The Association between Frailty and Quality of Life in Older People

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Thesis structure

The thesis has been structured and submitted as an alternative style of doctoral thesis which includes published material. There are a total of three studies included in the thesis. Studies One and Two have been published by peer-reviewed journals. Study Three has been submitted to the Quality of Life research journal. There is an introduction chapter containing three literature reviews preceding the manuscripts, and a discussion chapter following the presentation of the studies to connect the manuscripts into a coherent piece of work.

The three studies included in the thesis have been presented exactly as published or submitted, except in minor cases where formatting has been amended to ensure the thesis is a coherent whole (e.g. table numbers, reference formatting). Each chapter contains its list of references. An alternative thesis style was chosen as this approach can maximize the research outputs generated from a PhD. The alternative style of thesis is also aligned with the Graduate Board at the University of Leeds, who encourage all postgraduate research students to publish and disseminate their PhD results.

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Abstract

This thesis examines the association between frailty and quality of life (QoL) in older adults, emphasizing successful aging as a primary goal for individuals and healthcare systems. Frailty and QoL are crucial concepts in understanding aging, as they encompass major concerns and extend into broader domains of successful aging. Using data from the English Longitudinal Study of Ageing, this research comprises three interconnected studies.

The first study analyses frailty progression over 18 years, categorized by the number of long-term conditions (LTCs). Findings indicated that frailty increased with the number of LTCs for both genders, with males showing accelerated frailty with one or more LTCs, while females exhibited this acceleration with two or more LTCs.

In the second study, several structural factor models for the CASP-12, a measure of quality of life, were tested. The study also examined the consistency of the best model across various demographics and two time periods. The results showed that the CASP-12 with the second-order common factors is a better model, and it maintained strong invariance across genders, age, and education, as well as over two different time points when the sample was divided into three subsamples based on age group. However, this invariance was not observed for net wealth.

The third study investigated the two-way relationship between frailty and QoL, revealing a strong inverse and almost linear relationship over time. Although the cross-lagged relationship between QoL and frailty was statistically significant, the impact was minimal. Differences were noted at the group level, considering gender, age, net wealth, and multimorbidity, but not at the within-person level.

By considering these findings, healthcare providers and policymakers can develop more effective strategies to support the well-being of older adults.

Table of Contents

List of Figures

List of Tables

List of abbreviations

FFM: Functional Frailty Measure

QoL: Quality of Life

ELSA: English Longitudinal Study of Ageing

CGA: Comprehensive Geriatric Assessment

FI: Frailty index

HRQOL: health-related QoL

ICECAP: ICEpop CAPability measure for Adults

WHO: World Health Organization

LCA: Latent Class Analysis

LTCs: Long-term conditions

MI: Measurement invariance

SF-36: Short Form Health Survey

KDQOL-36: Kidney Disease QoL 36-item survey

OPQOL: old people Quality of Life

CFA: Confirmatory factor analysis

MG-CFA: multi-group Confirmatory factor analysis

IRT: Items response theory

2PL: The two-parameter Logistic

WLSMV: Weighted Least Squares Mean and Variance

TFI: Tilburg Frailty index

AIC: Akaike's information criterion

RML: robust Maximum likelihood

FIML: Full information Maximum likelihood

CLPM: Cross-lagged panel model

LCM-SR: Latent curve model with structured residuals

MNLFA: Moderated Nonlinear Factor Analysis

MIMIC: Multiple Indicators and Multiple Causes

Chapter 1 Introduction

1.1 Chapter Summary

This chapter delves into the concept of successful ageing, examining its key components, influencing factors, and methods of measurement. It then explores the definitions, measures, and determinants of frailty and quality of life (QoL). The relationship between these concepts is explored to underscore the importance of studying the interplay between frailty and QoL as they collectively embody various aspects of successful ageing. Following this, three comprehensive literature reviews were conducted, identifying significant research gaps. Addressing these gaps forms the core aims of this thesis.

1.2 Successful Ageing

The increasing longevity of individuals has led to a growing prevalence of multimorbidity, frailty, and disability among the elderly population (1). In the UK, one in five people are currently aged over 65 and demographically this proportion is expanding rapidly (2). Regrettably, between 2015 and 2035, a significant number of individuals are projected to develop two or more diseases (3). Recognizing that this implies impending challenges for health and social care, it is imperative for both governments and individuals to develop proactive strategies to promote successful ageing among older adults.

Successful ageing, however, is a complex and multifaceted concept, encompassing physical, psychological, and social well-being and preserving autonomy and identity (4). Menassa, Stronks (5) provided indicates that there are 12 normative terms used to refer to or evaluate human ageing, with "successful ageing" being the most widely used, followed by "healthy ageing", "ageing well" and "active ageing". These terms are often used interchangeably in the literature to describe the concept of maintaining a functional ability that enables individuals to meet their needs and contribute to society within their environment, as defined by the World Health Organization (WHO) (6). Browning, Enticott (7) further defined "ageing well" as the ability to continue living in the community with good physical and psychological health, as measured by an index comprising self-rated health, functional health, and psychological well-being measures. This highlights the challenges physical health decline (chronic illnesses, mobility issues, and sensory impairments), functional health deterioration, psychological issues (mental disorders, loneliness, and cognitive decline), social isolation, lack of support, and environmental barriers. Also, economic challenges, such as financial insecurity and limited healthcare access, further reduce independence, QoL, and life satisfaction for older adults (8).

Successful ageing is a dynamic process which is influenced by historical and cultural context and social relationships. It leads to better QoL and minimizes the costs associated with ageing (9, 10). While we cannot completely avoid the costs of ageing, through proactive interventions and a focus on health promotion, we can significantly improve the ageing trajectory, ensuring that older adults remain healthier, more independent, and socially connected for longer (11, 12). It is also important to recognize that there are individual differences regarding ageing, which highlights that older people may have diverse ageing trajectories as they grow older (13). Therefore, public policy should move away from a one-size-fits-all approach and instead consider individual characteristics and gender differences. Understanding these nuances is vital for developing tailored strategies that effectively support the ageing population and promote overall well-being (14).

A multidimensional approach to successful ageing offers a more comprehensive understanding than focusing solely on single health outcomes (5). This approach proves invaluable for comprehending and promoting the successful ageing within ageing populations (1). Various attempts have been made to measure successful ageing. For instance, Browning, Enticott (7) utilized a composite measure to identify trajectories of ageing well, incorporating self-rated health, psychological well-being, and independence in daily living as joint indicators among individuals aged over 65 years at baseline. Successful ageing was assessed using two indicators—physical functioning and optimism—by Klein, von dem Knesebeck (15). These different approaches underscore the complexity of successful ageing and the need for multifaceted assessments to capture its nuances.

Browning, Enticott (7) also reported that putative factors for successful ageing include engaging in social and productive activities, moderating alcohol intake, not smoking, and undertaking moderate levels of physical activity. Additionally, specific factors were identified for women and men, such as restful sleep for women, low strain, good nutrition, and adequate social support for men. These factors contribute significantly to the promotion of successful ageing and underline the importance of lifestyle choices in maintaining physical and mental health as individuals age. By adopting these behaviours, older adults can enhance their overall well-being and potentially mitigate the impact of age-related health issues (16). However, it is essential to recognize that the effectiveness of these factors may vary depending on individual circumstances and environmental factors. For instance, while engaging in social activities may be beneficial for many older adults, those living in rural communities may face challenges in accessing such opportunities due to geographical isolation (4). Therefore, interventions aimed at promoting

successful ageing should be tailored to address the specific needs and contexts of different populations (5).

1.3 Frailty

From a clinical standpoint, frailty is characterized by the gradual decline in the efficiency of body systems and organs among the elderly, a process that can be accelerated by factors such as infections and falls (17). In essence, frailty represents a heightened vulnerability to adverse outcomes (18).

The primary aim of assessing frailty is to prevent or at least decrease the impact of adverse outcomes (19). Recognizing frailty enables healthcare professionals to take preventive actions and tailor care to mitigate risks (20). Frailty varies in severity, is dynamic, and it by most measures can improve or worsen (19).

Frailty is a significant concern for older individuals, and its prevalence may increase due to several factors. Advancing age is one of the primary factors impacting frailty steeply (17, 20, 21). Additionally, other factors contribute to the increasing prevalence of frailty among older people living in the community, such as being female (19) and/or having multiple long-term conditions (22). Poor diet, vitamin D insufficiency, and obesity also may exacerbate frailty (23). Conversely, physical activity, especially resistance exercise, helps prevent and treat frailty (24). The immune-endocrine axis and certain medications also influence frailty, though these areas need more study (19).

Many older individuals are hesitant to undergo clinical diagnosis for frailty, as they are reluctant to self-identify as frail (25). Additionally, the significant expense associated with comprehensive frailty testing, such as the Comprehensive Geriatric Assessment (CGA), poses major obstacles to effectively screening older adults (19, 26). The CGA is a standard clinical assessment for older individuals that includes medical, nutritional, functional, and psychological evaluations conducted by a multidisciplinary team. Although its mathematical nature is to calculate the frailty index of CGA (FI-CGA), which is based on the cumulative deficits model that will be explained shortly, it can be time-consuming and unpopular among clinicians. Moreover, the CGA may not be practical for frailty testing due to its comprehensive nature, which may not be feasible for routine clinical use (27).

Instead, Dent, Kowal (27) stated that there are numerous methods to measure frailty discussed in the literature, but the quality of these measurements varies significantly. They reported that frailty measures have several issues, primarily due to their variability and complexity. There is no

international standard, leading to a multitude of different tools with varying degrees of validation and prognostic ability. Some measures are quick and simple, while others are time-consuming and sophisticated, which affects their applicability in different settings. Additionally, many measures are modified versions of original tools, further complicating their reliability and consistency. The inconsistent validation and lack of cross-cultural studies also hinder the effective use of these measures in diverse populations. They argued that a reliable frailty measurement should be able to detect frailty, predict patient outcomes and response to potential treatments, and be based on biological theory.

Two commonly utilized models for diagnosing frailty are the frailty phenotype model and the cumulative deficits frailty index (19, 27). The Fried phenotype model assesses five dimensions: weight loss, fatigue, low energy, gait speed, and grip strength (28). Individuals are categorized into one of three groups based on the presence of these variables: robust (none present), pre-frail (one or two present), and frail (three or more present) (28). The cumulative deficit model is another approach to identifying frailty in older adults (29) and encompasses various deficits across five components: symptoms, signs, abnormal laboratory values, disease status, and disability (29). The Frailty Index (FI) score quantifies the level of frailty, assigning a value of one to deficits if present and zero if absent. The total number of deficits varies according to the FI, and it is calculated by summing all present deficits and dividing by the total number of deficits (17). FI score ranges from 0 to 1, with a higher score indicating greater frailty severity, offering an advantage in capturing the spectrum of frailty severity (29).The score is then divided based on a cut-off to get four levels of frailty: robust (<0.12), mild (≥ 12 and <0.25), moderate (≥ 0.25 and <0.40), and frail (≥0.40) (17, 30).

The Electronic Frailty Index (eFI) is a digital adaptation of the Cumulative Deficits Model, designed to leverage data from electronic health records (EHRs). It uses a standardized set of 36 health deficits that are typically recorded in EHRs, such as diagnoses, medication use, and symptoms, to calculate an individual's frailty score. The eFI is particularly suited for use in clinical settings, allowing healthcare providers to assess frailty without the need for additional patient assessments. This makes it a practical tool for quickly identifying frailty in older patients during routine care, particularly in countries like the UK where general practice records are widely used. Its ease of use and standardized approach make the eFI a valuable resource for integrating frailty assessment into everyday clinical practice (31).

Despite differences in data collection methods, the Cumulative Deficits Model and the eFI share key similarities in their approach to assessing frailty. Both models operate on the principle that frailty arises from the accumulation of multiple health deficits over time, emphasizing that frailty is a gradual process rather than a binary state. Each uses a continuous scale to measure frailty, allowing for a nuanced understanding of how frailty can vary among older adults. Additionally, both have demonstrated utility in predicting adverse outcomes like hospitalization, falls, and mortality, helping to identify individuals at greater risk and informing care decisions (29, 32, 33).

The primary differences between the Cumulative Deficits Model and the eFI lie in their data sources and implementation. The traditional Cumulative Deficits Model relies on direct clinical assessment or survey data, allowing researchers to tailor the selection of deficits to the specific needs of a study. In contrast, the eFI draws on routinely collected EHR data, using a predefined set of deficits to facilitate consistent measurement across different healthcare settings. This makes the eFI more efficient and scalable in clinical environments, while the Cumulative Deficits Model's flexibility can be more suitable for research contexts where customized deficit lists are needed. Additionally, the eFI is particularly advantageous in primary care settings, providing a quick, standardized method for identifying frailty, whereas the Cumulative Deficits Model may require more time and resources for data collection (29, 32, 33).

There is a growing trend to modify the cumulative frailty index by excluding specific domains, such as long-term conditions, and using the remaining deficits to measure frailty. This approach allows for a deeper understanding of how particular domains contribute to overall frailty within the cumulative model, rather than relying solely on the physical frailty model, like the Phenotype model. This method is effective if the modified index remains comparable to the original scale and retains its predictive validity for outcomes such as mortality (22, 34).

The cumulative deficits frailty index is preferred to the phenotype model since the model predicts mortality more accurately (35), and is more sensitive to a person's health status (36), which is necessary to detect changes in frailty due to interventions that often lead to small changes over time. Also, the FI does not consider single deficits because the accumulation of multiple deficits is a more accurate and predictive measure of frailty and associated health risks, making it a robust tool in clinical practice and research due to its comprehensive and inclusive design (37).

1.4 Quality of life

Quality of Life (QoL) is a broad concept that encompasses an individual's overall well-being and satisfaction with life. Psychiatrists and others in the mental health field are in a good position to develop a specific focus on the non-material aspects of QoL. This is particularly important at a time when people tend to value the quality of their relationships even more than material considerations. This perspective is supported by the World Health Organization's definition of QoL (38), which "assesses individuals' perception of their position in life in the context of culture, value systems, and their goals, expectations, standards, and concerns." (39). Because it looks at multiple aspects of life, QoL is often used in fields beyond health, such as sociology, urban planning, and social policy, making it a versatile measure for understanding people's lived experiences (40, 41).

QoL is extremely important in understanding ageing populations (42). Studies highlighted by Gale, Cooper, and others [30] demonstrate an inverse relationship between psychological well-being and ageing-related issues such as disability and survival. Higher life satisfaction is associated with fewer ageing-related problems, and it contributes to increased life expectancy among older adults globally (42). QoL includes both subjective and objective dimensions, taking into account the various aspects of human well-being (42). Subjective perspectives focus on individual perceptions, feelings, and experiences such as happiness, life satisfaction, and fulfilment, recognizing that each person's QoL is influenced by their values, preferences, and life circumstances. On the other hand, objective perspectives concentrate on measurable indicators such as physical health, material well-being, and social conditions. While this perspective generally remains consistent as people age, it also takes into account additional considerations such as age and health (38).

Tools like CASP-19 (Control, Autonomy, Self-realization, Pleasure) (43) and the ICECAP index (ICEpop CAPability measure for Adults) (44), capturing the multifaceted nature of well-being. Moreover, the ability of QoL instruments to detect changes and accurately capture meaningful shifts over time or in response to interventions depends on their sensitivity and responsiveness, which are important characteristics (45).

Health-Related Quality of Life (HRQoL), on the other hand, is a more specific concept that focuses on how an individual's physical, mental, and emotional health affects their daily living and well-being. HRQoL is concerned with the impact of health conditions, diseases, disabilities, and medical treatments on a person's ability to function and enjoy life. It often includes aspects like pain, physical functioning, mobility, energy levels, and emotional states such as anxiety or

depression. HRQoL is especially relevant in clinical research and healthcare, where it helps evaluate how medical interventions and chronic illnesses influence a person's life. While it is a subset of QoL, its targeted focus makes HRQoL a valuable tool for understanding the outcomes of health-related changes in specific populations (38, 46, 47). Instruments such as the SF-36 (Short Form Health Survey) (48), EQ-5D (EuroQol-5 Dimensions) (49) are frequently used to assess these domains, providing valuable insights into an individual's health status and its effect on daily activities.

Considering the characteristics of your sample when selecting a QoL tool is essential for several reasons. First, different QoL tools are designed to assess various aspects such as physical health, mental well-being, social relationships, and environmental factors. Understanding your sample's demographics, cultural background, and health conditions allows you to choose a tool that aligns with the specific dimensions of QoL relevant to your population. Second, ensuring validity is crucial; selecting a tool validated for similar populations enhances the accuracy of measurement by ensuring it effectively captures the QoL experiences of your sample. Third, sample characteristics influence reliability; choosing a tool that accounts for these factors improves consistency in measurement over time and different conditions. Additionally, sensitivity to changes in QoL is enhanced when the tool aligns with the unique characteristics of your sample, enabling accurate assessment of improvements or declines (45).

1.5 The relationship among the three concepts

Frailty and Quality of Life (50) are essential components of successful ageing and are closely intertwined with the visions discussed earlier such as, a good physical and mental health, a quality of social life and importance measuring that for the health givers organizations. Here, I attempt to distinguish between ageing and frailty, as well as successful ageing and QoL.

Ageing is a natural process so that an organism becomes less and less able to adapt to challenges from the internal and external environment. Frailty is a clinical syndrome, and not all people are frail during their life span. Frailty leads to an increase in the rate of deterioration of body system (51).

The distinction between successful ageing and QoL for older people can be understood by looking at their differing emphases. QoL goes beyond health, encompassing factors such as good social relations, the ability to participate in meaningful activities, and the absence of functional limitations, which are often more important to older people (52). In contrast, the widely accepted definition of successful ageing by Rowe and Kahn includes three components: low risk of disease and disability, high mental and physical function, and active engagement with life (52).

Thus, successful ageing focuses primarily on physical health and active living, while QoL considers a broader range of factors contributing to overall well-being.

Measuring frailty and QoL involves covering several domains that are important for helping older people age successfully. The challenges of increased frailty among older individuals may impact their ability to maintain independence and engage in social activities (4). Frailty not only affects physical health but also has implications for psychological well-being and social engagement, all of which are key aspects of ageing well. Additionally, maintaining good physical health, psychological well-being, independence, and social engagement are vital contributors to the overall QoL for older individuals (4). Therefore, understanding and addressing frailty and QoL together are essential for promoting successful ageing and enhancing the well-being of older adults.

1.6 Motivation to investigate the association between Frailty and QoL in older people

When investigating the relationship between frailty and quality of life for individuals living in the community, it is preferable to focus on the social perspective. This perspective acknowledges the significant role of social determinants such as social support, community engagement, and living conditions, which are critical for maintaining independence and overall well-being in frail individuals (38). By avoiding the overlap with health-related domains of frailty, the social perspective provides a clearer and more distinct assessment of how social factors influence QoL. Moreover, social perspective aligns with the needs and preferences of older adults who wish to age in place (53), emphasizing person-centred care and non-medical interventions that can significantly enhance their QoL.

Therefore, examining the (longitudinal) association between frailty and QoL from a social perspective can clarify whether one affects the other or if the inverse relationship is only temporary. This understanding will guide health and social care services in effectively managing their services, enabling individuals to reside in the community for extended periods and reducing the pressures they face (20).

1.7 English Longitudinal Study of Ageing

The English Longitudinal Study of Ageing (ELSA) is a longitudinal study taken from private households of people in England who are 50 years old or older (54). The original members of the ELSA cohort were selected from those who responded to the Health Survey for England (HSE) (55) in the years 1998, 1999, or 2001. Additionally, partners who were living with core respondents at the time of ELSA interviews were included irrespective of age. Although Wave 1

only included respondents who lived in private households, participants who moved into institutions after Wave 1 were still included in future waves.

ELSA attempts to reflect the population profile of older people living in England, so it collects information from three aspects of ageing: health, social participation and wellbeing, and finances (54). The sample was refreshed in waves 3,4,6,7,9 and 10 to maintain the sample size (56). ELSA's staff utilize a self-completion form and/or face-to-face interview to collect the data from the respondents. So far, 10 waves of data have been released. In this work, we only include the first nine waves since the work was completed before the release of Wave 10. Table 1-1 shows the collected data years approximately every two years and the sample size for each wave.

Table 1-1: Collected data years of ELSA and their sample size

	Wave1	Wave2	Wave3	Wave4	Wave 5	Wave 6	Waveb7	Wave 8	Wave 9
Collected data year	2002/3	2004/5	2006/7	2008/9	2010/11	2012/13	2014/15	2016/17	2018/19
N	12099	9432	9771	11050	10274	10601	9666	8445	8736

The research used data from the ELSA, which is provided by the UK Data Service. When using ELSA as secondary data, it is not necessary to obtain an approved letter, but it is required to cite the source of the data based on the End User Licence Agreement (EULA) available at: https://ukdataservice.ac.uk/app/uploads/cd137-enduserlicence.pdf.

ELSA was an appropriate data set to investigate the reciprocal influences between the QoL and frailty since it is longitudinal data, contains many items suitable to operationalize frailty using a frailty index model and a multinational quality-of-life instrument, which is CASP-19. Also, the number of participants is large, and the range of age of the sample is between 50 to 90 years old. There are participants older than 90, but their age is recorded as 99 to avoid identification. It is important to know age as this might influence the relationships studied.

There are official weights to make waves representative of the English population with respect to age and sex. The context here though is of a longitudinal study where weighting is more complex and consequently agreed weights are not available. For simplicity, and to ensure efficient modelling regarding sample size, unit weighting is applied.

Within each chapter, I will explain the selected analytical sample of ELSA based on the study's target.

1.8 Literature review

Here, three reviews were conducted to support the work undertaken in Chapters 2 through 4. Firstly, the longitudinal association between frailty and multimorbidity in older individuals was reviewed (subsection 1.8.1). The second review was of methods used to test the consistency of multidimensional QoL measures (subsection 1.8.2). Finally, the assessment of longitudinal associations between frailty and QoL were reviewed (subsection 1.8.3). The selected study period covers the last decade of published research papers, from 2014 to 2024. Two systematic reviews found a lack of longitudinal association between frailty and QoL, as well as the longitudinal association between frailty and multimorbidity, before this time period (57, 58). However, the selected study period for the statistical methods that test the consistency for QoL measures covers from 2003 to 2023.

Although the interest is in studying older people aged 50 and above, no age limit was set for the reviews.

1.8.1 Association between Frailty and Multimorbidity

The first literature review aims to investigate the association between frailty and multimorbidity over time in community-dwelling elderly individuals or those participating in cohort studies. Cross-sectional studies, conference abstracts, and presentation posters were excluded to the search, and only studies written in English were considered.

Two databases were used to conduct this research, including PubMed and Web of Science. The search terms in the two databases that I used are following (57), the search terms can be found in Appendix A (section A1).

The search process considered all results from 2014 to April 3, 2024. A total of 340 citations were found in both databases, out of which 61 were excluded for duplication using EndNote. Out of the remaining 279 publications, 235 were excluded (i.e., systematic reviews, protocol studies, conceptual studies or study the impact of frailty and multimorbidity independently on other outcomes), and 44 underwent abstract screening; finally, 13 met the inclusion criteria and were considered eligible. Figure 1-1 shows the process of selected studies.

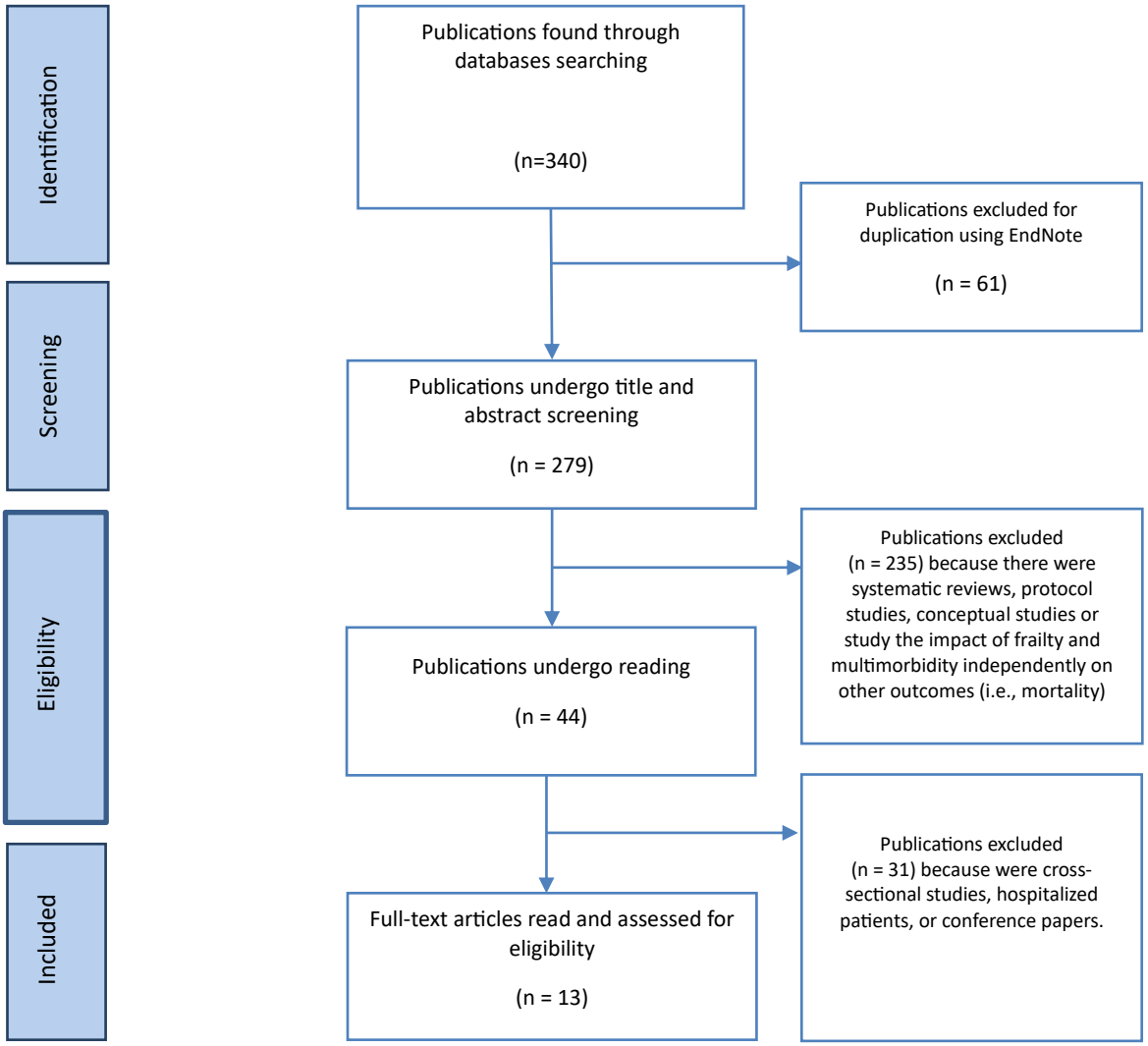
1.8.1.1 Results

Characteristics of the included studies

Table A4 in Appendix A presents studies with study populations aged 50 years on average. The sample size varied between 2,122 and 92,640. The percentage of females ranged from 0 to 64%,

and some studies did not report this information. It is worth noting that the included studies covered studies in Asia, Europe, and North America. Most of the participants in these studies lived in the community, and some of them lived with chronic diseases such as cancer. Twelve out of 13 studies included two-time points, with varying intervals between them. One study had three time points (59).

