality of life, which might in turn enable a more positive and constructive approach to frailty.

There was a strong association between anxiety and depression and eFI, which was not a result of confounding because these conditions had not met the criteria for inclusion as deficits in the eFI. This has potentially important clinical implications for the identification and management of coexistent frailty and mental health conditions. It is also relevant in the context of managing frailty as a long-term condition.

The eFI detected statistically and clinically significant change in frailty over time. Rates of frailty change varied according to socio-demographic and clinical characteristics. In general, people with higher levels of frailty experienced higher rates of frailty change, but a minority of individuals who had little or no frailty initially also experienced rapid frailty progression over two years. This offers important potential to further investigate frailty trajectories, with the aim of helping to target appropriate frailty interventions at the most critical and timely opportunities throughout. This might be particularly important at certain key transitions along frailty trajectories, for example at the transition point where active management moves into end of life care.

The content validity of the eFI could potentially be improved through linkage to other sources of routinely collected data, for example social care and/or secondary care data. Furthermore, applying filters to select only significant and/or active disease codes to include in its derivation could potentially improve the function of the eFI. There is a need for validated measures for individual components of a frailty measurement tool based upon multidimensional model of frailty, including in particular social networks, as well as a need to further investigate the content validity of the tool. Criterion validity of the eFI compared to CGA and its face validity with primary care teams were not investigated.

Some evidence was found to support the management of frailty through the framework of a long-

term condition, but this approach also has limitations and gives rise to some conceptual challenges. There is a strong relationship between frailty and comorbidity but also key differences between these two concepts. Combining disease and frailty approaches has the potential to help improve the identification, measurement and management of frailty risk, frailty severity and frailty progression. Mechanisms through which frailty worsens in the presence of comorbidity might include through pain, fatigue and social isolation. The range of constructs through which frailty relates to comorbidity highlights the strength and relevance of a multidimensional model and measurement tool for frailty.

The evidence generated in this study has wide potential relevance for future comprehensive frailty approaches, particularly regarding the outcome of quality of life. This includes the potential to help support a much more positive, constructive and asset based approach to frailty that would help to change both public and professional perceptions about the condition. It could also help to establish a common language to communicate important frailty concepts to a wider audience, thus supporting both workforce development and a greater public understanding of frailty. This frailty measurement tool also has considerable potential to inform and support the development of a much needed public health approach to the condition.

Frailty measurement can make a key contribution to supporting integrated person-centred journeys of care for people with frailty, by helping to target specific clinical interventions in a timely manner and potentially by helping to measure the impact and effectiveness of systems of care. Critical tipping points and transitions of care, particularly those towards the end of life, present both the greatest risks and the greatest opportunities to improvement in the quality and safety of care for people with frailty. Measuring frailty using different tools in different settings and at different stages of care presents major challenges in understanding, managing and improving safety and effectiveness at transitions of care. Across the NHS, there is a drive for implementation of new care models intended to deliver the major improvement programme described in the Five Year Forward View. Service transformation is likely to occur on an unprecedented scale over the new few years and a flexible, integrated and multidimensional approach to frailty measurement will be a key enabler for this change.

In conclusion, therefore, despite the challenges involved, the ambition must continue to be to move away from an approach to frailty measurement that adopts ‘different tools for different purposes’

and towards a single shared tool. Further research should build on the evidence generated in this study to inform the continuing development of a single, comprehensive multi-dimensional frailty measurement tool validated for use in primary care and across transitions of care. This general and holistic tool should also support the shift in care towards early intervention and supported self care, but must also be flexible enough to remain accurate, meaningful and useful in individual integrated person-centred journeys of care, through all stages of frailty and in all phases of care.