Figure 1-1: Flowchart of the studies selection process for the longitudinal association between frailty and multimorbidity



Frailty measures

Around two-thirds of the studies included in the analysis used phenotype frailty measures, while two studies used the frailty index approach (60-62). Additionally, two studies used both measures (59, 63). One study used an index developed by the Canadian Study of Health and Ageing (CSHA) (64).

Multimorbidity Measures

The 13 studies used three different approaches to measure multimorbidity. The first method involved counting the number of chronic diseases and regarding the number as a count variable (59). The second method counted the number of chronic diseases and then used a cut-off to define multimorbidity. Some studies defined multimorbidity with two or more chronic diseases (60, 65), while others used three or more chronic diseases (62). The third method was to divide the chronic diseases into a number of clusters using Latent Class Analysis (LCA) (66, 67) or using a fuzzy c-means cluster algorithm (68) or using the expertise of authors (61).

The number of diseases and clusters varied among the studies, ranging from 4 to 28 and 4 to 10. The most common long-term conditions among studies were hypertension, diabetes, cancer, cerebrovascular diseases, kidney diseases and osteoporosis while the common clusters were cardiovascular disease and neuropsychiatric disease. Ma, He (63) focused only on one cluster of multimorbidity, namely cardiovascular diseases (coronary heart disease, stroke, and diabetes).

Association between frailty and multimorbidity

Frailty and multimorbidity represent distinct yet interrelated concepts in the realm of geriatric medicine. Despite their differences, both frailty and multimorbidity share commonalities in their ability to predict adverse health outcomes. These outcomes include increased mortality, decline in physical function, higher prevalence of depression, and greater likelihood of polypharmacy. Woo and Leung (65) examined the independent and combined effects of multi-morbidity, dependency, and frailty on several outcomes and emphasize that the combination of multimorbidity and frailty has a greater impact on adverse outcomes than each alone.

Three studies have used the multivariable Cox proportional-hazards regression model to predict mortality in different scenarios. Strandberg, Lindström (69) predicted mortality by using three frailty levels (fit, prefrail and frail) within two multimorbidity levels (no = 0 or 1, yes = 2+) and found that a combination of multimorbidity and frailty levels is a better predictor of the risk of mortality than frailty alone. Nguyen, Wu (66) also used the same method and reported that there are different mortality patterns associated with frailty status and five multimorbidity classes. Chu, Ho (67) predicted mortality by using four multimorbidity patterns with/without

frailty and found that frailty had varying additive effects on mortality for older adults with distinct multimorbidity patterns.

Two studies looked at frailty as the main predictor of multimorbidity whether defining it as a count of chronic diseases or the number of clusters. Guaraldi, Brothers (60) addressed the relationship between frailty at baseline (measured with a frailty index) and incident multimorbidity (2+ chronic diseases), in HIV outpatients, finding a significant association (incidence rate ratio = 1.98; 95% CI = 1.65–2.36) by using a longitudinal generalized estimating equation method. Also, frailty was a risk factor for temporal progression from healthy to one or more chronic diseases which includes coronary heart disease, stroke, and diabetes among middle-aged and older people using a multistate model (63).

Other studies, however, have looked at multimorbidity as a predictor of the incidence of frailty. In one study, the multimorbidity score was computed by assigning weights to diseases based on their severity (64). The study used a linear regression and showed that the score for multimorbidity was associated with a slight increase in frailty score, but it was not statistically significant. On the other hand, the results of Tazzeo, Rizzuto (68) indicate that multimorbidity patterns characterised by cardiovascular and neuropsychiatric diseases are most strongly associated with physical frailty by using a multinomial logistic regression model. Moreover, Voshaar, Jeuring (61) found that the larger the number of different chronic diseases that were present, the steeper the increase of frailty over time using a linear regression model. Luo, Chen (70) study revealed that older adults in the United States with multiple health conditions experienced a worse level of frailty, and the link between frailty and multimorbidity varied across the four multimorbidity patterns using a semi-Markov multi-state model.

The bidirectional relationship between frailty and multimorbidity was examined by using a cross-lagged panel model by Feng *et al*. (59) so that measuring frailty by phenotype model and a FI and treated the number of 14 long-term conditions by counting. They found that previous frailty was found to have a positive correlation with subsequent multimorbidity, and *vice versa*. However, prior multimorbidity had a greater effect on subsequent frailty. Furthermore, frailty at the beginning and early changes in frailty were significant predictors of later changes in multimorbidity, and *vice versa*. The study noted potential bias in the result as the cross-lagged panel model (CLPM) does not consider individual and group effects.

1.8.1.2 Discussion

Reviewing the relationship between frailty and multimorbidity is complex partly due to varying definitions of these two concepts. Frailty and chronic diseases are closely related and have a

significant impact on an individual's health trajectory in later life. Frailty is characterized by a decreased ability to adapt to stress due to diminished functional reserves, while chronic diseases are long-term conditions that can lead to persistent health issues and functional decline (71).

Using phenotype as the frailty measure is more logical than using a frailty index (FI) to look at the association between frailty and multimorbidity because components of a FI include chronic diseases or LTCs. However, some studies using phenotype frailty consider only the physical aspect of frailty and diminish other components such as mental health and cognitive health (66). For example, Voshaar, Jeuring (61) suggested using a frailty index that includes some deficits related to chronic diseases to evaluate the effect of multimorbidity on frailty progression. They argue that the features of a frailty index are not dependent on the number or type of health deficits included. In addition, Guaraldi, Brothers (60) compared two frailty indices - one with chronic disease deficits and one without. They found that both indexes provided similar results in terms of identifying mortality risk. Interestingly, the frailty indices that incorporated more variables did not have a significantly better ability to discriminate mortality risk.

There were three ways to define multimorbidity, each with its advantages and disadvantages. The first and second methods involve counting the number of long-term conditions (LTCs) with the second method using a set cut-off point to divide into groups. These approaches are useful for comparing studies and taking into account the accumulation of LTCs over time. However, they do not consider how different diseases may affect frailty as they give each LTC equal weight.

The third method involves identifying clusters of LTCs that may impact frailty or its progression. While this approach considers the effects of various diseases, it assumes that each participant's cluster of LTCs remains constant over time. This assumption fails to account for the possible alteration of these clusters over time, which could compromise the method's accuracy.(68). Additionally, It is challenging to apply the data-driven multimorbidity patterns directly to the clinical classification of individual patients due to the cluster being based on the available list of LTCs and the statistical methods used (70). So, to investigate the relationship between frailty and multimorbidity over extended periods and to account for different LTCs listed in comparative studies, it would be appropriate to first count the number of LTCs and then define multimorbidity based on a specific cut-off (2+, 3+ or 4+). However, when considering a shorter period, dividing the LTCs into clusters can be helpful as it avoids changes in these clusters over time.

1.8.1.3 Conclusion and a research gap

After reviewing the studies on the longitudinal association between frailty and multimorbidity, it becomes evident that they have a mutual effect as focal variables. However, most of these

investigations were constrained by using only two time points, which limited the depth of analysis and nuanced understanding of the temporal dynamics between these two conditions. Also, it is evident that most studies primarily concentrate on delineating the linear longitudinal relationship between frailty and multimorbidity, potentially overlooking more nuanced dynamics. Thus, a notable gap persists in capturing variations within and between individuals adequately. Furthermore, elucidating the correlation between frailty and multimorbidity over extended periods remains challenging, compounded by a dearth of investigations into non-linear progressions between these conditions.

Embracing a count-based method for identifying multimorbidity, rather than clustering chronic diseases as well as using a FI after omitting LTCs considering it has at least 30 deficits, could offer insights into tracking frailty progression over time across varying levels of multimorbidity. Moreover, recent findings suggest that while a significant proportion of frail individuals exhibit multimorbidity, the reverse is less common (57), underscoring the profound impact of multimorbidity on frailty development. Moving forward, adopting multilevel growth models could facilitate a more comprehensive analysis, accommodating variations within and between individuals while exploring potential non-linear relationships (72).

1.8.2 Statistical methods to test the consistency of QoL measures

Consistency or Measurement Invariance (MI) indicates that an instrument will produce consistent measurements across distinct groups or conditions, such as age groups or several occasions (73). MI is one of the main psychometric properties of an instrument once it is established, and failure to consider the measurement invariance of the instrument may lead to a biased comparison of observed responses (74). Consequently, achieving MI makes the instrument more reliable and practical which helps, for example, healthcare professionals make appropriate clinical decisions (75).

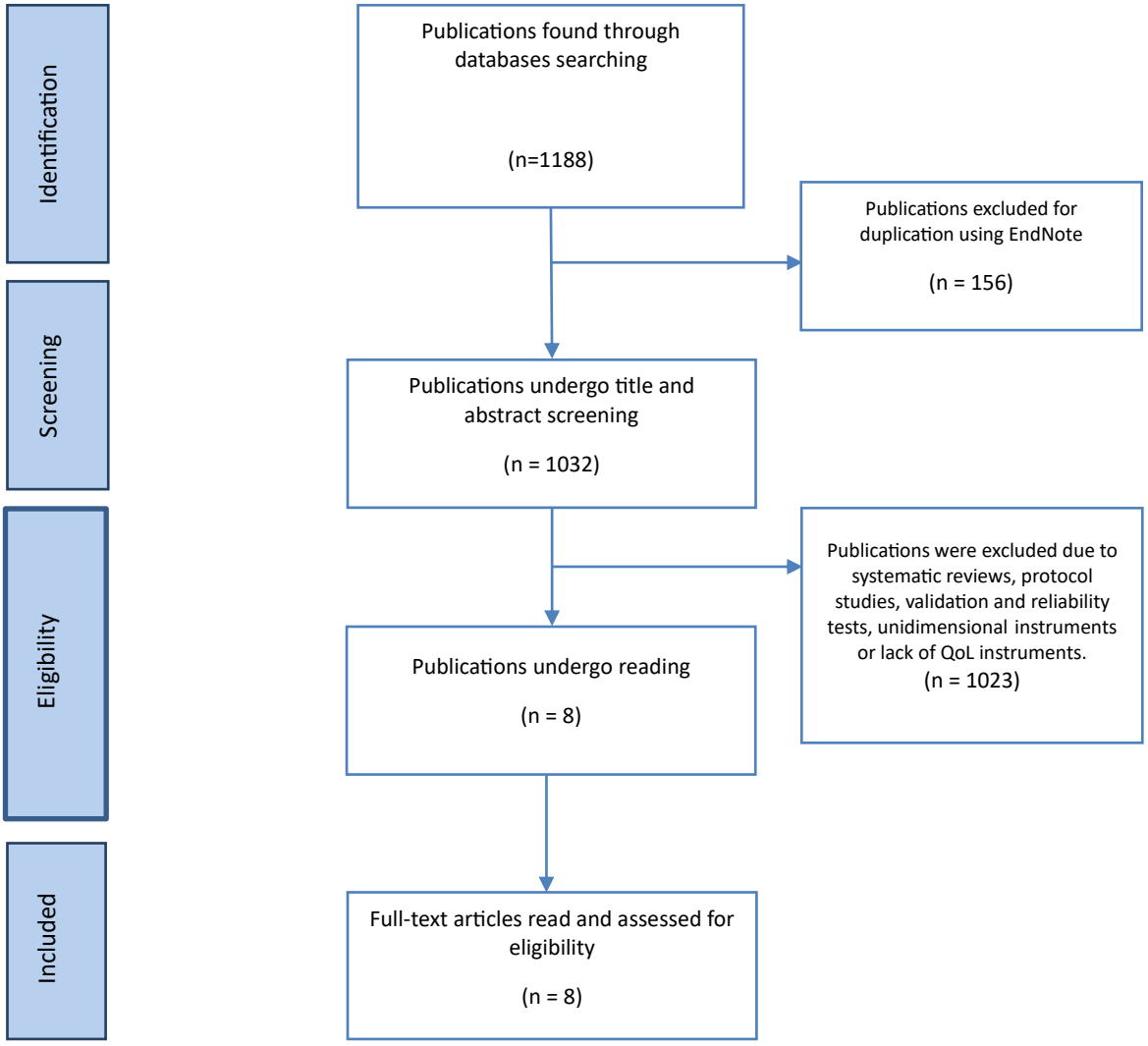
A literature review of statistical methods for establishing measurement invariance was conducted on quality-of-life measures. The literature review was limited to the multinational instruments of QoL for older people. Searches were performed for English articles in three databases, including Web of Science, PubMed and Ovid (Medline and Embase) dating back to 2003 until November 2023. The search terms were found in Appendix A (section A2). The initial search in all three databases produced 1188 results. After removing 156 duplicates and 1024 articles were excluded in two steps, 8 articles remained. Some articles were also identified from the references of the selected articles. Figure 1-2 shows the process of selected studies. Table A5 in Appendix C summarizes the included studies.

1.8.2.1 Results

Characteristics of the included studies

Table A5 in Appendix A presents studies of participants aged 18 years and over. Five of these studies targeted people who aged 50 years and more (76-80). The sample size varied between 137 and 61,355. The percentage of females ranged from 41% to 61%, and some studies did not report this information (77, 81). It is worth noting that the included studies covered studies in Asia, Europe, North America and Australia. Most of the participants in these studies lived in the community, while some of them were collected from specific patient groups, such as cancer patients (82). A mix between individuals who live in the community and those who live in long term care centres was used in one study. Most of studies used gender and age as variable groups. Only a few studies used education level (76, 78) , race (77, 81) or living place (78). One study tested longitudinal MI (82).

Figure 1-2: Flowchart of the studies selection process for the statistical methods that test measurement invariance for multidimensional QoL measures.



QoL measures and their factor structures

The studies included in the literature used various QoL measures including the Short Form Survey (SF-36) (81, 83), the WHOQOL-BREF Taiwan version (76), the Kidney Disease QoL 36-item survey (KDQOL-36™) (77), the WHOQOL-AGE (78), the CASP-12 (79), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (82), and the People's Quality of Life questionnaire (OPQOL) (80). Most measures include several domains, with physical and mental health being the most common. The OPQOL and CASP-12 measures are based on older people's perspectives, and CASP-12 has the advantage of being grounded in a theoretical background (79). All QoL measures, except for the WHOQOL-BREF Taiwan version and CASP-12, have been reported with a first-order structure. This means that QoL is measured

through its domains, and these domains can be correlated to each other within the framework of Confirmatory Factor Analysis (CFA). On the other hand, WHOQOL-BREF Taiwan version and CASP-12 have reported a second-order factor structure. This means that the overall QoL is measured by several domains, which in turn are measured by several indicators. In some studies, several factor structures for the QoL measure were tested, and the best-fitting one was selected for the MI test (78-80, 82).

Statistical methods to test MI

From the included studies, two statistical methods were used to test measurement invariance: the Multi-Group Confirmatory Factor Analysis (MG-CFA) (84) and Item response theory (IRT) models (85). The Multi-Group Confirmatory Factor Analysis is a common method to test MI across several QoL instruments. MG-CFA is a nested model of Confirmatory Factor Analysis (CFA), and CFA is a statistical technique used in structural equation modelling (86). CFA is used to assess the theoretical relationship between observed variables and latent variables. A latent variable is not directly observed but can be inferred from several observed variables. MG-CFA tests whether these relations are consistent across several groups with several nested models. Each model introduced more equality constraints across groups. Configural invariance tests the equivalence of the fixed and free factor loadings pattern. Weak invariance tests the equivalence of factor loadings across groups or time. Meanwhile, strong invariance examines the equality of latent means. Finally, strict invariance examines the invariant items' residual variance.

In educational and psychological research, IRT models are frequently utilised (87) but fewer are used in QoL studies (83). These models use logistic regression to illustrate the relationship between observed item responses (dichotomous or polytomous) and the underlying latent variable. The one, two, and three IRT parameter models are the three most commonly used models to analyse binary items. The simplest IRT model is the one-parameter Rasch model (88), which has only one parameter, the item difficulty. The two-parameter Logistic (2 PL) model (89) is an extension of the one-parameter Logistic model, and it permits the discrimination parameter to vary across items. The three-parameter Logistic (3PL) model (89) adds a guessing parameter to the 2PL model, recognizing that respondents may guess, for example, in multiple-choice questions. The IRT models for binary items can be used for polytomous items as well. Polytomous items are items with more than two responses. Commonly used IRT models for polytomous items are the Partial Credit Model (PCM: (90)) and the Graded Response Model (GRM: (91)). The partial credit model is an extension of the binary one-parameter Rasch model to a polytomous

model. The polytomous GRM permits the categorical response functions to vary, showing variations in the discrimination parameters across items.

Several fit indices were considered in the literature, such as chi-square distribution with a degree of freedom (df), comparative fit index (CFI) and robust root mean square error of approximation (RMSEA). The Chi-square test is impacted by sample size, meaning that as the sample size grows, the test becomes more responsive to even minor variations between the correlation matrix of observed values and the correlation matrix of expected values. Alternatively, CFI or RMSEA were used to assess the goodness of fit. The CFI and RMSEA range from 0 to 1, and the values of 0.90 (acceptable fit) or 0.95 (good fit) are used as cut-points for the CFI while 0.06 (good fit) or 0.08 (acceptable fit) for RMSEA (92). To compare three constrained models (weak, strong and strict), the ΔCFI criterion was utilized due to its lower sensitivity to sample size. Consequently, if there is a change in CFI of less than 0.01 along with a change in RMSEA of less than 0.015, the models can be considered to be comparable (93).

1.8.2.2 Discussion

Testing measurement invariance for QoL measures has not been given much importance based on the number of studies conducted. Studies that did not demonstrate consistency in the QoL variable groups selected are unable to manage non-invariance measurements. Moreover, longitudinal measurement invariance (LMI) is seldom taken into account in the literature. Only one study has examined two points in time. LMI is crucial for cohort study analysis because it ensures that the constructs being measured, such as QoL, remain consistent and comparable over time. This consistency is essential for accurately assessing changes in QoL and attributing them to real shifts in participants' experiences rather than measurement inconsistencies (94).

The nature of QoL measures that are mentioned here could classify into healthcare perspective measures and individual (especially older people) perspective. The measures that focus on health domains assists healthcare providers in making decisions based on a patient's emotions, while the measures established from older people needs and perspective offer a complete overview of elderly individuals with health issues, aiding healthcare professionals in performing a comprehensive evaluation. Thus, the choice of QoL measure depends on the perspective in which we are interested.

It is worth mentioning that in most of the studies included, QoL was measured through its domains rather than the concept as a whole. Only two studies have reported second-order factors structure. The second-order model can be utilized with dimensions or as a general factor, depending on the research interests. This makes it more concise and flexible (79).

The most commonly used statistical method to test MI for multidimensional QoL measures is MG-CFA. On the other hand, the use of IRT in public health studies is rare (83), and results for these two methods could differ (81). Using MG-CFA provides a great opportunity to compare the MI test results among related studies.

When conducting a MG-CFA test to measure invariance, it is important to achieve acceptable or favourable fit indices for the chosen factor structures. These indices should progressively meet both weak and strong thresholds, ideally showing a non-significant decline in their values across successive stages. However, when dealing with high levels of factor complexity, such as incorporating second-order factor structures, the process needs more steps (76). This requires the inclusion of MI assessments for each additional level of factor hierarchy, increasing the analytical depth and time investment needed.

There are common variable groups used in the included studies, such as gender and education that may lead to different interpretations of item descriptions (78). Although age groups varied among the studies (78-80, 83) that use it as variable group, all of them separate the one age group for older people, who may have had differing perceptions of QoL compared to those who were younger (78).

Handling the response values in MG-CFA as continuous or ordinal is controversial. Both approaches were used in the literature. According to Robitzsch (95), treating response values ordinally may impose a normal distribution on latent factors, which could potentially introduce inaccuracies in empirical applications. On the other hand, treating ordinal response values as continuous could result in biased correlations and parameter estimates (96). Continuous treatment assumes that the distance between ordinal categories is equal, which may not be accurate. For example, the difference between "agree" and "neutral" may not be the same as between "neutral" and "disagree". When working with large samples, any biases introduced by a particular approach are typically balanced out, resulting in more accurate parameter estimates and stronger statistical power. The central limit theorem guarantees that as the sample size increases, the distribution of the estimates becomes more normal, which minimizes the effect of the initial data treatment method, rendering these distinctions inconsequential in applied research (97). Therefore, it would be preferable to treat the indicators as continuous due to the ease of handling and interpreting.

Robust maximum likelihood has been used to estimate the model parameters when indicators were treated continuously (81). This was because the indicator showed a multivariate non-normal distribution. However, other studies that were included treated the indicators in an

ordinal manner and used various model parameter estimations such as Weighted Least Squares Mean and Variance corrected (WLSMV) (79, 80).

1.8.2.3 Conclusion and a research gap

Testing the MI for QoL measures has not been thoroughly explored especially LMI, resulting in inconsistencies in variable groups and limited longitudinal studies. QoL measures can be divided into healthcare and individual perspectives. The healthcare perspective aids in making healthcare decisions, while the individual perspective provides a comprehensive view of older adults' well-being. The choice of measurement depends on the research focus. Most studies measure QoL through its domains, with only a few utilizing second-order factor structures. MG-CFA is commonly used for testing MI, although it requires achieving acceptable fit indices at various complexity levels. Common variable groups such as gender, education, and age can affect item interpretation. There is a debate over treating response values as continuous or ordinal in MG-CFA, but differences may be negligible with large sample sizes.

Current research indicates that CASP-12, a truncated version of CASP-19, demonstrates superior fit indices statistics, suggesting it may be a more robust measure (98, 99). Additionally, various studies have utilized the CASP-12 scale to assess QoL across a broader age range (100, 101). There are inconsistencies regarding the optimal factor structure for the CASP-12. Consequently, testing various factor structures, including a second-order model, will be useful to inform researchers interested in measuring QoL in this population on a larger sample size, such as ELSA. Following this, measurement invariance for the CASP-12 across different variable groups, including age, will be tested to assess the robustness of the selected factor structure. This will ensure that the interpretation of results is not impacted by measurement errors arising from differences across variable groups.

1.8.3 Longitudinal association between frailty and QoL in older people

This literature review aims to investigate the longitudinal association between frailty and QoL over time in community-dwelling elderly individuals or those participating in cohort studies. Cross-sectional studies, conference abstracts, and presentation posters were excluded to achieve this, and only studies written in English are considered.

Two databases were used to conduct this research, including Web of Science and PubMed. The search terms were reported in Appendix A (section A3). The search process has included all

results since the year 2014 and until 18 April 2024. The initial search produced 253 results. After removing 118 duplicates and 124 irrelevant articles (i.e., unidimensional instruments for QoL, systematic review or cross-sectional study), leading the final included studies to be 9. Figure 1-3 shows the process of selected studies.

1.8.3.1 Results

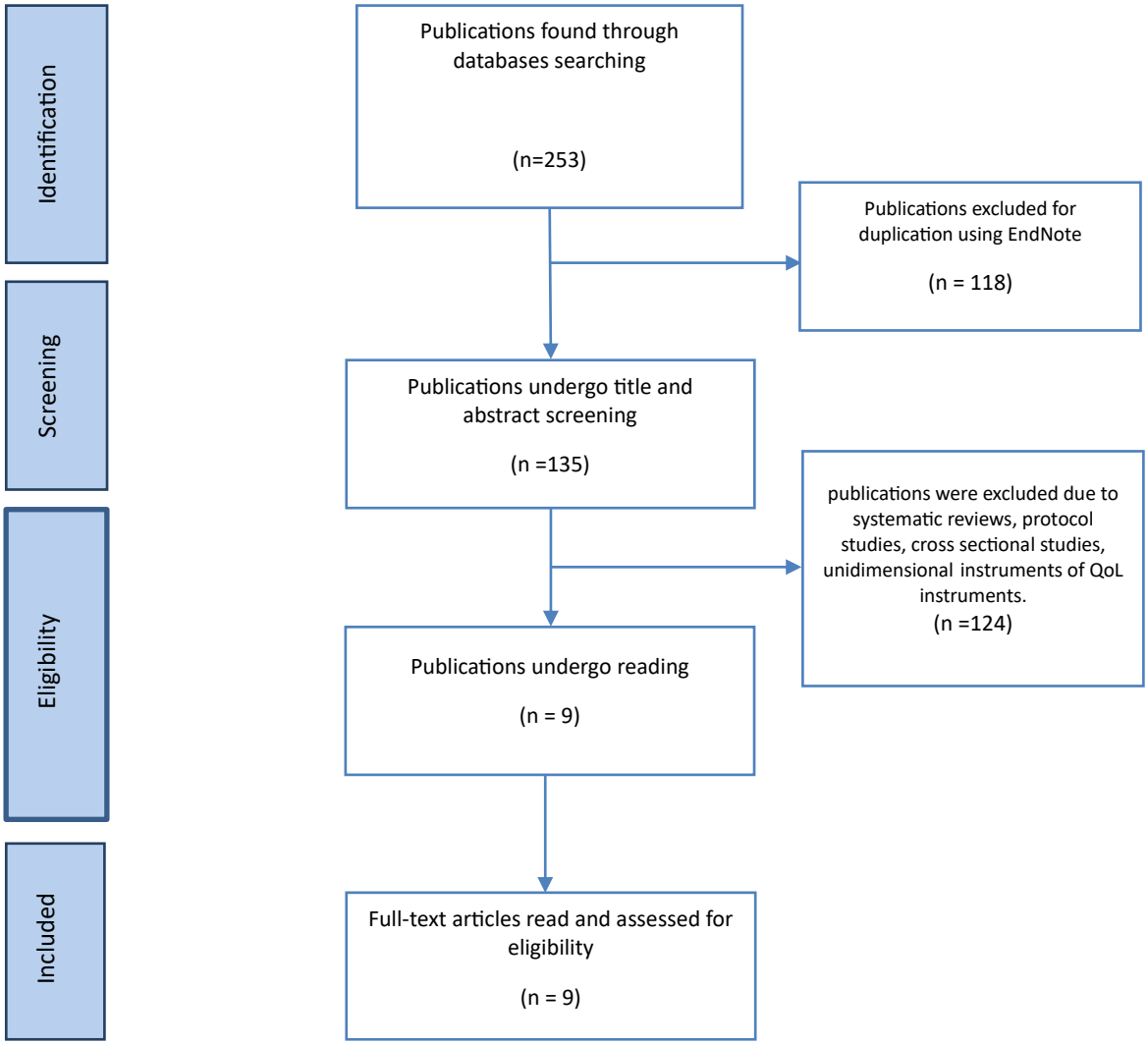
Characteristics of the included studies

The nine inclusion studies summarized in Table A6 in Appendix A. The studies were conducted with different datasets and in different countries. Moreover, the sample size at the baseline ranges between 269 and 19649. The percentage of females varied between 55% and 62%, although some of studies did not report this information. The age range for seven of them was 60 years old and above while two studies considered those aged 50 years old and more. Eight studies conduct a longitudinal analysis within 2 or three time points, and only one study account for 6 time points within 2.5 years 6 months apart. Most studies applied the analysis to the participants who live in the community. The majority of the studies were carried out in European countries, with only one study each in Brazil (102), Mexico (103), and Japan (104).