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Appendices

Appendix I: Preparation of denominator population data

I.i Denominator population socio-demographic data

The denominator population demographic dataset supplied contained age, gender, deprivation and disease status cohort data for each individual. This data was prepared as follows:

- Age was re-coded from a continuous variable into categories representing six 10-year age bands, from 40-49 years through to 90-99 years. Age categories were favoured over aged a continuous variable because it was felt that this approach would facilitate the interpretation of the clinical relevance of the results.
- Gender was used as presented.
- The Index of Multiple Deprivation (IMD) (166) is a continuous variable used to measure deprivation status. This is the official measure of relative deprivation in England. It ranks every neighbourhood in England from 1 (the most deprived) to 32,844 (the least deprived). For the purposes of this study the IMD was summarised into quartiles, with category 1 being the most affluent and category 4 being the most deprived.
- Disease status data was used as presented.

The denominator population consultation dataset was received in a separate file. The consultation dataset was therefore used to calculate the eFIs and these calculated eFIs were then linked back into the denominator population dataset as an additional variable, using the unique patient identifiers as described below, to create the final denominator population dataset which was used for analysis.

I.ii Denominator population consultation data

The denominator population consultation data sets contained the date, consultation title and Read Code recorded for all primary care consultations by the denominator population during a 5-year time period from 1st March 2007 to 28th February 2012. There were three files, defined by the software systems in use by the participating GP practices across the 5-year time period (EMIS, VAMP and System One). The steps followed in the initial data processing were as follows:

1. The variables in the three files containing the consultation data were renamed so that they were consistent across all three files.

2. Consultation lines that were not Read Coded were removed from each file because they would not contribute to the frailty index calculation.
3. The files were merged.
4. This resulted in single file containing all coded consultation lines for the denominator population.

I.iii eFI Read Codes

The eFI has 35 deficits and each deficit has a group of Read Codes codes associated with it. A small number of Read Codes are associated with more than one deficit. The appearance in an individual's coded consultation data of any one of the codes included in any given deficit defines the presence of that deficit. There was no weighting or threshold calculation. The eFI score was calculated by dividing the number of deficits present in the coded data for any individual by the total number of possible deficits, which was in this case 35. The eFI code set was prepared for use as follows:

1. The Read Codes in the eFI code spreadsheet were checked and sorted.
2. Each deficit was assigned a deficit number, with a range of 1 to 35, and the assigned deficit number was then attached each of individual codes associated with each deficit.
3. The formatting of the Read Codes in the eFI was crosschecked against the formatting of the Read Codes in the denominator consultation data base.

I.iv Calculating eFIs from consultation data

The eFI code sets were calculated and applied to the denominator population consultation data set through the following steps:

1. The eFI code file was merged into the denominator population consultation file to add a new variable, which was the deficit number assigned to any Read Code. The files were merged through using the Read Codes as the matched variable and adding the deficit number as the additional variable.
2. A small number of codes were included in more than one deficit and therefore more than one additional variable was generated for some coded consultations.
3. Coded consultations that did not have a new matched variable were then removed from the data set.

4. Coded consultations with more than one deficit variable were recoded columns into rows, so that one row appeared for each deficit number.
5. As each deficit was either present or absent for each individual during the time period under consideration, duplicates for patient identifier and deficit code were removed.
6. A single row was then created for each unique patient identifier by adding extra columns to accommodate all the deficits present for each individual patient.
7. Additional variables for all the deficits numbered 1-35 were created and populated with zero or one depending upon whether or not that deficit number appeared in the variables deficit for each patient.
8. The output of 7 was used to calculate the total deficit count for each patient.
9. The deficit count was divided by 35 in order to calculate the eFI for the full 5-year period for each individual.
10. The dataset generated at the end of stage 3 was then duplicated and split by date of consultation to give one dataset that was for the first 3 years of the study and another dataset that was for the first 4 years.

Steps 4-9 were repeated for the two split data sets, in order to calculate eFIs for both the 3 and 4 year time periods for each patient, in addition to the eFI for the full 5-year time period already calculated. The three different values were needed because the period prevalence of frailty based on the first 3 years provided a baseline measure of frailty in this population and the frailty score at the end of years 4 and 5 could be used to identify frailty change over 12 and 24 months respectively.