Frailty and QoL measures

In one study, the Tilburg Frailty Indicator (TFI) was employed (105). In the remaining studies, frailty was assessed using the phenotype in four instances (102-104, 106) and the accumulated deficits model in the other four (107-110). As for QoL measures, three studies (106, 109, 110) utilized CASP-19 or its abbreviated version, CASP-12, while an additional three employed WHOQOL or its abbreviated form, WHOQOL-BREF (103-105). OPQOL, SF-12, and EuroQol-5D were each employed in separate studies to measure QoL (102, 107, 108).

Figure 1-3: Flowchart of the studies selection process for the longitudinal association between frailty and QoL



Longitudinal association between frailty and QoL

The majority of the included studies explored the longitudinal correlation between frailty and QoL, with one serving as an outcome and the other as a predictor, consistently reporting an inverse relationship. Statistical methods varied depending on factors like how the outcome variable was handled (categorical or continuous), the inclusion of time as a predictor, and consideration of repeated measures. Additionally, some studies delved deeper into the longitudinal association between frailty and specific QoL domains (105). The most recent study investigated the bidirectional relationship between frailty and QoL (110).

Frailty as a predictor for QoL changes

Four studies treated frailty as a predictor of QoL changes. Gale, Cooper (106) reported that frailty at baseline predicted change in QoL at a later time point using linear regression. Kojima, Iliffe (107) reported that frailty predicted the changes in QOL over 2.5 years with 6 measures (6-month intervals) according to baseline frailty status. They used the two-level hierarchical linear model that deals with repeated measurements of QOL nested within each individual and described the trend with time within individuals (level 1 observation) and heterogeneity in the trend across individuals (level 2 observation). The study revealed that more frail individuals had a lower QoL at the start of the study. Those who had low levels of frailty (FI <= 0.27) experienced an improvement in their QOL over time, whereas those with higher levels of frailty (FI>0.27) experienced a decline in their QOL. The individuals who were the most frail experienced the most rapid decline in their QOL over time. Geessink, Schoon (108) found that frailty was independently associated with lower patient-reported QOL at baseline as well as after 12 months concerning health-related QOL using linear mixed models. Rivera-Almaraz, Manrique-Espinoza (103) results indicate that baseline frailty status was an independent predictor for a deteriorated QoL in the follow-up using a linear regression model. Veronese, Noale (109) stated frailty measured by Modified multidimensional prognostic index was associated with a higher risk of mortality and significantly lower QoL over 10 years using a linear mixed model.

Two studies looked at frailty as a predictor for domains of QoL. Andrade, Andrade (102) reported that frailty is a predictor for two domains of QoL. They showed that frailty was a predictor factor for reducing QoL in both its mental and physical components using mixed effects linear regression models. In addition, Gobbens and van Assen (105) study the impact of three frailty domains (physical, psychological and social) on four QoL domains: physical, psychological, social and environmental. They reported that physical frailty, in addition to one component in psychological frailty and one social frailty component predicted future scores on quality-of-life domains using a linear regression model.

QoL as a predictor for frailty incidence

Two studies treated QoL as a predictor of frailty incidence. Gale, Cooper (106) stated that psychological well-being may be a protective factor for the incidence of three frailty levels (mild, pre-frail and frail) using multinomial logistic regression. Gale, Cooper (106) also conducted a separate examination of scores for hedonic (pleasure) and eudaimonia (control, autonomy and self-realization) dimensions of the psychological well-being measure showed that higher scores on both were associated with decreased risk of frailty or pre-frailty. Mori, Nagai (104) study

found that improvement in the physical domain of QoL was significantly associated with an improvement in frailty status, independent of the baseline frailty status using modified Poisson regression analysis. However, no significant associations were found between any domains of QoL and worsening frailty status.

Bidirectional longitudinal association between frailty and QoL

Two studies investigated the bidirectional relationship between frailty and QoL. Gale, Cooper (106) conducted two separate models and tested the frailty as predictor for the QoL using a linear regression model while they used multinomial logistic regression to predict frailty states based on the score of QoL. The second study used a cross-lagged panel model over 5 years (110). The study revealed that initial frailty or early changes exert a stronger influence on subsequent QoL or its late changes compared to the reverse scenario. Essentially, frailty emerges as a longitudinal precursor in the bidirectional association. Moreover, the study suggested the presence of potential mediators, such as cognition, which could impact the longitudinal relationship between frailty and QoL.

1.8.3.2 Discussion

Longitudinal studies underscore the inverse correlation between frailty and QoL, investigating whether frailty predicts changes in QoL or *vice versa*. Furthermore, these inverse associations extend to encompass certain domains within both concepts. The most recent study (110) examined a bidirectional relationship between frailty and QoL, finding that frailty exerts a greater impact on subsequent QoL compared to the reverse direction of the relationship. Additionally, few studies advocated the exploration of various mediators, such as cancer or cognition, which might have elucidated this inverse relationship.

Some studies appropriately consider the nature of longitudinal data using suitable statistical methods, while others do not, as seen in those analysed by a linear regression model. Several studies utilized a linear mixed model to accommodate repeated measures, incorporating random effects into the model and leveraging available information, which is effective for handling missing data in longitudinal analyses. However, some studies opted for a linear model, missing out on this advantage, such as handling both fixed and random effects, managing correlated data (repeated measures), dealing better with missing data, providing more precise estimates, and supporting complex experimental designs (111). Regarding the ordinal outcome of phenotype frailty, two statistical methods were employed: multinomial logistic regression and proportional odds regression model. The latter is more appropriate as it considers the ordinal nature of the outcome values. A cross-lagged panel model was utilized to explore the bidirectional relationship

between frailty and QoL. While this model is suitable for such analyses, its parameter estimation does not account for the two levels of estimation: group-level and person-level.

Some studies have delved into examining the longitudinal relationship between specific domains of frailty and QoL, aiming to identify key domains that could help explain this inverse relationship. Among QoL measures, physical and mental health are commonly assessed domains. However, studying the relationship between frailty domains and QoL domains can sometimes yield misleading results due to overlap between frailty, which measures health, and certain health-related domains of QoL. Therefore, using QoL measures that exclude health-related domains, such as CASP-19, can offer advantages in addressing this issue.

The consideration of frailty and QoL as latent concepts with multiple measures for each posed a challenge in accurately determining their longitudinal relationship. Some studies aimed to identify mediators to elucidate this inverse relationship, with some mediators themselves being latent variables, such as cognition. While this approach offered some utility, it also introduced complexities in interpretation. Opting for well-defined and clear mediators, such as one or two long-term conditions or sociodemographic variables, could have proved useful and facilitate easier interpretation.

Conclusion and a research gap

One-way directional relationships between frailty and QoL have been investigated in both directions, with frailty often being a stronger predictor than the other way around. In terms of the bidirectional relationship, cross-lagged panel models have been used, but with some group-level estimations being missed.

By analysing the two-way relationship between frailty and QoL through a modified version of the cross-lagged panel model and conducting multiple analysis groups for CASP-12, parameter estimation can be improved and bias reduced.

1.9 Aims of the thesis

In my thesis, I will investigate the longitudinal relationship between frailty and QoL for older individuals who have resided in the English community for over 16 years, with multiple data collection points per participant.

The thesis aims to address the following research questions:

1- What is the impact of long-term conditions (LTCs) on the progression of frailty within the ELSA? Here progression refers to changes of frailty over time, or as individuals age. Additionally:
    a. Does this progression follow a linear or nonlinear trajectory as participants age, and:
    b. Does it differ between men and women?
2- To what extent does the CASP-12 questionnaire exhibit a well-defined factor structure with a second-order factor nested within four first-order domains—control, autonomy, pleasure, and self-realization—within ELSA?
    a. Is this factor structure interpreted similarly by respondents across various variable groups, with a particular emphasis on age to test applying this measure in wide range of age further of the those only aged between 65 to 75 years old?
    b. Since 45% of participants in ELSA joined from wave 2 onwards, participants at wave 1 were considered as one group, and all participants from wave 2 to wave 9 as another group to test whether the factor structure of the CASP-12 is invariant or not. Including participants from different time points will not only enhance the power of the analysis but also pave the way for testing LMI in future research endeavours.
3- Exploring the longitudinal relationship between frailty and QoL in two levels including within-person and group levels to answer these questions. At the within-person level three questions were addressed as follows:
    a. Does frailty increase for a person at a one-time point lead to QoL tending to decrease at a later time point?
    b. Does the QoL increase for a person at a one-time point lead to their frailty tending to decrease at a later time point?
    c. At a specific point in time, is a person's increase in frailty associated with a decrease in their QoL?

    At the group level, the study examines two research questions:

    d. Do participants who exhibit greater levels of frailty generally experience a reduced QoL?
    e. Do participants who show increased trajectories in frailty tend to show decreased trajectories in QoL?

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Chapter 2 The impact of long-term conditions on the progression of frailty

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2.1 Abstract

Objective

To explore longitudinally the impact of multiple long-term conditions (LTCs) on frailty progression separately for males and females.

Methods

A functional frailty measure (FFM) was used to examine putative determinants of frailty progression among participants aged 65 to 90 in the English Longitudinal Study of Ageing (ELSA), across nine waves (18 years) of data collection. A multilevel growth model was fitted to measure the FFM progression over 18 years , grouped by LTC categories (zero, one, two and more).

Results

There were 2396 male participants at wave 1, of whom 742 (31.0%) had 1 LTC and 1147 (47.9%) had ≥2 LTCs. There were 2965 females at wave 1 of whom 881 (29.7%) had one LTC and 1584 (53.4%) had ≥2 LTCs. The FFM increased 4% each 10 years for the male participants with no LTCs, while it increased 6% per decade in females. The FFM increased with the number of LTCs, for males and females. The acceleration of FMM increases for males with one long-term health condition or more; however in females the acceleration of FMM increases when they have two LTCs or more.

Conclusion

Frailty progression accelerates in males with one LTCs and females with two LTCs or more. Health providers should be aware of planning a suitable intervention once the elderly have two or more health conditions.

2.2 Introduction

Population ageing leads to increased demand for health and social care and associated cost pressures (1). By 2028, 25% of England's population will be aged 65 and over (2), with 8% classified as frail (3). Frailty increases with age and is associated with higher healthcare utilization (4), and its determinants are key for effective healthcare services provision. Studies have identified protective (e.g. higher wealth, increased social support) and harmful (e.g. lower wealth, educational achievement, presence of long-term conditions, being female) factors associated with frailty progression (5). However, there is a lack of evidence on the impact of multiple long-term conditions (LTCs) longitudinally as a separate determinant of frailty progression (5). LTCs are defined as "A long term condition is one that cannot currently be cured but can be controlled with the use of medication and/or other therapies" (6). Sanders, Boudreau (7) studied the impact of diabetes on frailty development, and Thompson, Theou (8) reported that two or more LTCs contributed to increasing frailty in older people.

This study aimed to explore longitudinally the impact of multiple LTCs on frailty progression separately for males and females due to behavioural, social, and biological differences (9).

2.3 Methods

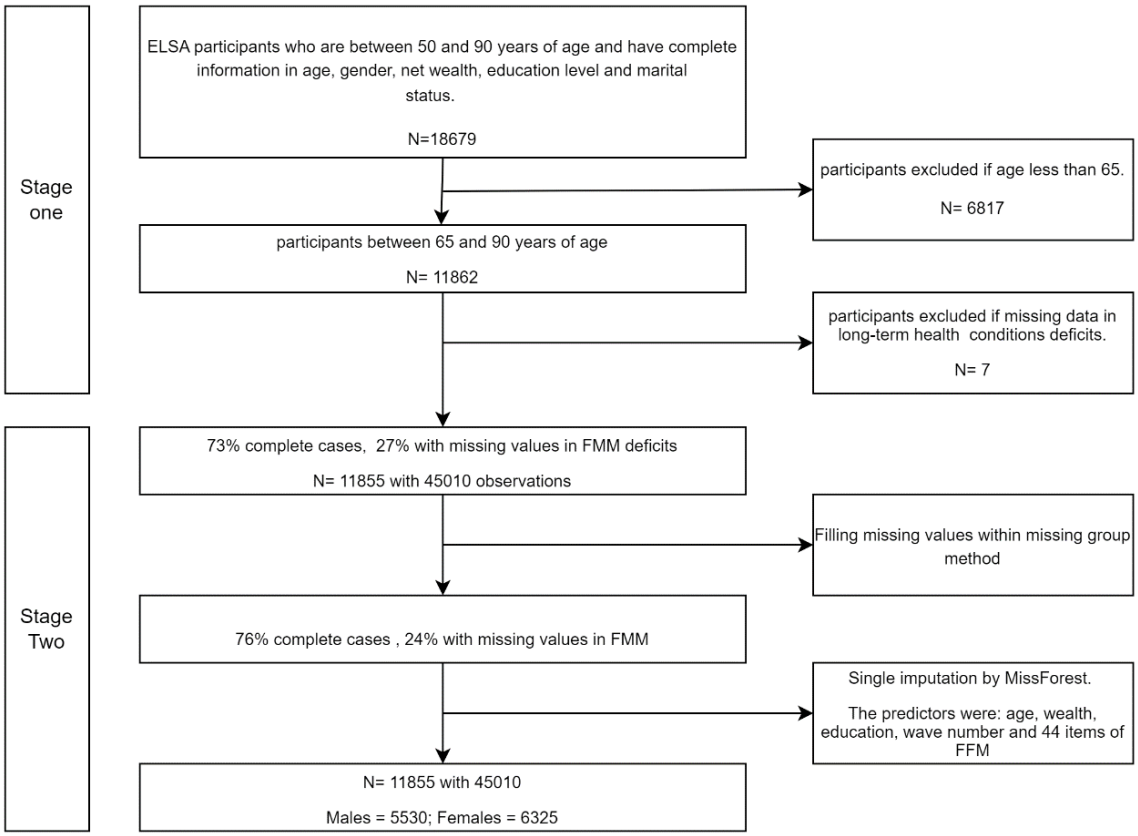
2.3.1 Data and analytical sample

The English Longitudinal Study of Ageing (ELSA) was used in this study. ELSA is a longitudinal study taken from private households of people in England aged over 50 (2). It attempts to reflect the population profile of older people living in England, so it collects information on three aspects of ageing: health, social participation and wellbeing, and finances. ELSA currently features nine waves of data collected over 18 years (10). We employed unit weights for each participant contribution since no appropriate weighting was provided by the ELSA team to ensure representation of the English population for all participants, aged 65 and above, across all nine waves.

Figure 2-1 shows the flowchart for the analytical sample. In the first stage, we determined the eligible participants, and at stage two, we explained how we handled missing data. The data analysis was conducted for females and males separately and so numbers for each sex are included in the flowchart. The participants under 65 years old were excluded since Searle, Mitnitski (11) reported that the age of 65 is considered a threshold for the start of an exponential relationship between frailty and age. In practice, higher levels of frailty are few among those

under 65, so our focus is on those participants of ELSA for whom frailty progression is an important issue.

Figure 2-1: The flowchart for the analytical sample + handled missing data



2.3.2 Outcomes

2.3.2.1 Frailty measure

The cumulative deficit model is one way to measure frailty in older people (12). This model uses a range of deficits that cover five dimensions: symptoms, signs, abnormalities, diseases status and disability (12). It is preferred since the model predicts mortality more accurately (13), and is more sensitive to a person's health status (14).

Marshall, Nazroo (15) have proposed a frailty index using the cumulative deficit model that is based on 62 deficits available in the ELSA dataset. Two deficits were removed from the memory test domain, “Prompt given for prospective memory test” and “number of animals mentioned” as they were not collected in all waves. Table b5 in Appendix B provides details of the deficits. The deficits were scored as one if present or zero if absent. Items with a range of values are converted to values between 0 and 1 to indicate the severity of the defect.

Since the aim of this work is to study the impact of multiple LTCs on frailty and frailty progression, we drop the 16 long-term conditions from the remaining 60 items of the ELSA frailty index to avoid mathematical coupling. The remaining 44 deficits were used to construct a Functional Frailty Measure (FFM). A similar approach has been taken by who extracted the morbidities from the frailty index to investigate the impact of comorbidity count on frailty development. Wade, Marshall (16) omitted pain and depression deficits from the frailty index to study their impact on frailty development.

We assessed the validity of the FFM by examining the relationship between all-cause mortality and FFM. Results suggest that FFM is a strong predictor of mortality (see table b6 in Appendix B). The FFM also satisfies the requirement of Searle, Mitnitski (11) in having more than 30 deficits. As a consequence of these aspects, FFM is a suitable measure for frailty.

2.3.3 Determinants

The list of 16 LTCs within the 60-item Frailty Index includes hypertension, angina, heart attack, congestive heart failure, abnormal heart rhythm, diabetes, stroke, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's, psychiatrist, Alzheimer's, and dementia. Our primary interest is in the impact of multimorbidity, defined as two or more LTCs based on the National Institute for Health and Care Excellence (17). Thus, the total count of LTCs was classified into three categories; none, one, and ‘two or more’ LTCs. In additions, three secondary determinants were selected: age, education level and net wealth with the removal of non-pension wealth. These four determinants were chosen because they were commonly used in comparative studies (15, 18) and had few missing values across the nine waves of ELSA (see table b7 b5 in Appendix B). Education was aggregated into three categories. We included NVQ 4/NVQ 5/Degree or higher degree in a high degree category and had no qualifications as a separate category named low education. The remaining educational qualifications were banded as a separate group of average educational attainment and included NVQ 3/GCE Advanced Level or NVQ 2/GCE Intermediate Level or NVQ 1/CSE Foundation level or another grade or foreign/other. The net wealth includes the sum of savings, investments, physical wealth and housing after financial debt is subtracted. It is adjusted for inflation using the Consumer Price Inflation Index (CPIH which includes housing costs). The base year was 2015 (see table b8 in Appendix B). The net wealth is classified initially by quintiles: richest, rich, average, poor, and poorest, and the upper two classes and lower two classes were combined to produce three categories: rich, average and poor.

2.3.4 Statistical approach

2.3.4.1 Handling missing data

Failure to deal with missing data in longitudinal studies can lead to biased and inefficient statistical analyses (19). We handled the missing data in two ways. First, the missing values were filled in using information from within the missing group. For example, if an individual has a missing value between two reported waves for a deficit, the missing value for a deficit is replaced with the same value. Second, for any remaining missing values, the MissForest algorithm was applied(20). Although it is a single imputation method, it has the benefit of accommodating the nonlinearities and interactions for the predictors and is comparable to multiple imputation methods (21).

A participant who reports a LTC at any wave is assumed to have the condition at subsequent waves. Due to the low rate of missing values in the secondary determinants, which are age, net wealth and education level, these observations were deleted (see table b7 in Appendix B).

The MissForest algorithm uses two-thirds of non-missing observations to build a prediction model and test the model by predicting one-third of non-missing observations or what is well-known out-of-bag observations. The error percentage for the MissForest was used as a norm to evaluate the imputation.

The total rate of missing data on the FMM deficits was 27%. The first approach, which is filling the missing data within group value, reduced the rate of missing data to 24%. The error percentage for the MissForest prediction was 12%.

2.3.4.2 Regression splines

It is an option to deal with the non-linear relationship between the dependent and the number of independent predictors. Here the regression spline was applied as an initial investigation of the relationship between FFM and age grouped by 1) gender and 2) LTCs so that it guides the selection of the multilevel growth model which can adjust for other covariates.

The general idea for the regression splines method is dividing the range of a dependent variable by specific points called "knots", then using a piecewise cubic function to estimate the curve for each part. In general, it is preferred to add more knots in a region of high curvature and use fewer knots in flat regions. We applied this method in our analysis by using *bs* function in R which uses B-splines (22).

2.3.4.3 Multilevel growth model

A multilevel growth curve model was fitted to predict changes in the FFM over the 18 years covering the 9 waves accounting for several determinants. Multilevel models consider the non-independence of an individual's scores on the frailty index over time (23). FFM was treated as time-varying continuous variables at nine-time points, and due to a nonlinear relationship between frailty and age, the quadratic term of age was added to the full model. The entire model of FFM included: age, age^2, education level, net wealth, LTC categories and two-way interaction between age and LTC categories were added as fixed effects as well as age and age^2 as random effects.

The upper limit of age was 90, and it was included as a continuous covariate centred around 70 and then divided by 10 to ease interpretation. All three determinants selected, which are age, education and net wealth, were time-varying.

Implementing multilevel models in longitudinal data might be more complicated because an individual's current measure may often be correlated to prior measures (24). Using the autocorrelation function (ACF), we observed autocorrelated errors within individuals (see figure b9 in Appendix B). Consequentially, we used robust standard errors (RSE) (25). Robust standard errors give a growth model that is robust against autocorrelation and heteroskedasticity.

Restricted maximum likelihood (REML) estimates were used. We turn to the standard maximum likelihood method if we only want to compare nested models with different fixed effects (26). To find the better model, Akaike's information criterion (AIC) was used. It is calculated as (AIC = -2(log-likelihood) + 2*K*) , where likelihood is a measure of model fit, and *K* is the number of model parameters. Each model will be ranked by the AIC from best to worst and then the higher ranked model will be selected (22). In addition, the ANOVA function in R was utilized to see whether there was a significant difference between compared models. The package *nlme* (V3.1-155) (27) for R (4.2.2) was used to conduct the analysis. We conducted a sensitivity analysis using a multilevel growth model after excluding all observations with missing data.

2.4 Results

2.4.1 Sample characteristics

Tables 2-1 and 2-2 show the summary statistics for all determinants and FFM scores across the nine waves for males and females. The sample size across the nine waves for males ranges

between 1856 and 2489 participants and between 2333 and 2489 for females. Across the nine waves, there are more female participants than males.

In males and females, due to the refreshment samples in waves 3,4,6,7, and 9, the average age over time is between 73 and 74 years old. Also, high- or medium-education participants increased while the rate for those with low education decreased over time. Gradually, wealthy participants increased while the poorer participants declined. The healthy participants, who do not have any health conditions or have only one, declined over time, but those with two health conditions or more had increased over time.

The prevalence of LTCs in ELSA supports the definition of multimorbidity as two or more conditions. We observed that the count of two LTCs were steady across time for the participants, but it increased when participants had three or more LTCs (not shown here).

The number of male and female individuals varied over nine waves. For males 1271 (23%) were present in only one wave; two waves: 913 (16.5%); three waves: 795 (14.4%); four waves: 683 (12.4%); five waves: 533 (9.6%); six waves: 536 (9.7%); seven waves: 283 (5.1%); eight waves: 120 (4.5%) and nine waves 266 (4.8%). For females, 1369 (21.6%) were present in only one wave; two waves: 988 (15.6%); three waves: 897 (14.2%); four waves: 742 (11.7%); five waves: 637 (10.1%); six waves: 600 (9.5%); seven waves: 385 (6.1%); eight waves: 307 (4.9%) and nine waves 400 (6.3%). On average, the male and female individuals participated in 3.7 and 3.9 waves, respectively.

2.4.2 Regression spline between FFM and Age

Figure 2-2a shows the smoothed relationship between the FFM against age grouped by gender using regression splines. It shows that females have a higher frailty rate than males over time, and indicates that the relationship between age and FMM is non-linear. Also, the FFM increases as the number of LTCs increase for males, as shown in figure 2-2b, and for females, as shown in figure 2-2c. Moreover, multimorbid participants on average have a higher frailty as they aged in both genders.