I.v Linking eFIs to denominator population socio-demographic data

The calculated eFIs were applied to the denominator population demographic data as follows:

1. The calculated values for the eFIs at the 3, 4 and 5 year time points were merged as additional variables into a file which contained the age, sex and IMD for the denominator population, by matching the datasets on the unique patient identifiers.
2. Missing values for the three calculated eFIs were added as ‘0’. Individuals with an eFI of ‘0’ at all three time points reflected the individuals who had either been removed from further processing at either i) step 2 in 4.4.8.2 because they had no coded consultations at all in the 5 year period, or ii) step 3 in 4.4.8.4 because they had no consultations coded with any

code in any of the deficits during the 5 year period. Individuals with an eFI of zero at the 3 or 4 year time points but with a value of greater than zero at 5 years reflected those individuals who did have consultations coded in relation to deficits during the full five year period, but not necessarily within the 3 or 4 year period.

Appendix II: Preparation of survey population data

II.i Study population dataset

The study population was a subset of the denominator population, which was patients aged 40 years and over who had consented to the linkage of their baseline and follow-up survey and consultation data. This population could not be identified directly from the denominator population dataset because different patient identifiers were used in the survey population and the denominator population. This was for reasons of confidentiality and data security, in order to ensure that survey data could not be linked to consultation data for any individual unless their express written consent had been given. The data required to construct the study population dataset for analysis was received in four different source files, which used the same unique patient identifiers and therefore could be linked.

The first file was the consultation dataset for all the people who had responded to the baseline survey in 2010 and given their consent for their survey data to be linked to their consultation data. The second file contained the socio-demographic and disease group data for this population of consenting survey responders. The third and fourth files contained the survey data for those people who had responded to the survey at baseline and at 12 month follow up respectively.

The study population was the group of people who had responded to the survey both at baseline and at 12 month follow up. A new dataset was created containing just these individuals and the following relevant data from the other associated files was then merged as additional variables:

- eFIs at 3, 4 and 5 years calculated from consenting survey population consultation dataset, as described below
- socio-demographic and disease status cohort data
- survey data at baseline
- survey data at 12 month follow up

This created the final study population dataset, which was used for analyses.

II.ii Preparation of socio-demographic and clinical data

The socio-demographic and clinical data for the study population was prepared in the same way as that for the denominator population (appendix I).

II.iii Calculating eFIs from the consenting survey population consultation data

Although the consenting survey population was a subset of the denominator population, they were not an identifiable subset because the patient identifiers differed between the two datasets. The eFIs calculated for the denominator population could not therefore be applied to the consenting survey population dataset containing the survey data. Instead the eFIs were calculated separately from the consenting survey population consultation data using the same steps as the calculation for the denominator consultation dataset described in appendix I.

II.iv Linking the calculated eFIs to the consenting survey population dataset

The calculated eFIs were applied to the consenting survey population demographic data using the same steps as described for the denominator population demographic dataset in appendix I.

Appendix III: Hospital Anxiety and Depression Scale (HADS) Survey Questions in 2C Study Questionnaire (160)

For each question, put a cross beside the statement that comes closest to how you have been feeling in the last 4 weeks.

1) I feel tense or 'wound up'
    - Most of the time
    - A lot of the time
    - From time to time, occasionally
    - Not at all
2) I still enjoy things I used to enjoy
    - Definitely as much
    - Not quite as much
    - Only a little
    - Hardly at all
3) I get a sort of frightened feeling as if something awful is about to happen
    - Very definitely and quite badly
    - Yes, but not too badly
    - A little but it doesn't worry me
    - Not at all
4) I can laugh and see the funny side of things
    - As much as I always could
    - Not quite so much now
    - Definitely not so much now
    - Not at all
5) Worrying thoughts go through my mind
    - A great deal of the time
    - A lot of the time
    - From time to time but not too often
    - Only occasionally