Table 2-1: Summary statistics for five determinants and FMM for males across the nine waves

	Wave	1	2	3	4	5	6	7	8	9
	N	2396	2039	1856	2223	2326	2489	2405	2383	2353
Age (M,SD)		73.40 (6.22)	73.51 (6.18)	73.90 (6.28)	73.28 (6.05)	73.50 (6.25)	73.35 (6.43)	73.54 (6.36)	73.59 (6.31)	73.95 (6.38)
Education (n,%)	High	467 (19.5)	474 (23.2)	571 (30.8)	753 (33.9)	850 (36.5)	902 (36.2)	889 (37.0)	890 (37.3)	1090 (46.3)
	Med or foreign	794 (33.1)	722 (35.4)	670 (36.1)	790 (35.5)	841 (36.2)	926 (37.2)	962 (40.0)	974 (40.9)	865 (36.8)
	low	1135 (47.4)	843 (41.3)	615 (33.1)	680 (30.6)	635 (27.3)	661 (26.6)	554 (23.0)	519 (21.8)	398 (16.9)
Net wealth (n,%)	Rich	921 (38.4)	794 (38.9)	750 (40.4)	924 (41.6)	987 (42.4)	1078 (43.3)	1071 (44.5)	1038 (43.6)	1097 (46.6)
	Average	473 (19.7)	426 (20.9)	399 (21.5)	456 (20.5)	488 (21.0)	514 (20.7)	515 (21.4)	495 (20.8)	480 (20.4)
	Poor	1002 (41.8)	819 (40.2)	707 (38.1)	843 (37.9)	851 (36.6)	897 (36.0)	819 (34.1)	850 (35.7)	776 (33.0)
FMM[a] (M,SD)		0.18 (0.13)	0.18 (0.14)	0.17 (0.14)	0.17 (0.13)	0.17 (0.13)	0.16 (0.14)	0.16 (0.13)	0.16 (0.13)	0.15 (0.13)
LTCs[b] (n,%)	0	507 (21.2)	342 (16.8)	270 (14.5)	374 (16.8)	345 (14.8)	353 (14.2)	317 (13.2)	307 (12.9)	285 (12.1)
	1	742 (31.0)	588 (28.8)	518 (27.9)	589 (26.5)	612 (26.3)	630 (25.3)	576 (24.0)	542 (22.7)	534 (22.7)
	2+	1147 (47.9)	1109 (54.4)	1068 (57.5)	1260 (56.7)	1369 (58.9)	1506 (60.5)	1512 (62.9)	1534 (64.4)	1534 (65.2)

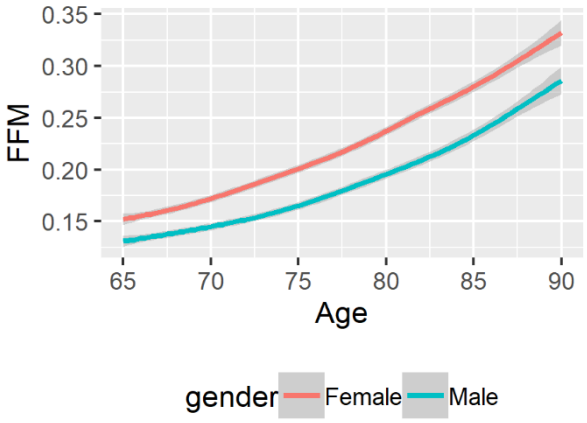
[a]FFM: Functional frailty measure; [b]LTCs: Long-term conditions

Table 2-2: :Summary statistics for five determinants and FMM for females across the nine waves

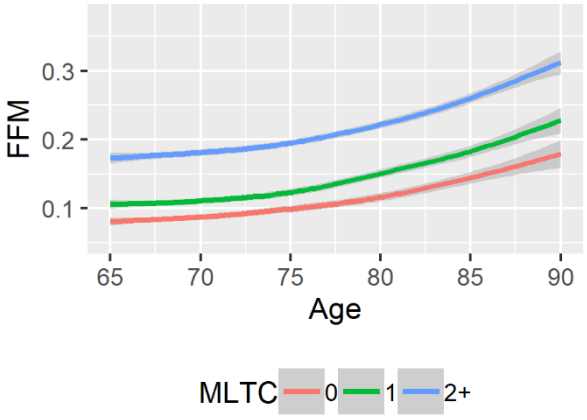
	Wave	1	2	3	4	5	6	7	8	9
	N	2965	2543	2333	2653	2769	2842	2836	2771	2828
Age (M,SD)		74.12 (6.45)	74.32 (6.43)	74.63 (6.59)	73.96 (6.46)	74.14 (6.59)	73.82 (6.52)	73.88 (6.51)	74.04 (6.53)	74.21 (6.62)
Education (n,%)	High	373 (12.6)	372 (14.6)	427 (18.3)	536 (20.2)	620 (22.4)	596 (21.0)	649 (22.9)	667 (24.1)	868 (30.7)
	Med or foreign	822 (27.7)	784 (30.8)	800 (34.3)	947 (35.7)	1061 (38.3)	1179 (41.5)	1226 (43.2)	1262 (45.5)	1243 (44.0)
	low	1770 (59.7)	1387 (54.5)	1106 (47.4)	1170 (44.1)	1088 (39.3)	1067 (37.5)	961 (33.9)	842 (30.4)	717 (25.4)
Net wealth (n,%)	Rich	979 (33.0)	829 (32.6)	791 (33.9)	888 (33.5)	949 (34.3)	1010 (35.5)	1053 (37.1)	1002 (36.2)	1110 (39.3)
	Average	577 (19.5)	507 (19.9)	474 (20.3)	580 (21.9)	574 (20.7)	631 (22.2)	616 (21.7)	571 (20.6)	605 (21.4)
	Poor	1409 (47.5)	1207 (47.5)	1068 (45.8)	1185 (44.7)	1246 (45.0)	1201 (42.3)	1167 (41.1)	1198 (43.2)	1113 (39.4)
FMM[a] (M,SD)		0.22 (0.15)	0.22 (0.15)	0.21 (0.15)	0.21 (0.14)	0.21 (0.15)	0.19 (0.15)	0.19 (0.15)	0.19 (0.14)	0.18 (0.14)
LTCs[b] (n,%)	0	500 (16.9)	325 (12.8)	249 (10.7)	298 (11.2)	282 (10.2)	271 (9.5)	278 (9.8)	254 (9.2)	261 (9.2)
	1	881 (29.7)	650 (25.6)	542 (23.2)	625 (23.6)	588 (21.2)	608 (21.4)	568 (20.0)	528 (19.1)	532 (18.8)
	2+	1584 (53.4)	1568 (61.7)	1542 (66.1)	1730 (65.2)	1899 (68.6)	1963 (69.1)	1990 (70.2)	1989 (71.8)	2035 (72.0)

[a]FFM: Functional frailty measure; [b]LTCs: Long-term conditions

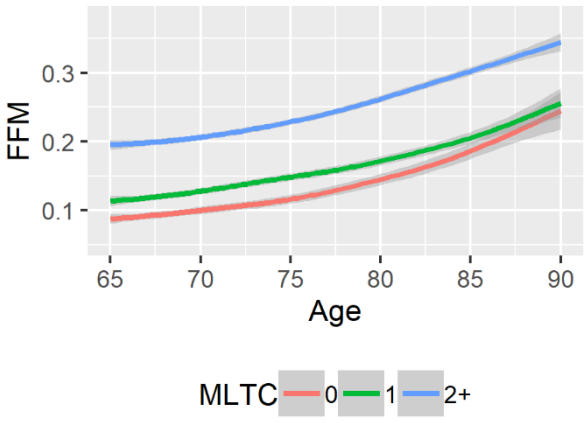
Figure 2-2: FMM against Age using regression splines. a) FMM vs age grouped by gender. b) FMM vs age grouped by gender LTCs for males. c) FMM vs age grouped by gender LTCs for females.



(a)



(b)



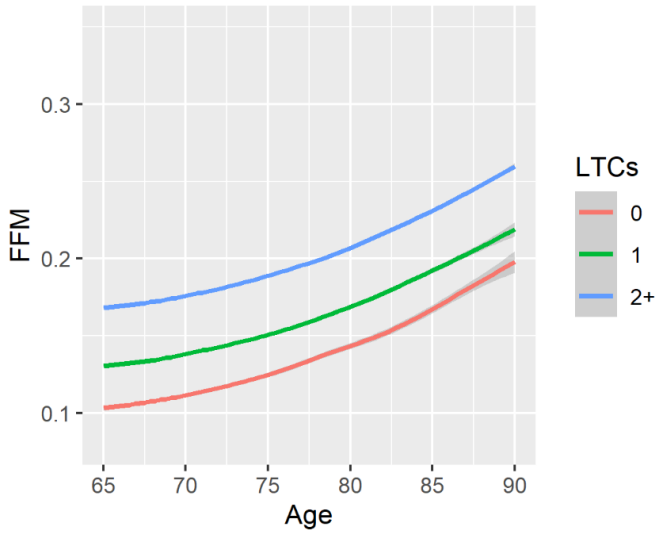
(c)

2.4.3 Multilevel growth model

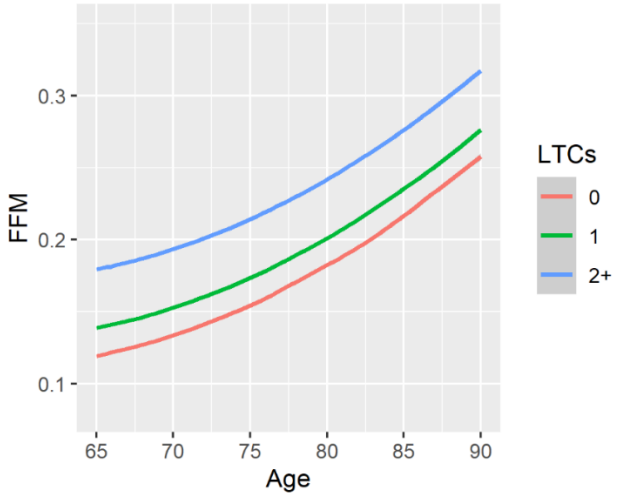
Table 2-3 shows the outputs of the multilevel growth models for males and females. The general mean for the FFM for male is 0.17 (SD = 0.12) while for females is 0.20 (SD = 0.13) as shown in unadjusted models. AIC were improved for both models after adjusting to scale age, net wealth, education, two-way interaction between scale age, age^2 and LTCs categories. Considering the variation between the participants by adding age and age^2 as random effects contributed to better fit for male and female models.

In the adjusted models, frailty (as measured by FFM) increases nonlinearly for males with 4% each 10 years for the participants with no LTCs, average wealth and middle education, while it increased 6% per decade in females. The rich and educated participants (males and females) were less frail while the poor and uneducated participants were frailer. For both genders, as the number of LTCs increases, the FFM score also increases. Also, the acceleration of FMM increases for males with one LTC or more; however in females the acceleration of FMM increases when they have two LTCs or more. Figure 2-3 shows the acceleration of FMM for both genders are non-linear.

Figure 2-3: The interaction between the age and FFM. a) : The interaction between the age and FFM grouped by LTCs for males. b) : The interaction between the age and FFM grouped by LTCs for females. The acceleration of FMM increases for males with one LTC or more



(a)



(b)

The adjusted multilevel growth models for complete cases showed similar results as the primary analysis, but the most two-way interaction terms in the male and female models were no longer significant (see table b10 in Appendix B).

2.5 Discussion

In this study, we have shown that FFM increases with the number of LTCs, respectively, for males and females. We also found that the number of LTCs affects FFM progression for males with one LTC or more, and for females with two or more LTCs. Moreover, the relationship between age and FFM, the measure of frailty without LTCs, was nonlinear for those over 65.

Our findings were consistent with previous studies. Thompson, Theou (8) reported that multimorbid people have a higher frailty score than non-multimorbid people using the accumulation deficit model. Also, the effect of age and wealth status on frailty was consistent with the findings of Marshall, Nazroo (15) findings. They found that the younger and wealthy participants were less frail over time. Moreover, highly educated people are often less frail (28).

The number of wealthy and educated participants have increased over the nine waves, at the same time the participants with two or more LTCs increased, and the average of FFM scores across the time decreased. It can be evidence that a good wealth status and a high education contribute to delaying frailty progression or at least those wealthier and more educated participants can manage their health despite LTCs more efficiently than others.

Table 2-3: Conditional multilevel growth model for FMM for Male and female

	Male						Female					
	Unadjusted model			Adjusted model			Unadjusted model			Adjusted model		
Fixed effects	β	RSE		β	RSE		β	RSE		β	RSE	
(Intercept)	0.17*	0.002		0.12*	0.003		0.20	0.002		0.14*	0.004	
Age $c_{(75)}/10$				0.03*	0.004					0.05*	0.004	
Age^2 $c_{(75)}/10$				0.01*	0.005					0.01*	0.005	
Net wealth (ref. Average)												
Rich				-0.01*	0.002					-0.01*	0.002	
Poor				0.02*	0.002					0.02*	0.002	
Education (ref. Middle)												
High				-0.01*	0.003					-0.01*	0.003	
Low				0.03*	0.003					0.03*	0.003	
Health condition (ref. HC=0)												
HC (1)				0.03*	0.003					0.02*	0.004	
HC (2^+)				0.06*	0.004					0.06*	0.004	
Age $c_{(75)}/10$: HC (1)				0.01*	0.005					-0.003	0.005	
Age^2 $c_{(75)}/10$: HC (1)				0.01*	0.006					0.004	0.006	
Age $c_{(75)}/10$: HC (2^+)				0.03*	0.005					0.008*	0.005	
Age^2 $c_{(75)}/10$: HC (2^+)				0.03*	0.006					0.019*	0.006	
Random effects		lower	upper		lower	upper		lower	upper		lower	upper
Intercept (SD)	0.12	0.11	0.12	0.11	0.11	0.11	0.13	0.13	0.13	0.12	0.12	0.12
Age $c_{(75)}/10$ (SD)				0.09	0.08	0.09				0.06	0.06	0.07
Age^2 $c_{(75)}/10$ (SD)				0.07	0.06	0.07				0.06	0.05	0.06
Error (SD)	0.08	0.08	0.08	0.06	0.06	0.06	0.08	0.08	0.08	0.07	0.06	0.07
Model fit												
AIC	-35189.48			-40730.02			-40439.67			-46306.36		

*p< .01

Two LTCs could be a reasonable threshold for the health providers to commit more attention to dealing with those participants as soon as possible to delay frailty progression. Some LTC cases in males and females have to be considered separately with further care once the participant has Parkinson's or Dementia for males and Psychiatric and Alzheimer's disease for females.

It is preferred to apply the cumulative deficit model rather than a phenotype model to study the impact of frailty in order to create interventions that reduce frailty among older people (29). For example, some participants might not benefit from a physical intervention program, such as a group exercise, due to their struggle with cognitive or psychological issues. Using a multidimensional frailty measure could be more appropriate to measure various frailty components for older people in a community, enabling identification of the weaker dimension(s) that can be targeted with intervention from health givers.

One of the strengths of this study is that it uses large, high-quality data from the English population with a large sample size. Furthermore, we were able to investigate the association of several factors with FFM development for an extended period (18 years) because of the vast collection of longitudinal data and large sample size available in the ELSA. Moreover, it supports studies that investigate the relationship between frailty and multimorbidity to do more research.

Study results should also be interpreted in light of potential limitations. We used the FFM rather than the frailty index, but we explained how the FMM is sufficient. Secondly, in the cumulative deficit model It is common to use “deficit” that are difficult to change and may not accurately reflect frailty's "reversible" nature. Also, researchers choose "deficit" items based on their subjectivity or what is available in the use dataset in the cumulative deficit model. Nevertheless, this model is useful for within-cohort comparisons (30). Next, the rate of missing data in some frailty deficits was relatively high. However, we applied two single imputation methods and then conducted the sensitivity analysis. Implementing multilevel models in longitudinal data might be more complicated because an individual's current measure may often be correlated to prior measures (24). We observed the presence of autocorrelation among individual errors using the autocorrelation function (ACF). We treated this issue by applying robust standard error. Besides that, we should have included further determinants, such as physical activity and lifestyle determinants. However, many of them were measured only at wave one, which we cannot include in our analysis because it will increase the rate of missing data since the refreshment samples were not asked to report earlier determinants.

In summary, these results provide the first step to studying the effect of multimorbidity on frailty progression in older people who live in the England community. Health providers should be

aware of planning a suitable intervention once the elderly have two or more health conditions. There is a further need to investigate the interactions between health conditions and frailty progression.

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Chapter 3 Measurement invariance of a quality-of-life measure, CASP-12, within the English Longitudinal Study of Ageing (ELSA)

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Study Two	
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3.1 Abstract

CASP-12 is a frequently used quality of life scale for older people, but limited efforts have been made to test the factor structure or to explore the measurement consistency of the scale across key characteristics. The aim of this study is to examine if the CASP-12 questionnaire has a well-defined factor structure with a second-order structure factor nested within four first-order domains: control, autonomy, pleasure, and self-realization. The study also aims to investigates if this factor structure is interpreted similarly by respondents of different genders, ages, educational levels, net wealth, and at two time periods, using a multi-group confirmatory factor analysis (MG-CFA).

The results show that CASP-12 with lower four first-order domains (CASP-12-4D) is consistent across genders and two time periods and satisfies the second-order strong-invariance criteria. Furthermore, the instrument demonstrates consistency in weak levels across three age groups (50-59, 60-69, and 70-90), educational levels and net wealth, but not strong invariance. The sample was divided into three subsamples based on age groups to address this issue. The consistency of CASP-12-4D has met the second-order strong invariance level requirement across gender, age, education level and two-time periods. Net wealth however still fails to meet the strong invariance levels. The CASP-12-4D version will suit social and public health research which controls for age and wealth status.

3.2 Introduction

Assessing Quality of Life (QoL) has become crucial for delivering effective health and social care services to the elderly population (1). Numerous studies have examined the intricate relationship between QoL and potential influencing factors using a variety of cohort datasets. For instance, these investigations have effectively measured the impact of familial support (2), or medical occurrences like the diagnosis of cancer (3) on QoL. The concept of QoL however is multifaceted, posing challenges in its measurement (4, 5). Thus, focusing on a population sharing similar physical, mental, and social characteristics, such as the elderly, can enhance the consistency of QoL measurements (5, 6). This approach ensures that any detected changes in QoL accurately mirror shifts in the underlying concept, rather than being influenced by variations in measurement techniques (7), a critical aspect of clinical and public health research (8).

One of the QoL scales, CASP-19, consists of 19 items organized into four domains - Control, Autonomy, Self-realization, and Pleasure. Developed from Maslow's psychological theory(9), CASP-19 aims to assess the QoL of individuals aged 65 to 75 (10). Despite numerous large datasets being utilized to investigate CASP-19 through the application of its second-order common factors, inconsistencies have arisen in the results (11). In response, Wiggins, Netuveli (12) proposed a more concise version of CASP-19, comprising 12 items, which more dependably captures QoL than the original scale. Oliver et al (2021) reported several versions of the CASP-12 structure factors. Limited efforts however have been made to report the measurement consistency of CASP-12. Measurement invariance refers to the consistency in how an instrument is interpreted among various groups of individuals (7).

In many studies, researchers often forget to consider measurement errors when looking at Quality of Life (QoL) among different groups. This oversight can lead to biased results (13). Health research commonly compares subgroups to help with clinical decisions (13). It is therefore crucial to consider how personal factors might affect how people respond to different situations, including when using CASP-12.

It's important to remember that older adults are not all the same. Factors like retirement, losing a spouse, dealing with chronic illnesses, and financial struggles can affect them differently. Also, as people get older, changes in their lives may lead to different priorities and motivations. That's why age is a key factor in understanding the quality of life for older adults (14). Gender, age, and education level also play a role in how older individuals perform on language tests (13, 15). Life circumstances, such as women being more likely to be widowed, can influence how they

respond to assessments of their quality of life (14, 16). Often, studies group together personal details like gender and education when studying older people (13, 17).

Additionally, a person's wealth affects various aspects of life, like getting good healthcare, staying active, and eating well. Having less money may sometimes mean sacrificing important things, like spending time with family. This trade-off means that people with different levels of wealth may see what makes a good quality of life in different ways (18).

The authors have found no previous studies which explored the uniformity of the common second-order factor structure of CASP-12, encompassing four factors, across diverse groups in England. As a result, the current study has two aims: (1) to test three second-order structure factors of the CASP-12 using data from the English Longitudinal Study of Ageing (ELSA), and (2) to investigate whether the selected CASP-12 structure remains consistent across five variable groups: gender, age, educational levels, wealth, and two time periods.

3.3 Methods

3.3.1 Dataset

ELSA is a longitudinal research project which collects information from private households of individuals aged over 50 years residing in England (19). ELSA currently features nine waves of data collected over an 18-year period (20).

3.3.2 Measurements

Five categorical variables were selected for investigation, namely gender, age, education, net wealth, two time periods. Three age groups were compared: 50-59, 60-69, and 70-90 years. The reason for selecting these age groups was to assume participants within these ages share common perspectives for QoL. The participants were categorized into three education levels (high, average or foreign and low), following the approach of Alattas, Nikolova (21). The participants were categorized into three wealth levels (rich, average and poor), following the approach used in a previous study (Alattas, Nikolova (21). To increase the analysis power, new participants were included from wave one to wave nine and then classify them into two period groups: wave one participants and wave two through wave nine participants. We compared two time periods, W1 vs W2 to W9, to see whether the perspective of the scale, CASP-12, between participants who joined at the first wave and those who joined at wave 2 onwards is invariant or not. Note that with this split, sample size for each group is comparable.

The CASP-12 instrument comprises 12 items that aim to evaluate an individual's QoL through four domains: control, autonomy, pleasure and self-realisation (12). The participants were asked

a series of questions and rated their responses using a four-point scale from 0 to 3 where 0 indicated 'never,' 1 'not often,' 2 'sometimes' and 3 'often.' Any questions that had negative wording were given a reverse score. Reverse scoring flips the direction of the numerical scoring scale. This means that a score of 0 would be assigned to "often", while "sometimes" would get a score of 1, "not often" would receive a score of 2, and "never" would be assigned a score of 3. The total score was obtained by adding up the responses to each question. A higher score indicated a better QoL. Table 3-1 presents all 12 items of the CASP-12.

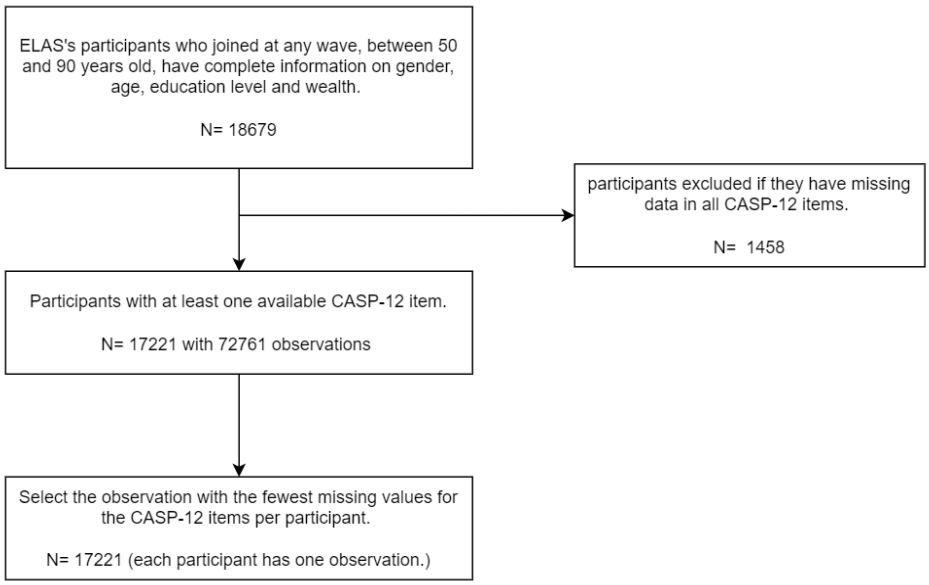
Table 3-1: CASP-12 items with their domains

Item (number)	**Domain**
My age prevents me from doing the things I would like to do (*C1*)	Control
I feel that what happens to me is beyond my control (*C2*)	
I feel left out of things (*C3*)	
I can do the things I want to do (*A1*)	Autonomy
I feel that I can please myself what I do (*A2*)	
A lack of money stops me from doing things I want to do (*A3*)	
I look forward to each day (*P1*)	Pleasure
I feel that my life has meaning (*P2*)	
I enjoy the things that I do (*P3*)	
I feel full of energy these days (*S1*)	Self-realisation
I feel that life is full of opportunities (*S2*)	
I feel that the future looks good for me (*S3*)	

3.3.3 Analytical sample

Figure 3-1 shows the steps taken to select the analytical sample. A total of 18679 participants were included from the ELSA study across nine waves. They were selected based on complete information available for four variables, including gender, age (between 50 and 90), education level and net wealth. Participants were excluded if no information was available for any 12 items of the CASP-12. Additionally, repeated measures for included participants were removed as the measure with the least missing values of CASP-12 was kept. The final sample size after exclusions was 17221 participants.

Figure 3-1: Procedure for selecting the analytical sample



3.3.4 Statistical approach

First, the summary statistics for the sample and five determinants were examined. Then a graphical analysis was conducted to explore the relationship between the participants age and the total scores of the CASP-12 as well as its four domains using regression splines. To achieve this, the *bs* function in R was utilized which employs B-splines for the analysis (22).

Since we are interested in QoL as one component, Confirmatory Factor Analysis (CFA) was conducted for several second-order structure factors for CASP-12. The requirements applicable to establish the second-order factor of the selected CASP-12 model are: (a) lower (first) order factors are highly correlated, and (b) there is a higher order factor that accounts for their relations (23). Thus, three second-order structured factors and a first-order structure factor (CASP-12-FO) were conducted. The three second-order structure factors are as follows: the first is a common second-order factor with four first-order factors (control, autonomy, pleasure, and self-realization), denoted here CASP-12-4D. The second is a common second-order factor with three first-order factors (CASP-12-3D), so the Control and Autonomy domains had combined. The third is like CASP-12-3D but with 11 items (CASP-11-3D), which item (A3) has been removed. The reason for deleting this item is that its loading factor value was less than 0.40, as shown in the results section.

Since the response values of the CASP-12 items are greater than two and all of the items have a moderate or high skewness, they were treated as continuous variables and the robust maximum likelihood was used to estimate the parameters of CFA (24). In our analysis, we opted for the

Robust Maximum Likelihood (RML) method over the Satorra-Bentler scaled chi-squared statistic. This decision was influenced by the limitation of the latter in handling incomplete data, as noted by Savalei and Rosseel (25). Furthermore, RML is deemed more appropriate for datasets exhibiting moderate deviations from normality, as indicated by Li (26).

The question of whether to treat response values on a scale as continuous or ordinal is a subject of ongoing discussion. According to (24) treating response values ordinally may impose a normal distribution on latent factors, potentially introducing inaccuracies in empirical applications. Given our substantial sample size, any distinctions between different methods may be practically negligible and thus considered inconsequential.

A multi-group Confirmatory Factor Analysis (MG-CFA) was undertaken to ensure that measurements are consistent of the CASP-12 across five variable groups: gender, age groups, educational levels, net wealth and two time periods. Sequentially, five levels of measurement invariance (MI) were tested following Chen, Sousa (23), and each level introduced more equality constraints across groups with the consideration for second- and first-order factors. Configural invariance tests the equivalence of the fixed and free factor loadings pattern. Weak invariance tests the equivalence of factor loadings across groups for first-order loadings and second-order factor loadings in two separate steps. Meanwhile, strong invariance, additionally to weak invariance, examines the equality of intercepts of indicators and means for first-order latent factors in two separate steps.

Three fit indices were considered: robust chi-square distribution with a degree of freedom (*df*), robust comparative fit index (**R**CFI) and robust root mean square error of approximation (**R**RMSEA). The Chi-square test is impacted by sample size, meaning that as the sample size grows, the test becomes more responsive to even minor variations between the correlation matrix of observed values and the correlation matrix of expected values. Alternatively, RCFI or RRMSEA were used to assess the goodness of fit. The CFI and RMSEA range from 0 to 1, and the values of 0.90 (acceptable fit) or 0.95 (good fit) are used as cut-points for the CFI while 0.06 (good fit) or 0.08 (acceptable fit) for RMSEA (27). To compare five constrained models, the ΔRCFI criterion was used due to its lower sensitivity to sample size. Consequently, if there is a change in RCFI of less than 0.01 along with a change in RRMSEA of less than 0.015, the models can be considered to be comparable (28).

If the selected factor structure of CASP-12 did not meet the criteria for strong invariance among the five variable groups, the participants would be divided into subgroups based on the variable group with the poorest MG-CFA fit indices. Each subgroup would then be tested separately for

MI. Due to missing observations in the sample, we selected an observation with the least missing values from the CASP-12 items for each participant. Also, we used all available information for participants with some missing values in the CASP-12 items by applying the full information maximum likelihood (FIML) method. FIML was used to deal with missing data with parameter estimates being calculated using all of the available information (29). The analysis was performed in R and all of the CFA models were estimated using the *lavaan* version 0.6-12 package (30).

3.4 Results

Table 3-2 presents the distributions of gender, age, educational level, net wealth and two-time periods. Out of the total sample, 54% were women. Half of the sample (51%) were aged between 50-59. Two-thirds of the sample consists of participants who are educated at a high or average level.