6) I feel cheerful

- Not at all
- Not often
- Sometimes
- Most of the time

7) I can sit at ease and feel relaxed

- Definitely
- Usually
- Not often
- Not at all

8) I feel as if I am slowed down

- Nearly all the time
- Very often
- Sometimes
- Not at all

9) I get a sort of frightened feeling like ‘butterflies’ in my stomach

- Not at all
- Occasionally
- Quite often
- Very often

10) I have lost interest in my appearance

- Definitely
- I don’t take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

11) I feel restless as if I have to be on the move

- Very much indeed
- Quite a lot
- Not very much

- Not at all

12) I look forward with enjoyment to things

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

13) I get sudden feelings of panic

- Very often indeed
- Quite often
- Not very often
- Not at all

14) I can enjoy a good book or radio or television programme

- Often
- Sometimes
- Not often
- Very seldom

Appendix IV: Fatigue Score (FACT-f) Survey Questions in 2C Study Questionnaire (160)

How true do you find each of these statements, in the past 4 weeks…

'Not at all' 'A little bit' 'Some what' 'Quite a bit' 'Very much'

1) I feel fatigued
2) I feel weak all over
3) I feel listless ("washed out")
4) I feel tired
5) I have trouble starting things because I am tired
6) I have trouble finishing things because I am tired
7) I have energy
8) I am able to do my usual activities
9) I need to sleep during the day
10) I am too tired to eat
11) I need help doing my usual activities
12) I am frustrated by being too tired to do the things I want to do
13) I have to limit my social activity because I am tired

Appendix V: Social Network Survey Measures in 2C Study Questionnaire (160)

Social network survey questions

1) How many of your children do you see at least once a month?
    - None
    - 1-3
    - 3-5
    - 6 or more
2) How many close relatives do you see at least once a month?
    - None
    - 1-3
    - 3-5
    - 6 -9
    - 10 or more
3) How many close friends do you see at least once a month?
    - None
    - 1-3
    - 3-5
    - 6 -9
    - 10 or more
4) Is there any one special person you know that you feel very close to; someone you feel you can share confidences and feelings with?
    - Yes or No
5) How many hours each week do you participate in any groups such as social or work group, church connected group, self-help group, charity, public service or community group?
    - None
    - 1-2 hours
    - 3-5 hours
    - 6-10 hours
    - 11-15 hours

- 16 or more hours

The Social Network Measures for these features were derived as follows:

1) Extent of personal social contacts was derived from the survey responses three questions, the responses to these questions, which were aggregated into a single score as follows:

a) How many of your children do you see at least once per month?

b) How many close relatives do you see at least once a month? How many friends do you see at least once per month?

The responses to the individual questions were recoded into the following categories: none=0, 1-2 contacts=1, 3-5 contacts=2, >6 contacts=3 A total score was then calculated for each individual, which fell in the range 0-9.The extent of personal social contacts per month was then characterised through these final scores as 0=none, 1-3=low social contacts, 4-6=medium social contacts, 7-9=high social contacts.

2) Level of emotional support was derived from a question in the survey that was as follows:

- Is there any one special person you know that you feel very close to; someone you feel can share confidences and feelings with?

The response to this question was either 'yes' or 'no' and this was used as a measure of whether or not the individual had emotional support.

3) Degree of social participation was derived from a question in the survey that was as follows:

- How many hours each week do you participate in any groups such as a social or work group, church connected group, self-help group, charity, public service or community group?

The responses to this question were re-coded into the following categories: none=0, 1-2 hours=1, 2-10 hours=2, 11 or more hours=3.

The degree of social participation was then characterised through these final score as 0=no social participation, 1=low social participation, 2=medium social participation, 3=high social participation.

Appendix VI: Quality of Life (EQ-5D) Survey Questions in 2C Study Questionnaire (160)

For questions 1-5 put a cross beside the statement that best describes your own health state today

1) Mobility
    - I have no problems in walking about
    - I have some problems in walking about
    - I am confined to bed
2) Self-care
    - I have no problems with self-care
    - I have some problems washing and dressing myself
    - I am unable to was or dress myself
3) Usual activities (work, study, housework, family or leisure activities)
    - I have no problems with performing my usual activities
    - I have some problems with performing my usual activities
    - I am unable to perform my usual activities
4) Pain/discomfort
    - I have no pain or discomfort
    - I have moderate pain or discomfort
    - I have extreme pain or discomfort
5) Anxiety/depression
    - I am not anxious or depressed
    - I am moderately anxious or depressed
    - I am extremely anxious or depressed
6) To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marker 0. Please indicate by drawing a line on this scale how good or bad you think your own health is today.

Appendix VII Healthcare use

A measure of 'healthcare use' was calculated using the total count of the number of lines of consultation data for each individual in the study population. This count included both coded and non-coded entries for the consenting survey population for a stated period and was calculated for three time periods, namely all consultations in the first three years, all consultations in the first 4 years and all consultations for the full 5 years.

The ‘healthcare use’ measure was created as a new calculated variable. The consultation data was aggregated for each patient ID to generate a new variable that was the total number of consultations in the given time period for each individual patient.

This approach used the total number of lines of consultation data for each individual. It did not aggregate the consultation data by date of entry. Therefore, where multiple problems had been presented and recorded separately at a single consultation, that consultation would be represented more than once in this measure. This approach is useful because it reflects not just the number primary care consultations but also their complexity. This approach was used in a previous study to explore predictors of primary care consultation rates in people aged 65 years and over(78) .

The healthcare use measure used also included all entries for other clinical activities in addition to face-to-face consultations, including those for blood tests and hospital letters and reports. The intention of this approach was to reflect as comprehensively as possible the extent of healthcare use in the study population, and not just face-to-face primary care consultations.

The healthcare use measure also divided this total healthcare use into the activity that contributed to the eFI calculation (in other words those consultation entries identified by a Read Code within the eFI code set) and the activity that did not contribute to the eFI (in other words consultation entries which were either not coded or were identified by a Read Code which was not within the eFI code set). This approach was adopted in order to enable investigation of the relationship between the eFI and general healthcare use, without it being confounded by the healthcare use linked to frailty which would inevitably have a direct relationship with the eFI because of the way in which it is constructed from Read Coded consultations.

Appendix VIII 2C Study Ethics Approval

A copy of the ethical approval for the 2C study is included below.

Cheshire Research Ethics Committee
Research Ethics Office
Victoria Building
Bishop Goss Complex
Rose Place
Liverpool
L3 3AN
Telephone: 0151 330 2070
Facsimile: 0151 330 2075

19 March 2009

Dr Umesh T Kadam
Senior Lecturer in General Practice (Epidemiology)
Keele University
arc National Primary Care Centre
Keele University
Staffordshire
ST5 5BG

Dear Dr Kadam

Full title of study: **The consequences of cardiovascular disease and osteoarthritis comorbidity on short and long-term health status and health care in primary care**
REC reference number: **09/H1017/40**

The Research Ethics Committee reviewed the above application at the meeting held on 11 March 2009. Thank you for attending to discuss the study.

Ethical opinion

Thank you for your reassurance that should participants die during the study period, the matter would be dealt with sensitively based on procedures developed as a result of a similar study.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to submit the Site-Specific Information Form to any Research Ethics Committee. The favourable opinion for the study applies to all sites involved in the research.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the

relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
CV James Prior		17 February 2009
Participant Consent Form	5	17 February 2009
Participant Information Sheet	3	13 February 2009
Letter of invitation to participant	1	11 February 2009
Questionnaire: General Health Monthly	3	13 February 2009
Questionnaire: General Health	5	17 February 2009
Peer Review		
Letter from Sponsor		17 February 2009
Summary/Synopsis		
Covering Letter		
Protocol	4	17 February 2009
Investigator CV		
Application	2.0	17 February 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1017/40	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Mr Jonathan Deans, FRCS
Chair Cheshire REC

Email: rob.emmett@liverpoolpct.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: *Professor Peter R Croft*
[R&D office for NHS care organisation at lead site]