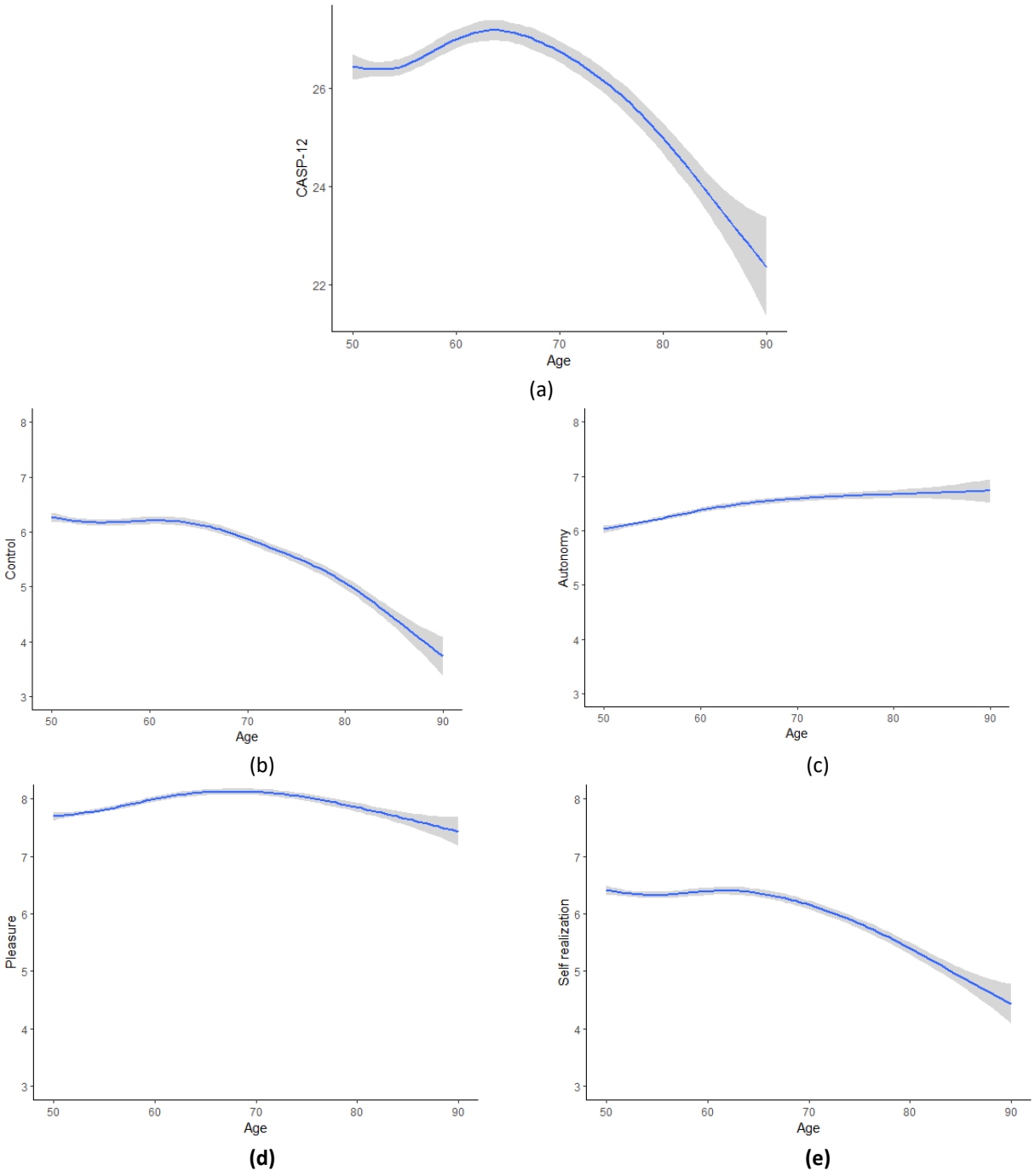
Table 3-2: Summary characteristics of the sample

N= 17221	N	%
Gender		
Men	7850	46%
Women	9371	54%
Age		
50-59	8726	51%
60-69	4084	24%
70-90	4411	25%
Education level		
High	4841	28%
Average or foreign	6765	39%
Low	5615	33%
Wealth		
Rich	6897	40%
Average	3373	20%
Poor	6951	40%
Two-time periods		
Wave 1	9749	57%
Wave 2 to wave 9	7472	43%

Both wealthy and poor participants each represented 40%, with those classified as ‘average’ wealth accounting for 20%. More than half of the sample (57%) were from wave 1, while 43% participants were from waves 2 to 9. Figure 3-2 illustrates the association between the total scores of CASP-12 and its four domains with age.

The number of participants who have complete data on CASP-12 items is 16816. Fig. 3-2a indicates a negative relationship between the total scores of CASP-12 and age for individuals aged 70 and above. As shown in Fig. 3-2b and Fig. 3-2e, participants began to lose control and self-realization when they reached this age. However, their autonomy gradually increased (Fig. 3-2c). Among the CASP-12 domains, the pleasure domain had the highest scores, with an average score close to 9 (upper score) for most ages (Fig. 3-2d).

Figure 3-2: The relationship between the CASP-12 score and several group variables using regression splines; only the participants with no missing values in the CASP-12 (N= 16,816).



A CFA was conducted on three common second-order structure factors of CASP-12 as well as four first-order factor as shown in Table 3-3. The results showed that CASP-12-4D and CASP-12-FO achieved an excellent fit (RCFI = 0.95 and RRMSEA = 0.067) for CASP-12 and (RCFI = 0.95 and RRMSEA = 0.066). The standardized parameter estimates for both factor structures were displayed in Figure 3-3.

Table 3-3: Model fit statistics of Models CASP-12, CASP-12-3D, CASP-11-3D and CASP-12-FO

Structure factor	R χ2	df	RCFI	RRMSEA
CASP-12-4D	3135.55*	50	*0.945*	*0.067*
CASP-12-3D	4664.58*	51	0.917	0.081
CASP-11-3D	4392.02*	41	0.918	0.089
CASP-12-FO	2955.35*	48	*0.949*	*0.066*

CASP-12-4D: is a common second-order with four domains (control, autonomy, pleasure and self-realization); CASP-12 -3D is a common second-order with only three demotions (control/autonomy, pleasure and self-realization). CASP-11-3D: the item A3 was deleted from CASP-12-3D; CASP-12-FO: only four first-order factors; *p<0.01

Figure 3-3 shows that there is a higher (second) order factor that accounts for four lower (first-order) factor relations and four lower (first-order) were of the CASP-12 highly correlated. Thus, CASP-12 is applicable.

A second-order MG-CFA test of the CASP-12-4D was conducted separately for five variable groups: gender, age groups, educational levels, net wealth and time periods. Following this, a series of rigorous model tests was undertaken for five levels of invariance (configural, two weak invariance levels, and two strong invariance levels). As demonstrated in Table 3-4 RCFI value of the CASP-12-4D is around the benchmarks for a good fit as well as RRMSEA values for all five variable groups. Next, although RCFI value of CASP-12-4D met the invariance up to a second-order strong level for gender and two-time periods (ΔRCFI < 0.01 and RRMSEA <0.015), the instrument failed to achieve that across age groups, educational level and net wealth. Note that the value of ΔRCFI exceeded the cutoff (0.01) between the weak and strong levels for these three variable groups. The value of ΔRRMSEA did not exceed the cut-off (0.015) except for age groups.

Figure 3-3: Standardized factor loadings for the CASP-12-4D (left side) and for the CASP-12-FO (right side). All estimates p < 0.01. C, A, P and S refer to the items for each domain of the CASP-12 that are shown in Table 1

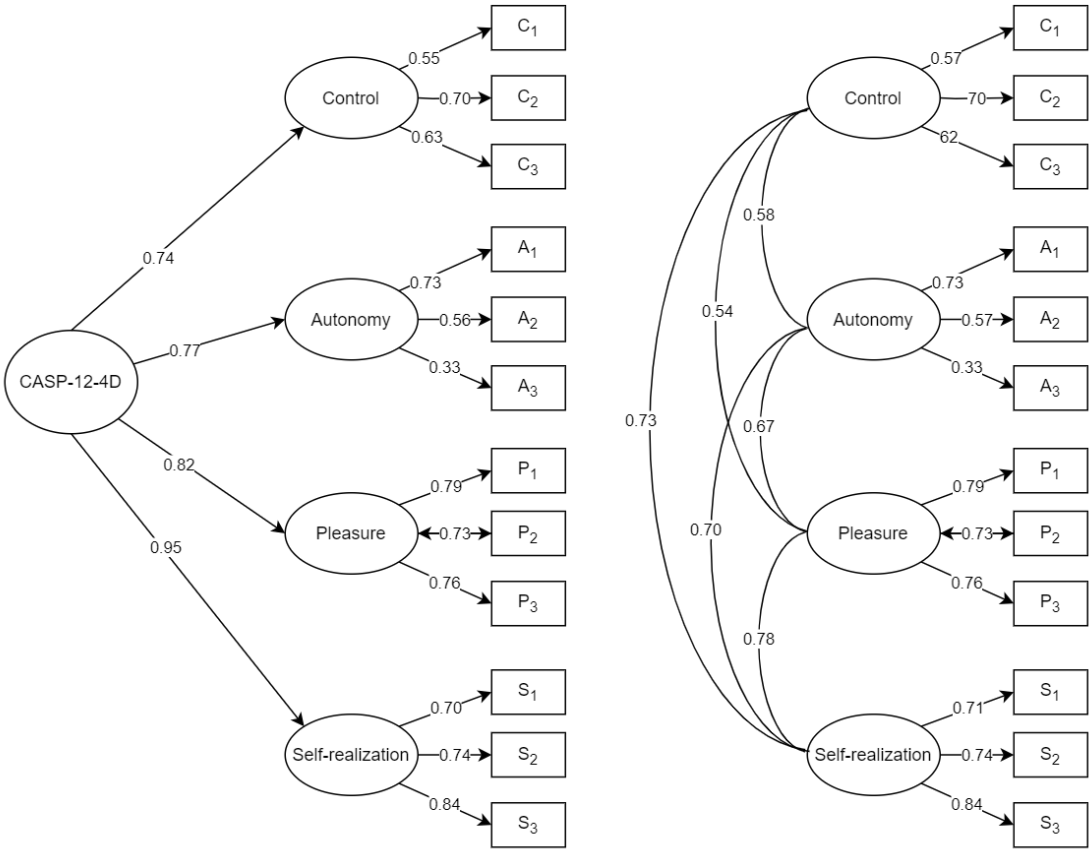


Table 3-4: Five levels of Multi-Group Confirmatory Factor Analysis (MG-CFA) for the second-order of the CASP-12-4D grouped by gender, age, educational level, net wealth and two-time periods.

	Robust $\chi 2$	Δ Robust $\chi 2$	df	RRMSEA	Δ RRMSEA	RCFI	Δ RCFI
Gender							
Configural invariance	3258.86*	--	100	0.067	--	0.944	--
Weak invariance (FOFL)	3258.79*	-0.07	108	0.065	-0.002	0.944	0
Weak invariance (SFOFL)	3250.56*	-8.23	111	0.064	-0.001	0.944	0
Strong invariance (FOFLI)	3481.26*	230.7	118	0.064	0	0.94	-0.004
Strong invariance (SFOFLI)	3503.82*	22.56	121	0.064	0	0.94	0
Age							
Configural invariance	3006.86*	--	150	0.064	--	0.95	--
Weak invariance (FOFL)	3249*	242.14	166	0.064	0	0.946	-0.004
Weak invariance (SFOFL)	3312.89*	63.89	172	0.063	-0.001	0.944	-0.002
Strong invariance (FOFLI)	5796.73*	2483.84	186	0.081	0.018	0.901	-0.043
Strong invariance (SFOFLI)	6587.64*	790.91	193	0.085	0.004	0.888	-0.013
Education level							
Configural invariance	3181.57*	--	150	0.066	--	0.946	--
Weak invariance (FOFL)	3250.14*	68.57	166	0.063	-0.003	0.945	-0.001
Weak invariance (SFOFL)	3238.15*	-11.99	172	0.062	-0.001	0.945	0
Strong invariance (FOFLI)	4117.78*	879.63	186	0.067	0.005	0.929	-0.016
Strong invariance (SFOFLI)	4272.81*	155.03	193	0.067	0	0.927	-0.002
Net wealth							
Configural invariance	3233.9*	--	150	0.066	--	0.942	--
Weak invariance (FOFL)	3251.86*	17.96	166	0.063	-0.003	0.941	-0.001
Weak invariance (SFOFL)	3236.69*	-15.17	172	0.062	-0.001	0.941	0
Strong invariance (FOFLI)	4166.66*	929.97	186	0.068	0.006	0.923	-0.018
Strong invariance (SFOFLI)	4309.89*	143.23	193	0.068	0	0.921	-0.002
Two-time periods							
Configural invariance	3173.84*	--	100	0.06	--	0.945	--
Weak invariance (FOFL)	3206.4*	32.56	108	0.065	0.005	0.944	-0.001
Weak invariance (SFOFL)	3255.68*	49.28	111	0.064	-0.001	0.942	-0.002
Strong invariance (FOFLI)	3781.58*	525.9	118	0.067	0.003	0.934	-0.008
Strong invariance (SFOFLI)	4013.5*	231.92	121	0.068	0.001	0.93	-0.004

FOFL: first-order factors loadings; SFOFL: second- and first-order factors loadings; FOFLI: second- and first-order factors loadings and intercepts of measured indicators; SFOFLI: second- and first-order factors loadings and intercepts of measured indicators and means for first-order factors *P<0.01

Table 3-5: Five levels of Multi-Group Confirmatory Factor Analysis (MG-CFA) for the second-order factor of the CASP-12-4D in three separate samples based on age, grouped by gender, two age groups, educational level, net wealth and two-time periods

	50-59; N= **8726**							60-69; N= **4490**							70-90; N=**4005**						
	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA
Gender																					
Configural invariance	1394.67*	--	100	0.959	--	0.06	--	857.82*	--	100	0.945	--	0.065	--	979.14*	--	100	0.931	--	0.073	--
Weak invariance (FOFL)	1396.38*	1.71	108	0.959	0	0.058	-0.002	875.15*	17.33	108	0.943	-0.002	0.063	-0.002	979.95*	0.81	108	0.931	0	0.07	-0.003
Weak invariance (SFOFL)	1403.89*	7.51	111	0.959	0	0.057	-0.001	878.16*	3.01	111	0.943	0	0.063	0	978.29*	-1.66	111	0.931	0	0.069	-0.001
Strong invariance (FOFLI)	1539.71*	135.82	118	0.955	-0.004	0.058	0.001	940.27*	62.11	118	0.939	-0.004	0.063	0	1063.43*	85.14	118	0.925	-0.006	0.07	0.001
Strong invariance (SFOFLI)	1549.64*	9.93	121	0.955	0	0.058	0	952.82*	12.55	121	0.939	0	0.063	0	1068.2*	4.77	121	0.925	0	0.069	-0.001
Age (two groups)																					
Configural invariance	1326.25*	--	100	0.961	--	0.059	--	852.86*	--	100	0.945	--	0.065	--	978.71*	--	100	0.93	--	0.072	--
Weak invariance (FOFL)	1321.74*	-4.51	108	0.961	0	0.056	-0.003	843.24*	-9.62	108	0.945	0	0.062	-0.003	988.52*	9.81	108	0.93	0	0.07	-0.002
Weak invariance (SFOFL)	1333.19*	11.45	111	0.961	0	0.056	0	840.11*	-3.13	111	0.945	0	0.061	-0.001	987.75*	-0.77	111	0.93	0	0.069	-0.001
Strong invariance (FOFLI)	1431.93*	98.74	118	0.958	-0.003	0.056	0	884.32*	44.21	118	0.943	-0.002	0.061	0	1117.14*	129.39	118	0.92	-0.01	0.071	0.002
Strong invariance (SFOFLI)	1486.04*	54.11	121	0.956	-0.002	0.056	0	902.69*	18.37	121	0.942	-0.001	0.06	-0.001	1175.95*	58.81	121	0.915	-0.005	0.072	0.001
Education																					
Configural invariance	1438*	--	150	0.959	--	0.059	--	914.01*	--	150	0.943	--	0.065	--	1038.48*	--	150	0.93	--	0.073	--
Weak invariance (FOFL)	1454.62*	16.62	166	0.959	0	0.057	-0.002	918.72*	4.71	166	0.943	0	0.062	-0.003	1047.905*[c]	9.425	166	0.929	-0.001	0.069	-0.004
Weak invariance (SFOFL)	1457.4*	2.78	172	0.959	0	0.056	-0.001	913.12*	-5.6	172	0.943	0	0.061	-0.001	1058.64*	10.735	172	0.928	-0.001	0.068	-0.001
Strong invariance (FOFLI)	1718.85*	261.45	186	0.951	-0.008	0.058	0.002	1046.67*	133.55	186	0.934	-0.009	0.063	0.002	1148.22*	89.58	186	0.923	-0.005	0.068	0
Strong invariance (SFOFLI)	1788.71*	69.86	193	0.949	-0.002	0.058	0	1067.43*	20.76	193	0.934	0	0.062	-0.001	1164.39*	16.17	193	0.923	0	0.067	-0.001
Net wealth[a]																					
Configural invariance	1396.61*	--	150	0.957	--	0.058	--	869.1*	--	150	0.944	--	0.062	--	957.16*	--	100	0.931	--	0.072	--
Weak invariance (FOFL)	1446.15*	49.54	166	0.956	-0.001	0.057	-0.001	870*	0.9	166	0.943	-0.001	0.059	-0.003	974.21*	17.05	108	0.93	-0.001	0.07	-0.002
Weak invariance (SFOFL)	1442.84*	-3.31	172	0.956	0	0.056	-0.001	866.54*	-3.46	172	0.943	0	0.058	-0.001	972*	-2.21	111	0.93	0	0.069	-0.001
Strong invariance (FOFLI)	1960.91*	518.07	186	*0.939*	**-0.017**	0.063	0.007	1167.3*	300.76	186	*0.921*	**-0.022**	0.066	0.008	1113.59*	141.59	118	*0.919*	**-0.011**	0.071	0.002
Strong invariance (SFOFLI)	2060.26*	99.35	193	*0.936*	-0.003	0.063	0	1223.76*	56.46	193	*0.917*	-0.004	0.066	0	1133.36*	19.77	121	*0.918*	-0.001	0.071	0

	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA	Robust χ2	Δ Robust χ2	df	RCFI	Δ RCFI	RMSEA	Δ RMSEA
Two-time periods																					
Configural invariance	1387.7*	--	100	0.958	--	0.06	--	852.59*	--	100	0.944	--	0.065	--	990*	--	100	0.931	--	0.073	--
Weak invariance (FOFL)	1384.18*	-3.52	108	0.958	0	0.058	-0.002	841.47*	-11.12	108	0.944	0	0.062	-0.003	989.5*	-0.5	108	0.931	0	0.07	-0.003
Weak invariance (SFOFL)	1403.99*	19.81	111	0.958	0	0.058	0	842.48*	1.01	111	0.944	0	0.062	0	988.96*	-0.54	111	0.931	0	0.069	-0.001
Strong invariance (FOFLI)	1512.12*	108.13	118	0.955	-0.003	0.058	0	906.36*	63.88	118	0.94	-0.004	0.062	0	1027.18*	38.22	118	0.929	-0.002	0.068	-0.001
Strong invariance (SFOFLI)	1576.48*	64.36	121	0.953	-0.002	0.058	0	954.74*	48.38	121	0.937	-0.003	0.062	0	1062.86*	35.68	121	0.926	-0.003	0.068	0

FOFL: first-order factors loadings; SFOFL: second- and first-order factors loadings; FOFLI: second- and first-order factors loadings and intercepts of measured indicators; SFOFLI: second- and first-order factors loadings and intercepts of measured indicators and first-order factors; *P<0.01; **a**: In the third sample (70-90), Only two wealth groups (rich/average and poor) since the estimated variance was negative of the self-realization domain for participants with average wealth. **c**: In the third sample (70-90), estimated variance was negative of the self-realization domain for participants with low education.

Next, we tested the second-order MG-CFA for three subsamples separately based on their age: 50-59, 60-69 and 70-90 years old because the MG-CFA fit indices were the poorest for age compared to the other variable groups that did not meet the requirement of the strong level (education and net wealth). Two age categories were defined within each age group. Table 3-5 shows CASP-12-4D's fit indices for all the three samples. For younger participants, CASP-12 exceeded the benchmarks for a good fit for all five variable groups (RCFI >0.95 and RRMSEA <0.060) while the fit indices for the older and oldest participants achieved the acceptable fit. (RCFI >0.90 and RRMSEA <0.080). Except for the net wealth variable group (ΔRCFI > 0.01), CASP-12 is consistent across all variable groups up to strong level for second- the first-order factors. In the oldest participants, the ΔRCFI for the first-order strong level of the two age categories (70-79 vs. 80-90) is equal to the cut-off value (0.01). In addition, the net wealth groups were reduced to two (rich/average vs. poor) since the estimated variance of the self-realization domain was negative for participants with average net wealth. The value of Δ RRMSEA of the net wealth variable group did not exceed the cut-off (0.015) in all five test levels for all subsamples.

3.5 Discussion

This study evaluated the short version of the CASP-12 through three second-order structure factors and reported that the common second-factor with four first-order structure factor (CASP-12-4D) and the common first-order structure factor had the highest fit indices compared to the other structure factors. Additionally, CASP-12 was consistent across genders and time periods meeting the strong second and first-order invariance criterion. However, it displayed (second and first-order factors) weak invariance in terms of age, educational levels and net wealth, but not strong invariance. The consistency of CASP-12-4D across gender, two age categories, education levels, and time periods was improved and met (second and first-order factors) strong invariance by considering three separate age groups (50-59, 60-69 ad 70-90). Net wealth still fails to meet the strong invariance levels, which might reflect the different perspectives of QoL between wealthy and poor people. Studies have reported inequality among them in several aspects, such as healthcare, living conditions, and engaging in leisure activities that often enable wealthier individuals in aged communities to experience a better quality of life compared to poor people who attempt to have basic needs most of the time (31).

CASP-12-4D could serve as a valuable tool for healthcare providers as well as social research by considering two domains of QoL (Control and self-realization) especially for those aged 70 and over. Also, by considering peoples' age and net wealth, the accuracy of interpreting CASP-12

score differences enhances. While there is no considerable difference in between rich and average participants (not detailed here), poor participants experience a more pronounced impact. Consequently, it is essential to conduct a sensitivity analysis if the participants' wealth status varies.

While the short version of the CASP (CASP-12) is generally favoured over its longer counterpart (CASP-19), the literature reveals various factor structures for the short version(32). These structures underwent international modifications to enhance their psychometric robustness (32). In our study, the CASP-12-4D and CASP-12-FO models exhibited superior performance, aligning with similar findings in European populations that shared limitations in the autonomy domain (32). Note that different factor structures were deemed optimal in other European studies. For example, CASP-12 with three domains (control/autonomy, self-realization, and pleasure) was found to fit better in some instances (12, 33). In a separate study, CASP-11 emerged after removing one item from the autonomy domain, as it demonstrated the lowest correlation coefficient (34). A majority of these studies were conducted across various waves in the Survey of Health, Ageing, and Retirement in Europe (SHARE) datasets (32). with only a limited number focusing on the English population (12, 33), often presenting CASP-12-3D. Notably, information on CASP-12-4D is relatively scarce in these studies, and the sample sizes tended to be small. Considering these factors, CASP-12-4D and CASP-12-FO may be preferable for use among older individuals in England, aligning well with the theoretical background of the four domains in the scale (CASP-12-4D). Their superior goodness-of-fit indices in a larger English population suggest their suitability for comprehensive assessments of QoL in England.

Although previous studies that tested the measurement invariance for CASP-12 is limited, and they only reported the partial measurement invariance, for example, study by Oliver, Sentandreu-Mañó (35) reported partial invariance of the CASP-12 across different age groups. In relation to wealth and its influence on Quality of Life (QoL), our findings align with those of other studies (36, 37). It is consistently observed that individuals from higher socioeconomic backgrounds tend to experience elevated status and enhanced Quality of Life.

It is essential to report several difficulties while conducting longitudinal measurement invariance for CASP-12-4D. The ELSA dataset contains nine waves, but participants' on average respond to four waves. Moreover, the time between the two points is quite long, two years. In addition, an initial result indicated that the model identification (RCFI>0.90) decreases with increased time points (waves). Therefore, there is a need to carry out further work to address these challenges.

The study possesses notable strengths, including substantial sample size and the inclusion of five distinct demographic groups for assessing second-order CASP-12-4D measurement invariance. Nonetheless, limitations exist. While the ELSA dataset contained several variables, we only focused on four variable groups, namely gender, age, education, and wealth. This decision was made due to more missing values in the other variables in subsequent waves.

In summary, the common second-order structure factor with four first-order factors (CASP-12-4D) shows higher fit indices than the other common second-order structure factors used in other studies. Except for wealth, second-order CASP-12-4D within three separate age groups demonstrates second and first-order strong consistency across diverse demographic groups, including gender, two age categories, educational level and two-time periods increasing the accuracy of the instrument measure when used in social and public health research applications. Further work is needed to test the longitudinal measurement invariance analysis of the second-order CASP-12 model.

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Chapter 4 Bidirectional Association Between Frailty and Quality of Life within English Longitudinal Study of Ageing

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Study Two	
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4.1 Abstract

Purpose: The relationship between quality of life (QoL) and frailty has previously been investigated cross-sectionally and longitudinally as unidirectional where QoL depends upon frailty and where frailty depends on QoL. Here a bidirectional relationship is examined.

Methods: This work uses a latent curve model with structured residuals to address the bidirectional association between QoL and frailty in older English people considering within-person and group levels. The study measures frailty using a functional frailty measure and quality of life using CASP-12. The sample size is 17529.

Results: There is a strong relationship between QoL (Quality of Life) and frailty, which is almost linear and inversely proportional over time. Although the cross-lagged coefficients from QoL to frailty and vice versa showed statistical significance, the impact was found to be minimal. The time between assessments (which are two years apart) and/or the few observations available per individual may have impacted the effect of this relationship. When accounting for gender, age, net wealth, and multimorbidity, some variations in the results were observed at the group level but not at the within-person level.

Conclusion: The study provides empirical evidence that supports a bidirectional association between QoL and frailty in older individuals who reside at home. These findings provide a basis for further investigation into enhancing elderly care approaches specific to the context of England.

4.2 Plain English summary

There's growing evidence suggesting a two-way relationship between frailty and quality of life, meaning they can each affect the other. Understanding this dynamic requires sophisticated statistical methods, like the ones used in this study. Our research aims to shed light on a crucial question: when caring for older individuals, should our healthcare system prioritize improving quality of life or addressing frailty? Pinpointing which factor has a greater influence can guide healthcare institutions in allocating resources effectively and supporting elderly individuals in leading fulfilling lives as they age. Surprisingly, our findings reveal a minimal, yet significant, impact of frailty and quality of life on each other over time. This remained consistent across various demographic factors such as gender, age groups, socioeconomic status, and health conditions. One possible explanation for this minimal impact is the lengthy time gap between our measurements, spanning two years for each participant. These insights contribute to a more

nuanced understanding of how we care for our ageing population, informing healthcare policies and practices to better meet the diverse needs of older individuals.

4.3 Introduction

As a country's population ages, as it does in many countries, there is a growing demand for healthcare services among older people (1). Healthcare professionals work to identify factors that help older people maintain their independence and well-being (2). This approach aligns with older people's desires to live a satisfying life, maintain their quality of life (QoL), and avoid becoming frail (3).

Frailty is a clinical condition where the efficiency of the body systems and organs of the elderly decline, resulting in a higher likelihood of adverse outcomes when they are affected by minor diseases (4). Frailty in older people increases the risk of several negative health outcomes, including disability, falls, hospitalization, institutionalization, and mortality (4). Frailty progresses more rapidly with age, and higher frailty is also associated with reduced quality of life (QoL) (5).

QoL is a multidimensional concept that includes psychological well-being, positive feelings, and functioning (6). Gale, Cooper (7) discussed several studies that show that psychological well-being has an inverse relationship with ageing problems such as disability and survival. Improving quality of life was associated with increased life expectancy for older people worldwide (8). Modern geriatric medicine aims to maintain a good quality of life by implementing appropriate interventions, as longevity does not necessarily ensure a high QoL in later life (9).

While previous studies reported a correlation between QoL and frailty, there are still some unanswered questions. Firstly, most of these studies have been cross-sectional in design, which leads to uncertainty regarding the direction of the effect (10). Secondly, while some studies have explored the relationship between QoL and frailty using prospective cohorts, they have been unidirectional and inconsistent in their findings (10). Some studies have reported frailty as a predictor of QoL (11, 12), while others have reported QoL as a predictor of frailty (7). One study examined the bidirectional relationship between frailty and quality of life (QoL) for European participants using a cross-lagged panel model (CLPM) (13). The study found that frailty and QoL have an inverse relationship, with frailty having a greater impact on this relationship. The study recommends early management of frailty to reduce the impact of low QoL on individuals and to provide an intervention plan. The main issue is that the study used a particular method that doesn't look at differences between people and changes within individuals over time. This could mean the findings might not provide the full picture (14, 15). To avoid any misleading

conclusions, a latent curve model with residual structure (LCM-SR) can be used. The LCM-SR approach was previously used to examine the bidirectional relationship between frailty and depression (16). Insights from the findings from this type of analysis can inform healthcare providers and policymakers about interventions to manage and prevent frailty in older people living in the community.

This study aims to explore the relationship between quality of life (QoL) and frailty among older individuals in England. It investigates three hypotheses at the within-person level:

1. When frailty increases for a person at one time point, their quality of life tends to decrease at a later time point.
2. When the quality of life increases for a person at one time point, their frailty tends to decrease at a later time point.
3. At a specific point in time, a person's increase in frailty is associated with a decrease in their quality of life.

At the group level, the study examines two hypotheses:

1. Participants who exhibit greater levels of frailty generally experience a reduced quality of life.
2. Participants who show increased trajectories in frailty tend to show decreased trajectories in QoL.

4.4 Methods

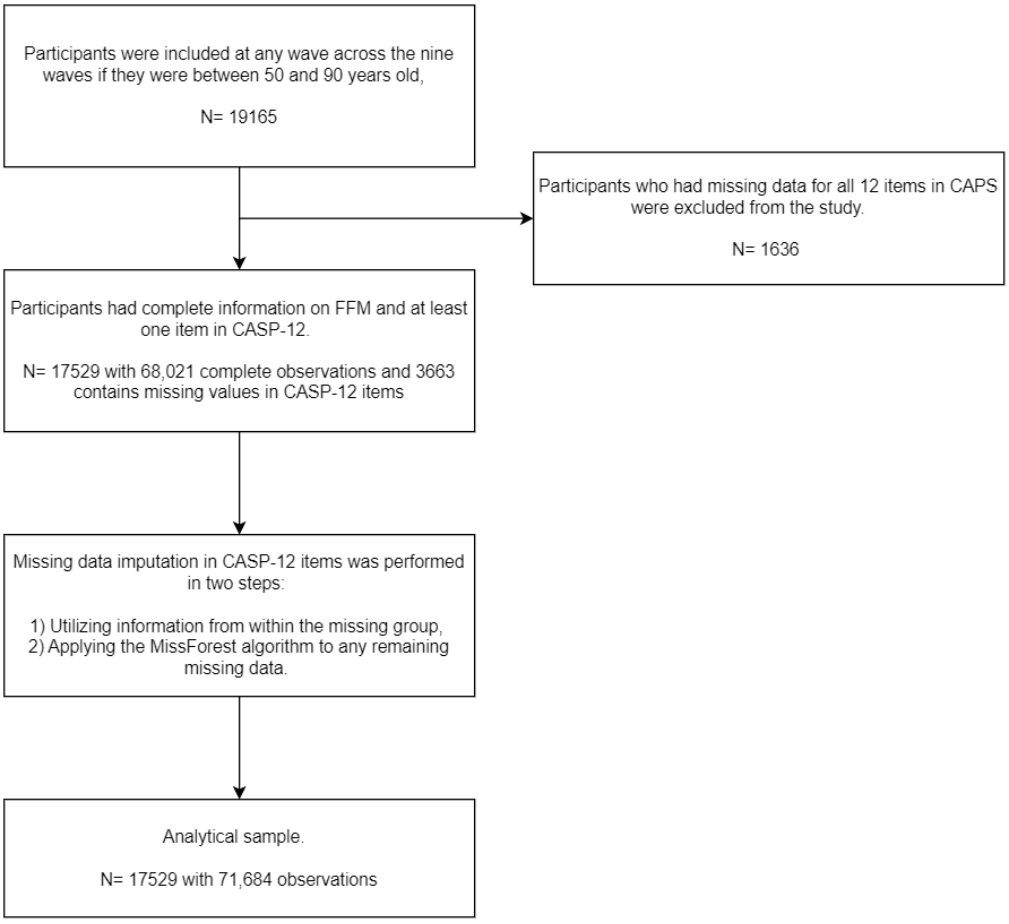
4.4.1 English Longitudinal study of Ageing

The English Longitudinal Study of Ageing (ELSA) was used. ELSA collects information from private households of individuals aged over 50 years residing in England (17). ELSA attempts to reflect the population profile of older people living in England, so it collects information from three aspects of ageing: health, social participants and wellbeing, and finances (18). ELSA currently features ten waves of data collected over a 18-year period (19). Moreover, the ELSA dataset draws refreshed samples in several waves 3,4,6,7,9 and 10 to compensate for sample attrition. ELSA's staff utilize a self-completion form and/or face-to-face interview to collect the data from the respondents (18). In this study, baseline and follow-up samples were included up to wave 9. Table c1 in Appendix C displays the data collected approximately every two years and the sample size for each wave.

4.4.2 Sample construction

In this study, 19165 participants aged 50-90 reported at least one measure of frailty or QoL across the nine waves. The number of missing values for the frailty measure was quite small, while for the QoL measure, it was around 10 to 15% (see Table c2 in Appendix C). Most of the missing values were for the whole CASP-12 items while others were for a part of the QoL items. As a result, the observations with missing values in the frailty measure were removed and the missing values for the whole CASP-12 items. Regarding the missing items on the QoL measure (1 to 11 items), two different methods were used sequentially to impute the missing values, see below, for the cases where one item at least responded to. The analytical sample size was 17529. Figure 4-1 shows The procedures for the analytical sample

Figure 4-1: The procedures for the analytical sample



4.4.3 Measures

4.4.3.1 Quality of life

Control, Autonomy, Self-realization, and Pleasure scale (CASP-12) was used to measure QoL. CASP-12 comprises four first-order factors (domains): Control, Autonomy, Self-realization and Pleasure. Three items for each domain and each item is scored 0 “never”, 1 “sometimes”, 2 “most often”, and 3 “often” (20). Table c3 in Appendix C shows the 12 items of the CASP-12. Item scores are added up to create total scale scores. The score of CASP-12 can range from 0 to 36, with higher scores indicating a better quality of life. The scores of the CASP-12 were divided by 36 (the highest score of the CASP-12) to be comparable with frailty measure scores.

4.4.3.2 Frailty

Functional frailty measure (FFM) was used to operationalize frailty (21). It includes 44 self-reported deficits related to physical and mental health aspects. Table c4 in Appendix C shows the 44 deficits of the FFM. Each item was coded as 0 if a deficit is not present or one if it is present. If a deficit has more than two values, we rescaled it between 0 and 1, for example the self-reported hearing items consist of a scale of five responses ranging from one to five, where one represents the worst and five represents the best. To standardize the responses, we converted each of the five options to a numerical value: one became 0, two became 0.25, three became 0.5, four became 0.75, and five became 1. The frailty score was computed by summing up the scores for each participant and dividing by the total number of valid of responses (at least 39 deficits were available). The frailty index ranges between 0 and 1, where higher scores indicate a higher frailty level.

4.4.3.3 Covariates

Four covariates were selected: gender, age, net wealth and long-term conditions (LTCs), which are defined as a condition which cannot be cured but can be managed through the use of medication and other therapies (22). The participants were categorized into three net wealth levels (rich, average and poor), following the approach of Alattas, Nikolova (21). In this work, the name for wealth levels is replaced with (high, medium and low). LTCs were categorized into two parts: non-multimorbid (zero or one LTC) and multimorbid (two or more LTCs). Based on Alattas, Nikolova (21) study, 16 health conditions were included: hypertension, angina, heart attack, congestive heart failure, abnormal heart rhythm, diabetes, stroke, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's, psychiatrist, Alzheimer's, and dementia. Once the participants reported a LTC, the following observation were updated (21).

4.4.4 Handling missing data in CASP-12

Dealing with missing data is crucial in longitudinal studies as it can cause biased and inefficient statistical analyses (23). To handle missing data in CASP-12, we used two methods. Firstly, we filled in the missing values using information from within the missing group. For example, if an individual had a missing value between two reported waves for a deficit, the missing value for a deficit was replaced with the same value. Secondly, for any remaining missing values, we applied the MissForest algorithm (24). Although it is a single imputation method, it accommodates the nonlinearities and interactions for predictors and is comparable to multiple imputation methods (25).

4.4.5 Modelling strategy

To test our hypotheses above, we used a latent curve model with structured residuals (LCM-SR) (14, 15). The is a modification of the autoregressive latent curve model to explicitly separate within-person and group levels effects by including a time-specific residual structure. Figure 4-2 shows an illustration plot for the relationship between the CASP-12 and FFM using the bivariate multivariate LCM-SR and three consecutive waves of the ELSA data. The growth curve component of this model captures group level variability in both the participant initial levels and trends, represented by the random intercept (RI) and the random slope (RS), respectively. The factor loadings on the RS factors are fixed to 0, 1 and 2 to reflect the weight of time of measurement and specify a positive linear trend for both constructs.

In this study, we have nine consecutive time points. The factor loadings for RS are fixed to 0, 1, 2, 3, 4, 5, 6, 7 and 8. The cross-lagged panel model component provides information on autoregressive, cross-lagged and within time association of the residuals. As an additional analysis, we conducted multiple group analyses on the final best-fit model in four variables: gender, two age groups (50-69 and 70-90), net wealth (high, medium and low), and multimorbidity (non-multimorbid and multimorbid).

4.4.6 Statistical Analysis

A robust maximum likelihood estimator was used since the CASP-12 and FFM scores have skewness in some of the time points. Unbalanced samples across the nine waves handled with full information maximum likelihood (FIML) estimation. It estimates the model by using all information that is available from each participant, and it is a preferable approach under structural equation modelling (26). For model development, two models of LCM-SR were tested. Firstly, only the random intercept (RI) factors are added for the scores of the CASP-12 and FFM,

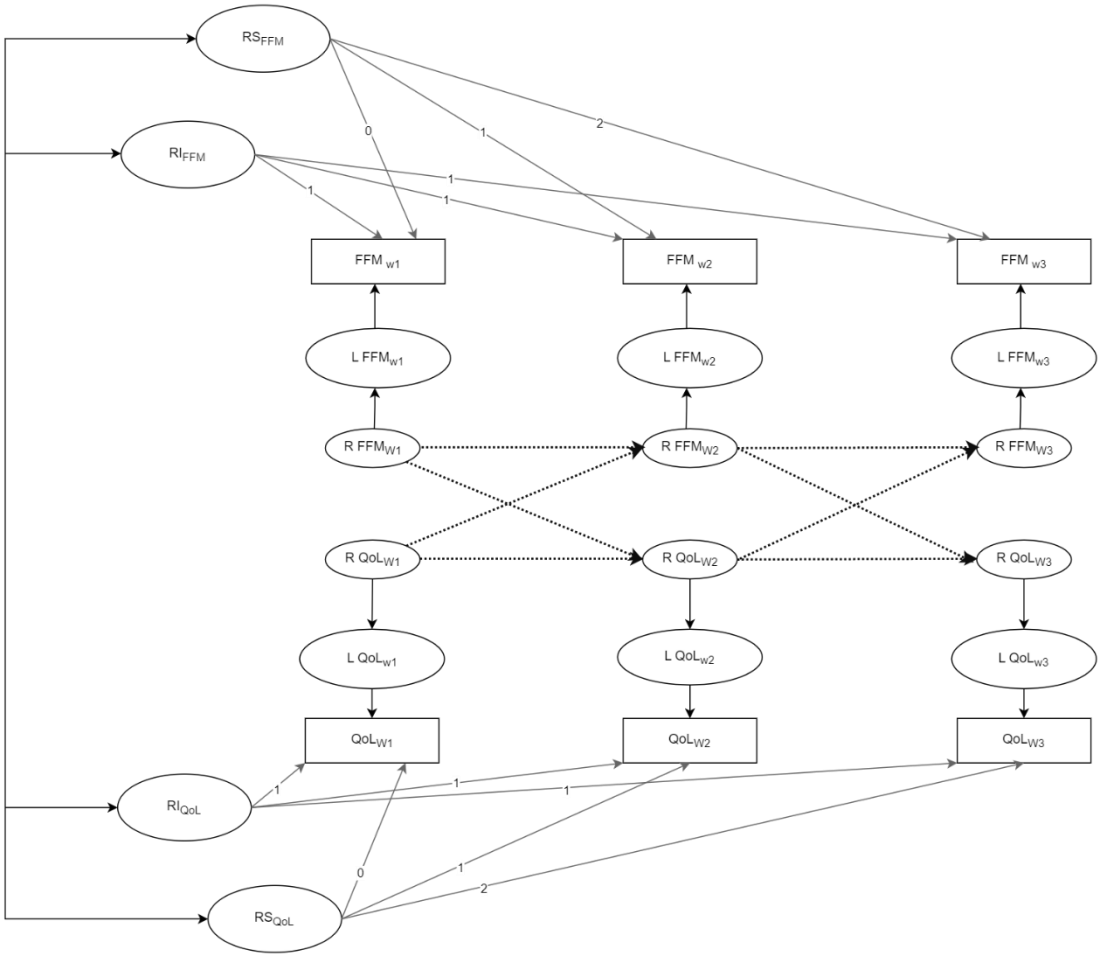
and the autoregression and cross-lagged parameters were constrained across the time points (Model A). Next, we added the random slope factors to the previous models as shown in Models B.

Three fit indices were considered: robust chi-square distribution with a degree of freedom (df), robust comparative fit index (RCFI) and robust root mean square error of approximation (RRMSEA). The Chi-square test is impacted by sample size, meaning that as the sample size grows, the test becomes more responsive to even minor variations between the correlation matrix of observed values and the correlation matrix of expected values. Alternatively, CFI or RMSEA were used to assess the goodness of fit. The RCFI and RRMSEA range from 0 to 1, and the values of 0.90 (acceptable fit) or 0.95 (good fit) are used as cut-points for the CFI while 0.06 (good fit) or 0.08 (acceptable fit) for RMSEA (27). A sensitivity analysis was conducted on individuals with at least one complete set of both FFM and CASP-12 data across the nine waves. The sample size was 17115. The analysis was performed in R software (4.3.3). and all of the CFA models were estimated using the lavaan version 0.6-12 package (28).

4.5 Results

Table 4-1 shows the sample size at each wave, ranging between 10232 and 7034. The number of individuals varied over waves. There were 4128 (23.55%) present in one wave; two waves 2231 (12.73%); three waves: 1955 (11.15%); four waves: 1623 (9.26 %); five waves: 1392 (7.94%); six waves: 1861 (10.62%); seven waves: 1220 (6.96%); eight waves: 1168 (6.66%); nine waves: 1951 (11.13%). Table 4-1 shows that most of the participants were female. The average age of the participants at wave 1 was 64, and 68 at wave 9. Nearly, half were wealthy across the nine waves. Additionally, the prevalence of multimorbidity increased over time. The average score of the CASP-12 was around of 26, and the average scores of FFM was around 0.15. Women, older individuals, lower net wealth, more chronic conditions, frailty and low QoL were the characteristics of the missing data in CASP-12 (See table c5 in Appendix C). Pairwise correlations and reliability estimates for the FMM and CASP-12 scores across the nine waves are shown in table c6 in Appendix C.

Figure 4-2: An illustration of the Latent curve model with Structured Residuals (LCM-SR) with random intercepts (RI) and slopes (RS) for three waves of MCASP-12 and FFM. The correlation within time points was deleted.



Some of the results presented in Table 4-1 are consistent with previous studies that have utilized ELSA data. For example, Marshall, Nazroo (29) reported summary statistics for a sample of ELSA participants at wave 1, which showed an average age of 65, 54% of females, and a frailty score of 0.16. Similarly, Niederstrasser, Rogers (30) reported summary statistics for a sample of ELSA participants at wave 2, which showed an average age of 67, a distribution of wealth categories similar to our findings, and a frailty score of 0.16 at wave 2. However, the analytical samples of these studies or others do not match our analytical sample, which makes comparing our results with theirs might not be appropriate. Most sample studies did not include refreshment samples in later waves. Marshall, Nazroo (29), excluded younger participants (i.e., <60) (5) or presented the summary statistics for the sample by classified them by a variable group, such as gender (31) or survival (5). In our study, long-term conditions (LTCs) were defined based on 16 health conditions, which differs from other studies that use ELSA. For instance, (31) included 26 health

conditions in their study at wave 2 in ELSA and reported that around 80% of participants had two or more LTCs. Additionally, using CASP-12 as a measure for QoL is rare.

Figure 4-3 displays an inverse correlation between CASP-12 and its four domains with FFM. Notably, the control and self-realization domains have a more pronounced decline than the other two. Table 4-2 shows the model fit indices for Model A and B. Notably adding RS factors, as shown in Model B, shows an improvement fit compared to Model A. We did not find any improvement in the model fits when autoregression estimation and cross-lagged parameters varied across the nine waves (not shown here). Next, we reported the parameter estimates for Models A and B, aiding in interpreting effects.

Table 4-3 shows the parameter estimations of Models A and B. At the within-person level (autoregressive, cross-lagged and correlation within-person level), Model A shows higher effects than Model B. Regarding the cross-lagged effect in Model B, the results indicated that the relationship between prior frailty and later QoL was stronger than between early QoL and subsequent frailty. An increase of one unit of the standard deviation of the CASP-12 at a particular time point predicts the negative change to one unit of the standard deviation of FFM at a later time or *vice versa* by around 4%. Moreover, there is a moderate inverse correlation between CASP-12 and FFM within the same time points of the participants in the two models (Models A and B). In other words, the participants who tend to score a high level of QoL with one unit of standard deviation also tend to have a low score with one unit of frailty and *vice versa*.

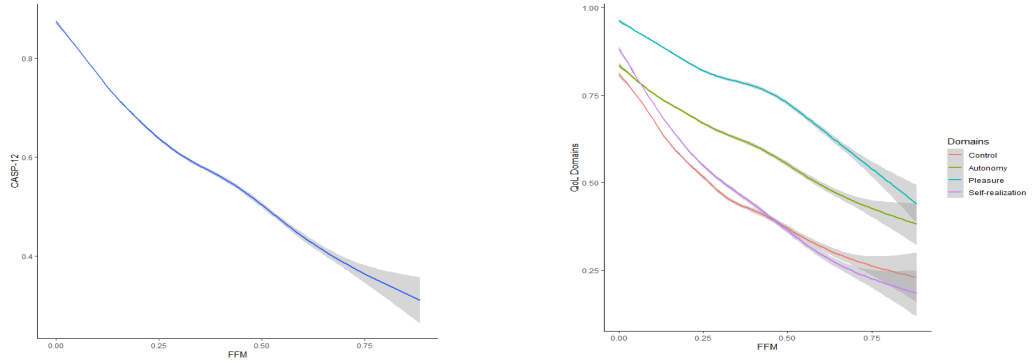
Regarding group-level effects, Model B provided further information on the effects of the random factors. First, the initial level (the random intercept) of CASP-12 is around 27 (0.739×36=26.60) and its standard deviation is around 5 (0.14x36 = 5.04), indicating moderate variability across individuals at baseline. On average, there is a linear decrease over time (random slope) in the CASP-12 score by 0.22 (0.006 × 36) between waves, and the standard deviations of the random slope was 4.32 (0.12x36 = 4.32), suggesting that there is also substantial variation in how QoL changes over time among participants. This implies that individuals experience differing trajectories of QoL, with some showing a steeper decline or different patterns than others. Second, The initial level of frailty is 0.15 and its standard deviation is less than 0.01. On average, there is a linear increase over time (random slope) by 0.005 in the FFM score between two consecutive waves, and the standard deviation of the random slope is less than 0.01, suggesting limited variability in frailty changes across individuals over time.

Also, the correlation of RI factors between CASP-12 and FFM, as well as the correlation of RS factors between CASP-12 and FFM, show a *stronger* negative relationship. The sensitivity analysis results were similar to those of the main analysis (see Tables c7 and c8 in Appendix C).

Table 4-1: Summary statistics for the sample across the nine waves

	Wave	1	2	3	4	5	6	7	8	9
N= 17529		10232	7972	7774	8924	8725	8691	7920	7034	7244
Age (mean (SD))		64.51 (9.87)	65.55 (9.39)	64.89 (9.93)	65.14 (9.16)	66.47 (8.91)	66.54 (9.11)	67.29 (9.15)	68.75 (8.77)	68.07 (9.72)
Gender n(%)	Female	5591 (54.6)	4438 (55.7)	4291 (55.2)	4919 (55.1)	4853 (55.6)	4814 (55.4)	4406 (55.6)	3934 (55.9)	4047 (55.9)
	Male	4641 (45.4)	3534 (44.3)	3483 (44.8)	4005 (44.9)	3872 (44.4)	3877 (44.6)	3514 (44.4)	3100 (44.1)	3197 (44.1)
Net Wealth n(%)	High	4147 (40.5)	3300 (41.4)	3227 (41.5)	3712 (41.6)	3539 (40.6)	3565 (41.0)	3242 (40.9)	2897 (41.2)	2973 (41.0)
	Medium	2078 (20.3)	1655 (20.8)	1560 (20.1)	1779 (19.9)	1748 (20.0)	1782 (20.5)	1585 (20.0)	1437 (20.4)	1478 (20.4)
	Low	4007 (39.2)	3017 (37.8)	2987 (38.4)	3433 (38.5)	3438 (39.4)	3344 (38.5)	3093 (39.1)	2700 (38.4)	2793 (38.6)
Long-term conditions	0	2898 (28.3)	1846 (23.2)	1823 (23.4)	2164 (24.2)	1818 (20.8)	1816 (20.9)	1599 (20.2)	1219 (17.3)	1427 (19.7)
	1	3302 (32.3)	2432 (30.5)	2295 (29.5)	2636 (29.5)	2427 (27.8)	2368 (27.2)	2046 (25.8)	1760 (25.0)	1772 (24.5)
	2+	4029 (39.4)	3685 (46.2)	3653 (47.0)	4115 (46.1)	4476 (51.3)	4505 (51.8)	4273 (54.0)	4049 (57.6)	4043 (55.8)
	NA	3 (0.0)	9 (0.1)	3 (0.0)	9 (0.1)	4 (0.0)	2 (0.0)	2 (0.0)	6 (0.1)	2 (0.0)
FFM (mean (SD))		0.16 (0.14)	0.16 (0.13)	0.15 (0.13)	0.15 (0.13)	0.16 (0.13)	0.15 (0.13)	0.15 (0.13)	0.15 (0.13)	0.15 (0.12)
CASP-12 (mean (SD))		26.85 (5.94)	27.00 (6.06)	25.90 (5.88)	25.89 (5.88)	25.93 (5.99)	25.77 (6.04)	26.48 (5.97)	26.47 (6.02)	26.64 (6.02)

Figure 4-3: An inverse correlation between CASP-12 and functional frailty measure (FFM)(a) and an inverse correlation between the four domains of CASP-12 and FFM (b)



(a) (b)

Table 4-2: Fit statistics of two LCM-SR models

Model	Chi-s	df	RTLI	RCFI	RRMSEA
A	3163.361*	160	0.968	0.967	0.067 (0.065 - 0.069)
B	1574.042*	151	0.985	0.986	0.045 (0.043 - 0.048)

Model A: random intercept (RI) factors are added for both the CASP-12 and FFM; Model B random slope factors were added for CASP-12 and FFM to the model A. *p-value<0.01.

Table 4-3: Standardized parameters for Models A and B

Model	A	B
Random effect: Means		
CASP-12 intercept** ×36	0.718* 25.85	0.739* 26.60
FFM intercept**	0.165*	0.150*
CASP-12 slope** ×36	--	-0.006* -0.22
FFM slope**	--	0.005*
Random effect: Correlation		
CASP-12 intercept vs FFM Intercept	-0.700*	*-0.707**
CASP-12 intercept vs CASP-12 slope	--	-0.110*
CASP-12 intercept vs FFM slope	--	0.140*
FFM intercept vs CASP-12 slope	--	-0.020
FFM intercept & FFM slope	--	0.101*
CASP-12 slope & FFM slope	--	*-0.795**
Autoregressive CASP-12 to CASP-12		
Wave 2	0.318*	0.201*
Wave 3	0.329*	0.222*
Wave 4	0.312*	0.211*
Wave 5	0.303*	0.207*
Wave 6	0.290*	0.197*
Wave 7	0.300*	0.206*
Wave 8	0.292*	0.204*
Wave 9	0.302*	0.211*
Autoregressive FFM to FFM		
Wave 2	0.404*	0.224*
Wave 3	0.399*	0.223*
Wave 4	0.397*	0.227*
Wave 5	0.381*	0.216*

Model	A	B
Wave 6	0.380*	0.219*
Wave 7	0.384*	0.222*
Wave 8	0.370*	0.213*
Wave 9	0.369*	0.209*
Cross-lagged CASP-12 to FFM		
Wave 2	-0.123*	-0.036*
Wave 3	-0.121*	-0.038*
Wave 4	-0.115*	-0.036*
Wave 5	-0.111*	-0.035*
Wave 6	-0.109*	-0.035*
Wave 7	-0.114*	-0.037*
Wave 8	-0.108*	-0.036*
Wave 9	-0.110*	-0.034*
Cross-lagged FFM to CASP-12		
Wave 2	-0.145*	-0.041*
Wave 3	-0.151*	-0.043*
Wave 4	-0.149*	-0.044*
Wave 5	-0.145*	-0.042*
Wave 6	-0.140*	-0.041*
Wave 7	-0.141*	-0.041*
Wave 8	-0.138*	-0.040*
Wave 9	-0.144*	-0.042*
Association within-wave		
Wave 1	-0.475*	-0.273*
Wave 2	-0.317*	-0.203*
Wave 3	-0.314*	-0.203*
Wave 4	-0.311*	-0.203*
Wave 5	-0.307*	-0.202*
Wave 6	-0.304*	-0.202*
Wave 7	-0.306*	-0.203*
Wave 8	-0.303*	-0.202*
Wave 9	-0.303*	-0.202*

** unstandardized ; *p<0.001;

4.5.1 Multiple group analysis

The model group's analysis was based on model B's specifications. The models that included gender showed differences in the within-person effects. The autoregressive parameters of CASP-12 across the nine waves were higher for females, while the autoregressive parameters of FFM were higher for males (see Table c10 in Appendix C). Thus, previous CASP-12 scores will have a greater impact on later CASP-12 scores in females, while FFM scores will have a higher impact on later FFM scores in males. Additionally, the cross-lagged parameters from CASP-12 to FFM were higher for males, while the cross-lagged parameters from FFM to CASP-12 were higher for females. Thus, previous CASP-12 scores will have a greater impact on later FFM scores in males, while FFM scores will have a higher impact on later CASP-12 scores in females. At the group level, the means of the RI for CASP-12 were similar in both genders, around 27. The mean of RI for FFM was higher in females than in males, with 0.15 and 0.13, respectively. The means of RS factors for CASP-12 and FFM were similar in both genders. The inverse correlation between RS factors for CASP-12 and FFM was higher in males (see Table c10 in Appendix C).

Regarding multiple group analysis for age, the autoregressive parameters of FFM across the nine waves were higher for the oldest participants (70-90). Additionally, the cross-lagged parameters from CASP-12 to FFM and *vice versa* were higher for the most senior participants across the nine waves. The inverse association between CASP-12 and FFM within-person level at the same time point is similar for the participant age (50-69) and the group of oldest participants age (70-90) across the nine waves. At the group level, the means of the RI for CASP-12 were similar in both age groups. However, the mean of RI for FFM was higher in oldest than older participants, with 0.15 and 0.13, respectively. Also, the means of the RS factors differed for CASP-12 and FFM: both RSs tend to be steeper in the oldest participants. The inverse correlation between the RI and the RS factors for CASP-12 and FFM was higher in the oldest participants (see Table c10 in Appendix C). So, age impacts the inverse relationship between frailty and QoL, and it is more pronounced among the oldest participants.

Regarding multiple group analysis for net wealth, the autoregressive parameters of CASP-12 and FFM across the nine waves were higher for participants with low net wealth. Additionally, the cross-lagged parameters from CASP-12 to FFM and *vice versa* were higher for participants with medium net wealth. The inverse association between CASP-12 and FFM within-person level simultaneously is higher for medium and low net wealth participants across the nine waves. At the group level, participants with low net wealth had the lowest mean RI for CASP-12, while the highest mean RI was for FFM. The participants with low net wealth tended to have steeper RS means for CASP-12 and larger FFM means. The inverse correlation of RI between CASP-12 and FFM and RS between CASP-12 and FFM were higher for participants with low net wealth (see Table c10 in Appendix C).

Multiple group analysis concerning LTCs (zero/one vs. 2+) showed that the autoregressive parameters of FFM across the nine waves were higher for multimorbid participants. Additionally, the cross-lagged parameters from CASP-12 to FFM were higher for multimorbid, while the cross-lagged parameters from FFM to CASP-12 were higher for non-multimorbid participants. The inverse association between CASP-12 and FFM within-person level at the same point is higher for multimorbid participants across the nine waves. At the group level, the mean of RI for CASP-12 was higher for non-multimorbid participants, and the means of RS for CASP-12 were lower decreasing for non-multimorbid participants, while the means of RI and RS for FFM were higher for multimorbid participants. The inverse correlation of RI between CASP-12 and FFM and RS between CASP-12 and FFM were higher for multimorbid participants (see Table c11 in Appendix C The observations with missing data for LTCs were omitted.

4.6 Discussion

This study explored how quality of life (QoL) and frailty are connected among 17529 English individuals over a 16-year period. The relationship between QoL, measured by CASP-12, and frailty, assessed by FFM, showed a consistent inverse pattern, almost following a straight line. Despite statistically significant cross-lagged coefficients between CASP-12 and FFM, indicating mutual influence over time, the actual impact appeared to be minimal.

There are not many studies that investigate the two-way relationship between frailty and quality of life (QoL) in observational studies (13). A cross-lagged panel model (CLPM) is one method that can be used to examine this kind of investigation (14, 15) although biased estimations could occur when an individual's characteristics are not distinguished from those of the sample group. Our findings suggest that there is a minimal but significant bidirectional relationship between frailty and QoL, indicating that neither has a dominant effect on the other. Differences in cohort samples and frailty measures may have contributed to these slight differences.

Additionally, it was observed that factors such as gender, age, net wealth, and multimorbidity had a significant impact on the relationship between Quality of Life (QoL) and frailty at a group level but were not as noticeable at the individual level. This indicates that although these factors play a role in the average relationship between QoL and frailty, they vary more when considering individual experiences over time. This could be due to the limited available information, such as the few observations per individual. The long intervals (two years apart) between measurements and sample attrition caused by unobserved reasons like hospitalization or death could be other reasons.

The present study has notable strengths. It is the first study to investigate the reciprocal relationship between quality of life (QoL) and frailty over 16 years with a considerable sample size using the LCM-SR method. The quality of the dataset was excellent. The analysis was adjusted for several crucial factors, including sex, age, wealth, and long-term conditions (LTCs).
There are some limitations for this work. One of the main limitations of this study is the presence of missing data in CASP-12 items. We addressed this issue by utilizing two imputation methods sequentially and we employed FIML to handle unbalanced samples across the nine waves under the structural equation model framework. Next, the space between the two time points was two years, which cannot capture more immediate impacts. The sample had a higher proportion of wealthier individuals although our analysis demonstrated that the results remain robust against net wealth differences. Although the sample size was large, we cannot assume

generalizability in this work since participant weighting in ELSA was not adjusted for representativeness.

To summarize, a bidirectional relationship between QoL and frailty is close to linear and inversely proportional over time. Although the bidirectional cross-lagged for CASP-12 and FFM coefficients were statistically significant, the magnitude of the effect is small. Even when we considered factors like gender, age, wealth, and having multiple health conditions, we noticed some differences in the overall results between different people, but not so much within the same person over time. The study provides empirical evidence that supports a bidirectional association between QoL and frailty in older individuals who reside at home.

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Statements and Declarations

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Writing – review and editing: Ali Alattas, Robert West, Silviya Nikolova, Farag Shuweihdi, Kate Best

Ethics approval: The research used data from the English Longitudinal Study of Ageing (ELSA), which is provided by the UK Data Service. When using ELSA as secondary data, it is not necessary to obtain an approved letter, but it is required to cite the source of the data based on the End User Licence Agreement (EULA) available at: https://ukdataservice.ac.uk/app/uploads/cd137-enduserlicence.pdf.

The citation for the ELSA dataset is as follows:

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Chapter 5 Discussion and conclusions

5.1 Chapter Summary

The three studies collectively provide an extensive analysis of the interplay between LTCs, frailty progression, and QoL among older adults, using data from the English Longitudinal Study of Ageing. Together, they offer significant insights into how LTCs influence frailty and how both frailty and QoL evolve over time, shaped by factors such as gender, age, wealth, and LTCs.

5.2 Summary findings and contributions to the literature

The journey begins with **Study One**, which delves into the impact of LTCs on frailty progression. FFM was proposed to measure frailty, and the counting approach was used to measure LTCs and two or more LTCs as a cut-off to define multimorbidity. The findings reveal that frailty accelerated (non-linearly) more rapidly in males with one LTC and females with two or more LTCs as participants aged. Those burdened with multiple LTCs exhibited higher frailty scores, underscoring the compounding effect of these conditions. The study further highlights the protective roles of wealth and education; wealthier and more educated individuals tend to be less frail over time. This insight suggests that socioeconomic status could have either delayed frailty progression or helped individuals manage their health better despite the presence of LTCs. As the narrative progresses to **Study Two**, the focus shifts to evaluating CASP-12, a short version of the CASP-19, in measuring QoL. The study identified the CASP-12 model with a second-order model and four-factor model (CASP-12-4D) as having the best-fit indices. CASP-12 with the second-order model demonstrated strong measurement invariance across genders and two periods (participants at wave 1 against participants at wave 2 to wave 9), indicating its reliability in these contexts. However, it showed only weak invariance concerning three age groups, education levels, and net wealth status, highlighting the diverse ways these factors could have influenced perceptions of QoL. Interestingly, when breaking down the data into age groups (50-59, 60-69, and 70-90), the model's consistency improved significantly, except regarding net wealth. This suggests that while CASP-12 is a reliable tool across different demographics, wealth disparities may reflect varied QoL perspectives, necessitating careful consideration when applying this measure. The financial item 'A lack of money stops me from doing things I want to do' in the autonomy domain has a low factor loading compared to all the other items on the CASP-12. This could have caused inconsistency in the results. This was considered in Study Three when multiple groups were applied for analysis.

The story reached a compelling conclusion with **Study Three**, which investigated the bidirectional relationship between frailty, measured by FFM, and QoL, measured by CASP-12, over 16 years. Utilizing a latent curve model with structure residuals (LCM-SR), the study uncovered the relationship was consistently inverse, indicating that as frailty increases, QoL tended to decrease, and vice versa. Despite the statistical significance of this interaction, its practical impact is minimal when looking at an individual level. Factors such as gender, age, net wealth, and multimorbidity significantly affected this relationship at the group level, although their influence diminished at the individual level. This suggests a complex, nuanced interplay where individual experiences of frailty and QoL could vary widely over time.

In weaving together these findings, the studies painted a picture of ageing in England. They underscored the critical importance of considering gender differences, socioeconomic status, and age-specific priorities in managing frailty and enhancing QoL, which was consistent with several studies in the literature (1-4).

The results of **Study One** aligned with other studies that confirmed the impact of long-term conditions (LTCs) on the progression of frailty. **Study One** also revealed that the acceleration of frailty increased non-linearly as participants age and gain more LTCs. Operationalizing frailty measures, FFM, by excluding long-term conditions (LTCs) and keeping the number of deficits above 30 was consistent with some studies (5, 6) , and was a reliable tool for measuring frailty, especially for those interested in studying the impact of LTCs on frailty.

The results of the **Study Two** showed that the recommended factor structure for CASP-12, which is the common second-order factor, was in line with previous study (7). Also, **Study Two** aligns with Oliver, Sentandreu-Mano (7) who found that CASP-12 is inconsistent across age groups before establishing its consistency partially by relaxing one item for CASP-12. Further exploration was conducted to achieve invariance for CASP-12 by dividing the sample into three age groups, but the measure was still non-invariant across the net wealth groups. This might reflect the different priorities at each stage of the life course and how wealth is a vital factor across these stages (8). Also, it shows that concerns about applying CASP-12 beyond the age range for target people for this instrument, which are older people aged between 65-75, have to be considered (9).

Investigations of the longitudinal bidirectional relationship between frailty and QoL were lacking in the literature (10). The results from **Study Three** varied from the results in other study that examined this longitudinal association (11). Hu, Chu (11) concluded that frailty dominated the change in later QoL with no consideration of personal and group levels. Considering that issue

by using a modified CLPM method to examine the longitudinal bidirectional relationship between frailty and QoL in Study Three has made a difference, it showed that frailty did not considerably change later QoL, or *vice versa* considerably (only minimal impact). These results suggest that the causal relationship between QoL and frailty may be weaker than previously assumed, highlighting the importance of other factors, such as social isolation, mental health, physical activity, and socioeconomic status, in influencing these changes over time. In terms of interventions, the results indicate that some efforts to reduce the progression of frailty will have a minor effect on enhancing the quality of life (QoL) in the English populations, and vice versa.

The connection between frailty and quality of life (QoL) can be seen as two sides of the same coin, showing how closely linked these concepts are. A stronger inverse correlation of around 30% across nine different time points suggests that both frailty and QoL are influenced by external factors. Social dynamics, financial stability, and support systems are likely to play important roles in shaping these outcomes (10). To gain a deeper understanding of this relationship, future research should investigate how these factors mediate the two-way influences between frailty and QoL, with the ultimate goal of identifying which aspect has a more significant impact on the other. By taking into account the domains of both concepts, we can develop more comprehensive interventions that address both frailty and QoL simultaneously, thereby promoting better health and well-being in older populations (12). Consequently, social care professionals may inquire with individuals in need of assistance to determine the specific support they require. It appears that women typically sought support to maintain or improve their QoL, while men tended to seek support to prevent severe frailty (See autoregressive parameters in table c 10 in Appendix C).

5.3 Strengths and limitations of the methods

5.3.1 Strengths

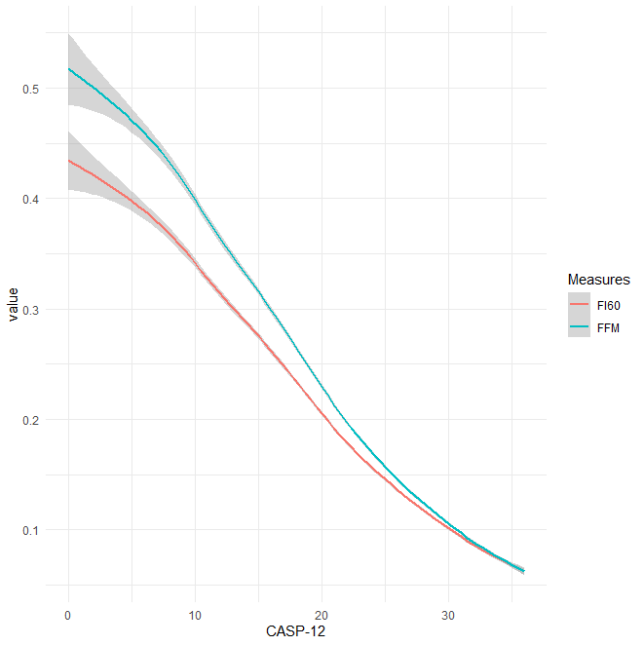
The studies benefited from the use of large and longitudinal analytical samples drawn from the ELSA. This dataset allowed for the examination of changes over time and the inclusion of new participants across later waves, increasing the statistical power.

The measures used in the three studies were well-suited to the research questions. The CASP-12, a QoL measure, has a strong theoretical background and demonstrated excellent fit indices, particularly with its second-factor model encompassing four primary factors: control, autonomy, pleasure, and self-realization. This makes it highly relevant to studies focused on older populations. Similarly, the Functional Frailty Measure (FFM) used in the studies consisted of over 30 deficits, making it a robust predictor of mortality and a comprehensive and reliable measure

of frailty due to its high correlation with the original frailty index, which included 62 deficits (13) as Figure 5-1 has shown.

Each study employed advanced statistical methods that provided several advantages. In **Study One**, the multilevel growth model effectively captured individual differences and trajectories over time, accounted for nested data structures, and allowed for the inclusion of time-varying covariates. Without this model, the analysis would have struggled to capture detailed individual trajectories, potentially masking important patterns in frailty progression. The nested data structure of the ELSA data would not have been adequately accounted for, leading to biased results and underestimated standard errors. Additionally, excluding time-varying covariates would have oversimplified the understanding of dynamic factors influencing frailty.

Figure 5-1: Two frailty measures FI-60 and FFM vs. CASP-12



In **Study Two**, the MG-CFA ensured the measurement invariance of CASP-12 across different subgroups, validated the consistency of the QoL measure, and provided a rigorous method for testing theoretical constructs, and this is also important because it is used in **Study Three**.

Study three employed a LCM-SR, which modeled the bidirectional relationship between frailty and QoL over time. The LCM-SR controlled for unobserved heterogeneity by accounting for individual differences that are not directly measured but may influence the relationship between

frailty and QoL. This is a crucial improvement over the CLPM, which often struggles to separate within-person changes from between-person differences, potentially leading to biased estimates. By incorporating structured residuals, the LCM-SR mitigates this issue, offering more accurate and reliable insights.

Missingness was assumed to be missing at random, so handling missing data was approached methodically in both **Study One** and **Study Three**. For FFM in **Study One** and CASP-12 in **Study Three**, missing data were initially addressed by filling in missing values using information from within the missing group (14). For example, if an individual had a missing value between two reported waves, the missing value was replaced with the same value from adjacent waves. Any remaining missing values were then handled using the MissForest algorithm, which, although a single imputation method, accommodates nonlinearities and interactions among predictors, making it comparable to multiple imputation methods. Additionally, full information maximum likelihood (FIML) was used to handle unbalanced data within the structural equation modeling framework, ensuring that all available data were utilized to produce unbiased parameter estimates.

The inclusion of relevant covariates (gender, age, net wealth, education level, and number of long-term conditions) in the studies helped control for potential confounding variables, enhancing the validity of the findings. These covariates ensured a more accurate assessment of the relationships being studied, contributing to the robustness of the results.

5.3.2 Limitations

One of the primary limitations of these studies is the potential issue with generalizability. Although the ELSA dataset is comprehensive, the lack of participant weighting specific to the study design could affect the representation of the broader population, meaning the findings may not be fully generalizable beyond the sample used. Moreover, although the ELSA dataset is rich in variable groups, I decided to use only gender, age, education, and wealth, as there were more missing values in other variables in the subsequent waves, such as smoking, alcohol consumption, obesity, polypharmacy, and friendship. Most of the participants I dropped from the analytical sample had missing data for the net wealth variable. 60% of them were female and, on average, more vulnerable (frail) than those who reported their net wealth.

In ELSA, it has been noted that certain ethnic minority groups are underrepresented (15, 16). This underrepresentation can impact the generalizability of findings related to these groups, as their unique experiences and health outcomes might not be fully captured. Additionally, accounting for ethnicity helps to understand health disparities in ageing populations better,

offering a fuller and more accurate interpretation of the data(17). Consequently, the study's conclusions about the ageing population in England may not entirely reflect the diversity of the country's older adults.

Another limitation concerns the reliance on self-reported measures. While self-reported frailty and QoL can introduce bias due to inaccurate reporting or recall issues (18, 19), for instance, in studies relying solely on self-reported data, there is a risk of measurement error and bias that can affect the validity and reliability of the findings. On the other hand, it also serves as a strength by offering direct insights into the participants' experiences, which is particularly relevant for studies focusing on quality of life and subjective health measures.

The Frailty Index (FI) is commonly used to assess frailty in older adults using the cumulative deficit model and the selection of deficits is often based on subjective judgment or data availability, leading to potential variability and biases in comparisons across studies. Furthermore, several deficits in the model are chronic and hard to reverse, which may not accurately represent the dynamic and potentially reversible nature of frailty. Focusing on long-term, unchangeable deficits may limit the model's ability to capture short-term changes in health status. In order to address these limitations, it is important to carefully choose the deficits to include, consider any reversible conditions, and take into account changes in health over time to create a more precise and adaptable measure of frailty. The FFM, which excludes 16 reversible deficits and performs similarly to the original frailty index, offers a way to tackle this issue while maintaining the sensitivity and adaptability of the measure.

Finally, investigating the bidirectional relationship between frailty and quality of life, without considering mortality, might lead to bias in the results. Using different statistical methods, such as a multistate model, will be one approach to tackle that. a state of death is generated and frailty states, rather than a frailty continuum, are used. This enables those who die to be considered in the modelling process - and removes a potential selection bias.

Dropouts in a cohort can significantly affect the findings of a study, particularly in longitudinal research examining the relationship between frailty and quality of life (QoL). Non-random dropouts—where certain participant characteristics influence retention—can introduce bias, potentially skewing results. For example, if healthier individuals are more likely to remain in the study, the observed relationship between frailty and QoL may be overstated. Additionally, reduced sample sizes due to dropouts can lead to decreased statistical power, making it more challenging to detect significant effects and limiting the generalizability of the findings to the broader population (20). To reduce the impact of dropouts in future studies, it is important to

use effective strategies to keep participants engaged. Using statistical methods like multiple imputation or single imputation such as, MissForest algorithm can help handle missing data and improve the accuracy of results. It's also beneficial to conduct sensitivity analyses to understand how different dropout rates could affect the conclusions of the study. Lastly, analyzing the differences between participants who drop out and those who stay involved can offer valuable insights for improving future study designs and retention efforts (20).

5.4 Implications of findings

5.4.1 Implications for practice

The findings from these three studies offer significant implications for practice, particularly in the areas of frailty prediction, that is prognosis, and QoL enhancement among older adults.

The application of the FFM in community settings can be instrumental in proactive health management. One benefit is that FFM can uncover the small changes over time that will assist the earlier diagnosis for frailty in the community. Importantly, gender differences should be considered, as frailty progression may vary between men and women, allowing for more personalized interventions. Additionally, research indicates that the concept of Quality of Life (QoL) changes as people age. The CASP-12 measure considers factors such as control, autonomy, pleasure, and self-realization, highlighting the importance of taking into account age-specific QoL priorities. Younger seniors may prioritize autonomy and physical activity, while older seniors may focus more on social connections and self-realization. This has implications for cohort studies as participants move between age groups. As individuals age, their QoL priorities and perceptions may change, requiring adjustments in study design and data collection methods to adequately capture these evolving priorities. This dynamic perspective on ageing underscores the significance of longitudinal assessments and adaptable research methodologies in cohort studies.

5.4.2 Directions for future research

5.4.2.1 Multistate model

Initial work employed a continuous-time multi-state survival model with interval censoring (21-23) across the first six waves of ELSA. This study observed the impact of frailty status on mortality and the indirect effect of quality of life (QoL) in mitigating that impact. Participants categorized as robust/mildly frail or moderately frail with a high QoL exhibited lower transition probabilities to worse health states and higher probabilities of transitioning back to better states.

Furthermore, the analysis highlighted that older individuals with low wealth had a higher probability of deteriorating to worse states and a lower probability of improving to better states.

The assumption of stationarity across the included time points however was violated. Therefore, there is a proposal to incorporate the duration spent in each state as an additional parameter when calculating transition probabilities among states. This adjustment might be implemented using a well-known Semi-Markov Multi-state Model with interval censoring**.**

5.4.2.2 Non-linear Measurement invariance test

Moderated Nonlinear Factor Analysis is a sophisticated analytical method that enhances the understanding of latent constructs by incorporating the effects of moderators and nonlinear relationships, making it a powerful tool in fields requiring precise measurement across diverse groups (24). MNLFA is an alternative, more flexible model for evaluating measurement invariance and differential item functioning, combining the strengths of multiple groups and MIMIC models (25).

5.5 Conclusions

Ageing is a significant phase for individuals living in England, where the population of older adults is increasing rapidly. Many older adults aspire to live independently and happily during this stage, striving to enhance or at least maintain their quality of life. Several factors, including age, and net wealth, play a crucial role in this pursuit. in addition, as people age, the number of long-term conditions (LTCs) tends to increase, leading to an acceleration of frailty, which varies between males and females and across different ages. The bidirectional relationship between frailty and quality of life (QoL) was found to have a minimal impact, with often neither dominating the other over time. This finding underscores the complex interplay of factors influencing the ageing process in England. Understanding these intricate and multifaceted factors is essential for improving the ageing experience and supporting older adults in achieving a better quality of life. By considering these variables and their interconnections, healthcare providers and policymakers can develop more effective strategies to support the well-being of older adults.

5.6 References

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Appendix A: Chapter One supplementary materials

A1. Search terms for the longitudinal accusation between frailty and multimorbidity.

PubMed

("comorbidity"[Title] OR "multimorbid*"[Title] OR "multimorbidity"[Title] OR "comorbid*"[Title] OR "comorbidity"[Title] OR "multiple chronic diseases"[Title] OR "co-morbidit*"[Title] OR "co-morbidity"[Title] OR "multiple diseases"[Title] OR "multi-morbidity"[Title]) AND ("frail elderly"[Title] OR "frail*"[Title] OR "frailty"[Title])

Web of Science

Search restricted to “Title”: ("multimorbid*" OR "multimorbidity" OR "comorbid*" OR "comorbidity" OR "multiple chronic diseases" OR "co-morbidit*" OR "co-morbidity" OR "multiple diseases" OR "multi-morbidity") AND ("frail*" OR "frailty")

A2. Search terms for multidimensional QoL measure and statistical methods to test measurement invariance

(Quality of life OR well-being) AND (measurement invariance OR invariance testing OR psychometric properties) AND (Older people OR elderly).

A3. Search terms for the longitudinal accusation between frailty and QoL.

(“Quality of life” OR well-being” OR “life satisfaction”) AND (frail* OR “frail elderly”) AND (cohort* OR longitudinal OR prospective OR "follow-up").

A4: The summary of the 13 studies included studies in the literature review of longitudinal association between frailty and multimorbidity

#	Study	Aim of study	Time points	Age	N / Female%	Population	Country
1	Woo and Leung (1)	"To examine the independent and combined effects of multi-morbidity, dependency, and frailty on four health outcomes (mortality, decline in physical function, depression, and polypharmacy). The influence of socioeconomic status on these relationships is also examined."	2	65+	4000 / did not report	In the community	Hong Kong
2	Guaraldi, Brothers (2)	"In the present study, we sought to construct a frailty index from health variables collected as part of assessments in an HIV clinic. We assessed the validity of the frailty index, described the characteristics of frailty in a large clinical cohort, and evaluated the ability of a frailty index to predict mortality and incident multimorbidity"	2	Mean 46	2722 / 32%	in HIV outpatients	Italy
3	Zheng, Guan (3)	"The present study was designed to estimate the prevalence and 1-year incidence of frailty in the Beijing Longitudinal Study of Aging II (BLSA II) cohort using the Rockwood method to evaluate the effect of frailty on adverse events in older adults."	2	55+	10039/ 61.3% at baseline	In the community	China
4	Hajek, Brettschneider (4)	"The aim of our study was to identify time-dependent factors affecting frailty in old age."	2	75+	3217 Wave 4 = 1602 / 66.8% Wave 5 = 1307/ 64.4%	Elderly individuals were recruited via GP offices at six study centres in Germany	German
5	Nguyen, Wu (5)	"In this study, we investigated the associations of multimorbidity patterns and frailty (19) with mortality using nationally representative data from	2	65+	7,197 / (57.6%)	In the community	USA

#	Study	Aim of study	Time points	Age	N / Female%	Population	Country
		the National Health and Aging Trends Study(NHATS)."					
6	Strandberg, Lindström (6)	"frailty as a phenotype is of special interest because it is not considered a disability state, and offers an additional method, independently of diagnosed diseases to predict mortality and outcome risk. Because there are few long-term studies on this, we explored their relationships during an 18-year follow-up in the longitudinal Helsinki Businessmen Study (HBS)"	2	Median 73	3490/ 0%	Population Information System of Finland for surviving HBS participants	Finland
7	Tazzeo, Rizzuto (7)	"This study aims to determine the cross-sectional and longitudinal associations between different multimorbidity patterns and physical frailty in older Swedish adults."	2	Mean 74.3	2,122 / 64%	In the community	Sweden
8	Voshaar, Jeuring (8)	"to examine whether the association between the FI and mortality is independent of multimorbidity (number of diseases as well as specific physical and mental health disease clusters) and/or interacts with multimorbidity, and (4) to examine whether multimorbidity or specific disease clusters are associated with an accelerated increase of frailty at a 5-year follow-up."	2	40+	92,640 / (58.0%)	In the community	Northern Netherlands.
9	Ho, Yeh (9)	In this 16-year, population-based cohort study, we analyzed the relationships between multimorbidity patterns and disability/frailty among older adults in Taiwan.	2	50+	2,194/ not known	In the community	Taiwan
10	Chu, Ho (10)	"to understand the prevalence of frailty among middle-aged and older adults having different multimorbidity patterns; and (2) to understand if	2	Mean 66.3	4748/ not known	In the community	Taiwan

#	Study	Aim of study	Time points	Age	N / Female%	Population	Country
		there is an additive effect of frailty with multimorbidity patterns on mortality among middle-aged and older adults aged over 50 years"					
11	Feng, Ma (11)	"the aims of this study were (i) to investigate the existence of a bidirectional relationship between frailty and multimorbidity, (ii) to explore the existence of a bidirectional relationship between changes in frailty and multimorbidity, and (iii) to better evaluate whether depression is a potential mediator of this bidirectional relationship."	3	50+	22 786	In the community	28 county (SHARE)
12	Luo, Chen (12)	"This study aimed to explore baseline multimorbidity patterns and examine their associations with the subsequent transitions between frailty states and death among older American adults."	Not known	65+	9450 / 57.1%	In the community	USA
13	Ma, He (13)	"Therefore, based on participants from UK Biobank, we used multi-state models to assess the role of frailty, measured by frailty phenotype, (17) and frailty index (FI) (18), in disease progression trajectory from disease-free state to single CMD, then CMM, and ultimate mortality. Considering that frailty is dynamic, associations of changes in frailty with CMM progression and prognosis were also estimated."	2	Mean 56.55	17 264	In the community	The UK

A5: The summary of the 9 studies included studies in the literature review of statistical methods to test the measurement invariance in multidimensional QoL measures

Study	Aim of study	Age	N / Female%	Population	Country	Variable groups
Lix, Acan Osman (14)	"This study examined the measurement equivalence (ME) of the 36-item Medical Outcomes Study Short Form Survey (SF-36), a widely-used measure of HRQOL, by sex and race in a population-based Canadian sample."	25+	9,423/66%	In the community	Canada	Sex and race These stratification variables were selected because previous research indicates they are associated with differences in the conceptualization of HRQOL and other patient-reported outcomes
Hardouin, Audureau (15)	"This study aims at analyzing Health related quality of life (HRQoL) data on the French general population between 1995 and 2003 using an Item Response Theory (IRT) model."	+18	26388	---	France	7 age categories, genders, 8 regions of residency, and 2 years of study
Lin, Li (16)	To examine the WHOQOL-BREF instrument for the elderly across some different demographics.	65+	244 / 41.4%	In the community	Taiwan.	Gender and education
Peipert, Bentler (17)	" To evaluate whether there is measurement invariance between Black and White respondents for KDQOL-36 scale."	Mean 66	39,843	Patients	USA	Balck and white
Lin, Wang (18)	First, we aimed to translate the WHOQOL-AGE for an East Asian sample (i.e., Taiwanese). Second, to verify the factor structure of the WHOQOL-AGE among the Taiwanese elderly. After ensuring the factor structure of the WHOQOLAGE, measurement	50+	522/59.2%	In the community and patients	Taiwan	genders, having different educational levels, living in different settings and age groups

Study	Aim of study	Age	N / Female%	Population	Country	Variable groups
	invariance was examined to understand whether elderly people with different genders, educational levels, living settings, and ages interpret the WHOQOLAGE differently.					
Oliver, Sentandreu-Mano (19)	" To test the factor structure of the CASP-12, so as to provide evidence on reliability and external validity, and to test for measurement invariance across age groups."	60+	61,355 / 55.9%	In the community	European populations	Three age groups (60–75 years old, 76–85 years old, and 86+ years old) since the original CASP scale was designed for 'early' older adults and not for the oldest-old.
Calderon, Ferrando (20)	To analyze the internal structure of the EORTC QLQ-C30, to examine the validity and normative data for cancer patients. (2) To test for strong measurement invariance across sex and tumor site.	18+	137/61%	Cancer patients	Spain	sex and tumor site and over time
Scott, Mazzucchelli (21)	Test the goodness of fit of the original factor structure of OPQOL via confirmatory factor analysis. Also, assess the measurement invariance of the OPQOL across age and gender	65+	432/54.8%	In the community	Australia.	Two age groups 65-75 vs 75+ and gender

A6: The summary of the 9studies included studies in the literature review of longitudinal association between frailty and QoL

Study	Aim of study	Time points	Age	N / Female%	Population	Country
Gale, Cooper (22)	"We used data from the ELSA to investigate the 4-year prospective association between scores on the CASP-19, a measure of psychological well-being that assesses perceptions of control, autonomy, self-realization and pleasure (Hyde et al. 2003), and risk of incident physical frailty in men and women aged 60 to 590 years."	Wave 2 and 4 in ELSA	60+	2557/ does not reported	In the community	The UK
Gobbens and van Assen (23)	"The aim of this study was to assess the predictive validity of the components of the TFI for quality of life domains physical health, psychological, social relations and environmental in community-dwelling older persons in a longitudinal study."	3 Two years apart	"75+	269 at baseline/ 56.8%	In the community	the Netherlands
Kojima, Iliffe (24)	"The aim of this study was to investigate associations between baseline frailty status and changes in QOL over time by using repeated-measures analysis among British community- dwelling older people."	6 (2.5 years)	65+	363/62.0 %	In the community	The UK
Geessink, Schoon (25)	"We aimed to study the differences in the association between frailty and self-perceived and health-related QOL between community-dwelling older people aged 65 years or above with and without a cancer diagnosis cross-sectionally and at 12 months follow-up."	2	65+	7493/58.4%	In the community	Netherlands
Rivera-Almaraz, Manrique-Espinoza (26)	"our main aim in this study was to estimate the independent associations of multimorbidity and frailty with three different outcomes: disability, quality of life and all-cause mortality. A secondary aim was to determine whether exist a significant interaction effect of the multimorbidity and frailty on those same outcomes."	2	50+	1410/ not mentioned	No	Mexico

Andrade, Andrade (27)	"The present study addresses this research gap by investigating the association between frailty and HRQoL among older adult residents of the city of São Paulo over time, and examining whether family functionality moderates the association between frailty and HRQoL of this population."	3 (5-6 years apart)	60+	1190 at baseline/ 60.3%	Health, Well-being, and Aging Study (SABE)	Brazil
Mori, Nagai (28)	"Next, we explored factors that contribute to the progression or improvement of frailty status in a two-year longitudinal analysis of participants in the FESTA study, while paying attention to QOL subdomains."	2	65+	840/ not shown	In the community	Japan
Veronese, Noale (29)	"the aim of the present study was to investigate associations between multidimensional frailty, assessed by MPI, with mortality and GQoLE indicators, in a large representative sample of older English adults, over 10 years of follow-up."	2 waves 2 and 7	60+	6244/55.5%	In the community	The UK
Hu, Chu (30)	"this study explores the bidirectional association between frailty and QoL and further examines whether a reciprocal association exists between changes in frailty and QoL in older adults. Additionally, it evaluates whether cognition mediates the potential bidirectional relationship utilizing a three-wave cross-lagged panel design based on a large nationally representative sample from the Survey of Health, Aging, and Retirement in Europe"	3	50+	19,649/55.7%	In the community	12 European countries

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Appendix B: Study One supplementary materials

Figure b1: FMM vs age grouped by LTCs (Females)

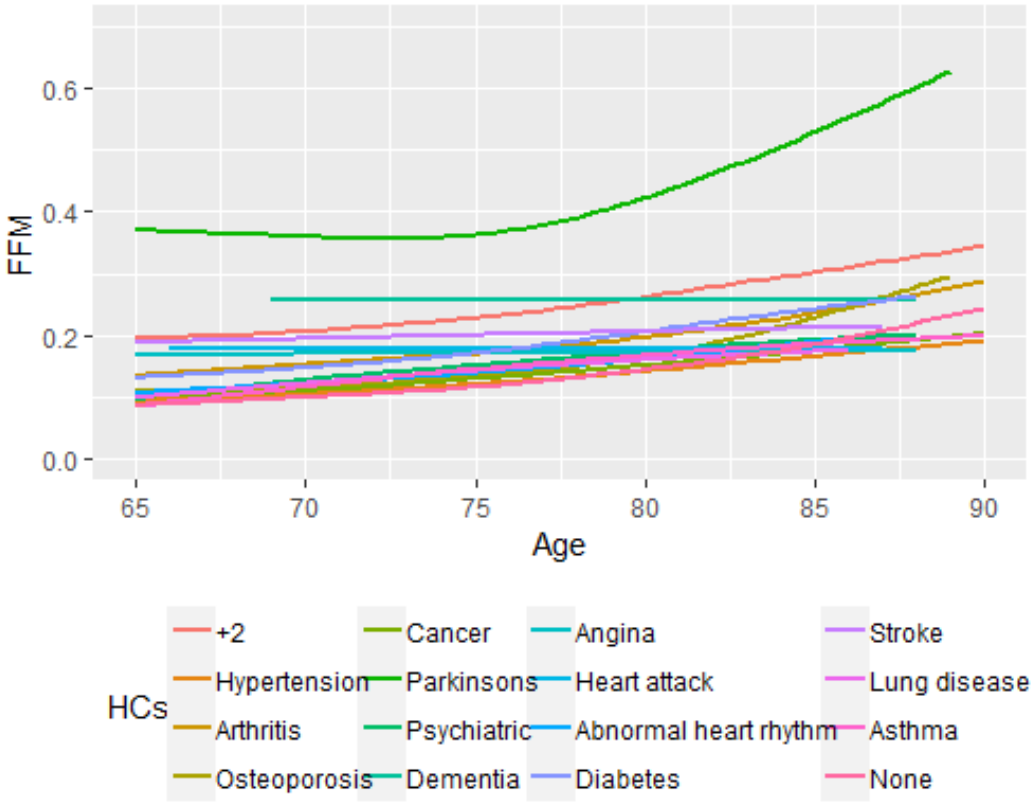
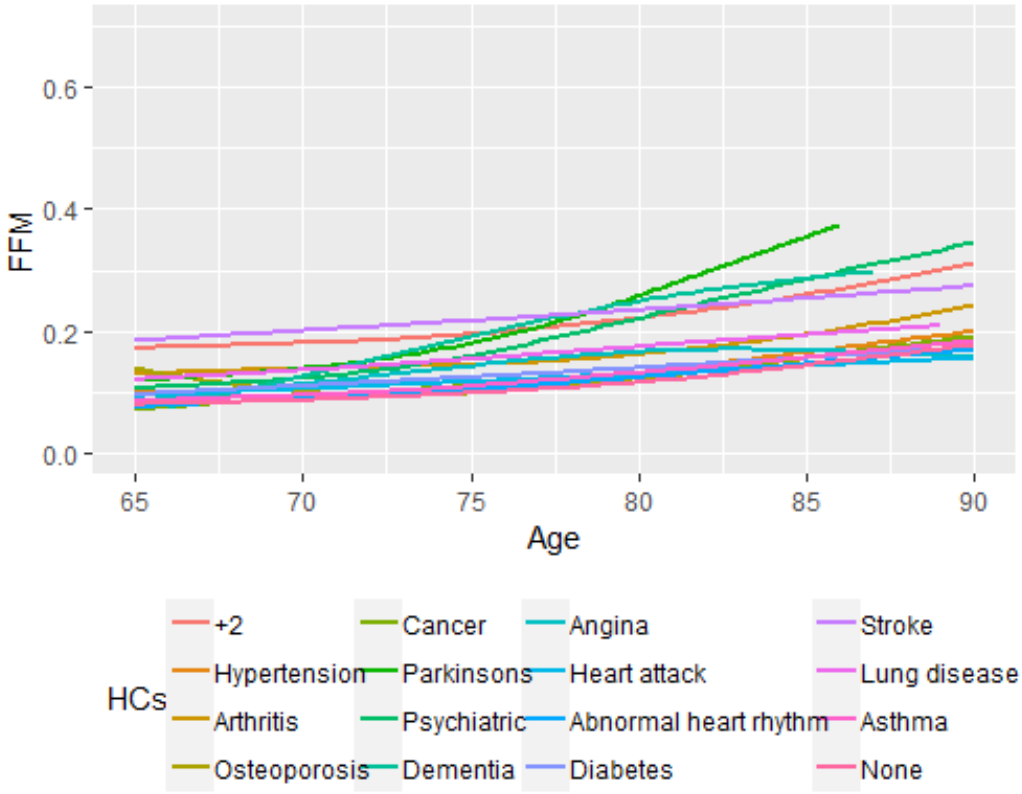


Figure b2: FMM vs age grouped by LTCs (Males)



Congestive heart failure and Alzheimer's have been omitted from both figures above since they are small observations.

Table b3: The mean of the FMM for females with three age categories grouped by: two or more health conditions (HC), a specific one HC or none HC.

		Age		
		65-74	57-84	85-90
Group		FFM	FFM	FFM
multimorbidity (2^{+})		0.208	0.262	0.325
One health condition	Hypertension	0.105	0.141	0.178
	Arthritis	0.151	0.193	0.274
	Osteoporosis	0.117	0.166	0.283
	Cancer	0.109	0.154	0.195
	Parkinson's	0.361	0.421	0.722
	Psychiatric	0.120	0.179	0.173
	Dementia	0.282	0.194	0.409
	Angina	0.163	0.173	0.265
	Heart attack	0.176	0.190	0.060
	Abnormal heart rhythm	0.121	0.166	0.117
	Diabetes	0.139	0.215	0.250
	Stroke	0.179	0.223	0.326
	Lung disease	0.117	0.176	0.131
	Asthma	0.111	0.160	0.192
None		0.097	0.143	0.219

Table b4: The mean of the FMM for males with three age categories grouped by: two or more health conditions (HC), a specific one HC or none HC.

		65-74	57-84	85-90
Group		FFM	FFM	FFM
multimorbidity (2+)		0.182	0.221	0.289
One health condition	Hypertension	0.098	0.129	0.181
	Arthritis	0.138	0.161	0.227
	Osteoporosis	0.106	0.125	0.242
	Cancer	0.093	0.121	0.196
	Parkinson's	0.143	0.244	0.467
	Psychiatric	0.119	0.247	0.366
	Alzheimer	0.359	0.363	0.336
	Dementia	0.104	0.270	0.186
	Angina	0.112	0.174	0.119
	Heart attack	0.101	0.136	0.165
	Congestive heart failure	0.105	---	---
	Abnormal heart rhythm	0.086	0.124	0.163
	Diabetes	0.108	0.138	0.207
	Stroke	0.206	0.208	0.361
	Lung disease	0.131	0.188	0.187
	Asthma	0.091	0.142	0.171
None		0.086	0.116	0.161

In table 1, two health condition were omitted, which were congestive heart failure and Alzheimer's, because there were not females participants have these conditions separately.

Table b5: 62 deficits for frailty index

Domain		Item	Domain		Item
Mobility1	1	difficulty walking 100 yards	Heart problems	32	high blood pressure or hypertension
	2	difficulty sitting 2 hours		33	Angina
	3	difficulty getting up from a chair after sitting long periods		34	heart attack
	4	difficulty climbing several flights of stairs without resting		35	congestive heart failure
	5	difficulty climbing one flight stairs without resting		36	abnormal heart rhythm
	6	difficulty stooping, kneeling or crouching		37	diabetes or high blood sugar
	7	difficulty reaching or extending arms above shoulder level		38	Stroke
	8	difficulty pulling or pushing large objects	chronic disease	39	lung disease
	9	difficulty lifting or carrying weights over 10 pounds		40	Asthma
	10	difficulty picking up 5p coin from the table		41	Arthritis
Mobility 2	11	difficulty dressing, including putting on shoes and socks		42	Osteoporosis
	12	difficulty walking across a room		43	Cancer
	13	difficulty bathing or showering		44	Parkinsons
	14	difficulty eating, such as cutting up food		45	Psychiatric
	15	difficulty getting in and out of bed		46	Alzheimer's
	16	difficulty using the toilet, including getting up or down		47	Dementia
	17	difficulty using a map to figure out how to get around a strange place	self-reported and operation	48	Self-reported eyesight
	18	preparing a hot meal		49	Self-reported general health
	19	shopping for groceries		50	Self-reported hearing
	20	making telephone calls		51	Fallen down
	21	taking medications		52	fractured hip
	22	doing work around the house or garden		53	had joint replacement
	23	managing money, such as bills and expenses		54	had pain whilst walking
Psychology	24	Whether felt depressed much of the time during the past week	memory test	55	correct day of month given
	25	Whether felt everything they did during the past week was an effort		56	correct month given
	26	felt their sleep was restless during the past week		57	correct year given
	27	Whether was happy much of the time during the past week		58	correct day given
	28	Whether felt lonely much of the time during the past week		59	~~prompt given for prospective memory test~~
	29	Whether enjoyed life much of the time during the past week		60	Number of words recalled immediately
	30	Whether felt sad much of the time during the past week		61	Number of animals mentioned
	31	Whether could not get going much of the time during the past week		62	Number of words recalled after a delay

Table b6: A discrete time model (logistic regression with cloglog link function)

Female					
	β	se	Exp(β)	Z_value	p
(Intercept)	-4.115	0.202	0.016	-20.345	<0.01
I(Age - 70)	0.071	0.006	1.073	12.77	<0.01
Scale FFM	0.461	0.041	1.586	11.305	<0.01
HC=1	-0.123	0.223	0.885	-0.551	0.581
HC=2+	0.003	0.201	1.003	0.016	0.987
time2	-0.381	0.16	0.683	-2.379	0.017
time3	-0.367	0.16	0.693	-2.294	0.022
time4	-0.337	0.154	0.714	-2.189	0.029
time5	-0.128	0.145	0.88	-0.886	0.376
time6	-17.159	291.243	0	-0.059	0.953
Male					
	β	se	Exp(β)	Z_value	p
(Intercept)	-3.86	0.20	0.02	-19.42	<0.01
I(Age - 70)	0.06	0.01	1.07	12.35	<0.01
Scale FFM	0.53	0.04	1.69	13.95	<0.01
HC=1	0.48	0.21	1.62	2.27	0.02
HC=2+	0.68	0.20	1.98	3.43	0.00
time2	-0.43	0.14	0.65	-3.05	0.00
time3	-0.29	0.14	0.75	-2.17	0.03
time4	-0.41	0.13	0.66	-3.05	<0.01
time5	-0.73	0.14	0.48	-5.05	<0.01
time6	-16.70	192.27	0.00	-0.09	0.93

We used the logistic regression model as a discrete-time model with *clogclog* link function rather than cox regression due the time points were registered in two years (interval-censored). We only used the first six waves because the death were reported until wave 6.

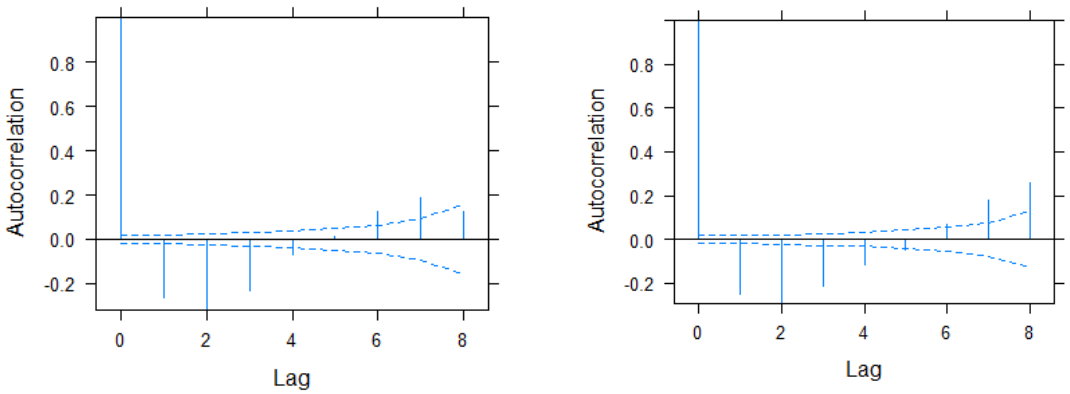
In table 4, we presented the results for the logistic regression model. We notice that the FFM in female and male models was considered a strong predictor for mortality; HR 1.59 and 1.69, respectively. Both models tested proportional hazards by interacting time and long-term health conditions. There is no sign of non-proportionality for all covariates in both models except the FFM in the male model.

Table b7: secondary exposure distribution over the nine waves

Wave	1	2	3	4	5	6	7	8	9
N	5455	4638	4308	5041	5252	5528	5434	5346	5300
Age (mean (SD))	73.79 (6.35)	73.97 (6.33)	74.36 (6.50)	73.71 (6.33)	73.91 (6.50)	73.65 (6.55)	73.73 (6.48)	73.88 (6.47)	74.15 (6.56)
Male	2440 (44.7)	2071 (44.7)	1914 (44.4)	2315 (45.9)	2408 (45.8)	2577 (46.6)	2500 (46.0)	2478 (46.4)	2406 (45.4)
Education (%)									
High	849 (15.6)	857 (18.5)	1026 (23.8)	1330 (26.4)	1504 (28.6)	1525 (27.6)	1568 (28.9)	1577 (29.5)	1984 (37.4)
Med or foreign	1645 (30.2)	1522 (32.8)	1509 (35.0)	1779 (35.3)	1942 (37.0)	2140 (38.7)	2237 (41.2)	2262 (42.3)	2141 (40.4)
Low	2944 (54.0)	2248 (48.5)	1758 (40.8)	1900 (37.7)	1772 (33.7)	1772 (32.1)	1546 (28.5)	1386 (25.9)	1138 (21.5)
Missing	17 (0.3)	11 (0.2)	15 (0.3)	32 (0.6)	34 (0.6)	91 (1.6)	83 (1.5)	121 (2.3)	37 (0.7)
Wealth class (%)									
Richest	924 (16.9)	761 (16.4)	701 (16.3)	827 (16.4)	918 (17.5)	1008 (18.2)	1026 (18.9)	992 (18.6)	1089 (20.5)
Rich	991 (18.2)	894 (19.3)	848 (19.7)	986 (19.6)	986 (18.8)	1095 (19.8)	1110 (20.4)	1069 (20.0)	1110 (20.9)
Average	1141 (20.9)	1014 (21.9)	933 (21.7)	1101 (21.8)	1135 (21.6)	1183 (21.4)	1173 (21.6)	1161 (21.7)	1124 (21.2)
Poor	1341 (24.6)	1089 (23.5)	1060 (24.6)	1210 (24.0)	1256 (23.9)	1278 (23.1)	1166 (21.5)	1145 (21.4)	1094 (20.6)
Poorest	989 (18.1)	840 (18.1)	663 (15.4)	786 (15.6)	841 (16.0)	859 (15.5)	850 (15.6)	911 (17.0)	804 (15.2)
Missing	69 (1.3)	40 (0.9)	103 (2.4)	131 (2.6)	116 (2.2)	105 (1.9)	109 (2.0)	68 (1.3)	79 (1.5)

Table b8: The years of Collecting ELSA data and the mean of CPI per two years.

Wave	year	price index	mean PI	mean PI/100
1	2002	75.7	76.2	0.762
	2003	76.7		
2	2004	77.8	78.6	0.786
	2005	79.4		
3	2006	81.4	82.35	0.8235
	2007	83.3		
4	2008	86.2	87.05	0.8705
	2009	87.9		
5	2010	90.1	91.85	0.9185
	2011	93.6		
6	2012	96	97.1	0.971
	2013	98.2		
7	2014	99.6	99.8	0.998
	2015	100		
8	2016	101	102.3	1.023
	2017	103.6		
9	2018	106	106.9	1.069
	2019	107.8		



(a) ACF plot for Female model **(b) ACF plot for Female model**

Figure b9: ACF for males and females model

Table b10: Multilevel growth model for males and females (only complete cases)

	Male						Female					
	Unadjusted model			Adjusted model			Unadjusted model			Adjusted model		
Fixed effects	β	RSE		β	RSE		β	RSE		β	RSE	
(Intercept)	0.15*	0.002		0.11*	0.003		0.19*	0.002		0.13*	0.004	
Age $c_{(70)/10}$				0.03*	0.003					0.04*	0.004	
Age^2 $c_{(70)/10}$				0.01*	0.004					0.01*	0.005	
Net wealth (ref. poor)												
Richest				-0.01*	0.002					-0.01*	0.002	
Average				0.02*	0.002					0.02*	0.002	
Education (ref. low)												
High education				-0.01*	0.003					-0.01*	0.003	
Meddle education				0.03*	0.003					0.03*	0.003	
Health condition (ref. HC=0)												
HC (1)				0.02*	0.003					0.02*	0.003	
HC (2^+)				0.06*	0.003					0.06*	0.004	
Age $c_{(70)/10}$: HC (1)				0.003	0.004					-0.01	0.005	
Age^2 $c_{(70)/10}$: HC (1)				0.001	0.005					0.002	0.006	
Age $c_{(70)/10}$: HC (2^+)				0.02*	0.004					0.001	0.005	
Age^2 $c_{(70)/10}$: HC (2^+)				0.01*	0.005					0.01	0.005	
Random effects		lower	upper		lower	upper		lower	upper		lower	upper
Intercept (sd)	0.10	0.10	0.10	0.09	0.07	0.11	0.11	0.11	0.12	0.10	0.10	0.10
Age (sd)				0.06	0.03	0.15				0.06	0.05	0.06
Age^2 (sd)				0.04	0.01	0.20				0.04	0.03	0.05
Error (sd)	0.06	0.06	0.06	0.05	0.05	0.05	0.07	0.06	0.07	0.06	0.06	0.06
Model fit												
AIC	-35668.49			-38867.66			-38830.52			-42190.92		

*$p < 0.01$

Appendix C: Study Three supplementary materials

Table *c1*: Collected data years of ELSA and their sample size

	Wave1	Wave2	Wave3	Wave4	Wave 5	Wave 6	Waveb7	Wave 8	Wave 9
Collected data year	2002/3	2004/5	2006/7	2008/9	2010/11	2012/13	2014/15	2016/17	2018/19
N	12099	9432	9771	11050	10274	10601	9666	8445	8736

Table *c2*: Summary statistics for the 19165 participants aged 50-90, including all those who participated in at least one wave of FFM or CASP-12 in the ELSA data set across the nine waves.

>= 50 % <=90	Wave	1	2	3	4	5	6	7	8	9
N= 19165		11426	9062	9227	10612	9970	10215	9334	8223	8429
Age (mean (SD))		64.85 (10.05)	66.00 (9.68)	65.02 (10.27)	65.37 (9.46)	66.77 (9.22)	66.60 (9.43)	67.33 (9.40)	68.77 (8.97)	67.96 (9.99)
Gender n(%)	Female	6224 (54.5)	5015 (55.3)	5056 (54.8)	5796 (54.6)	5488 (55.0)	5578 (54.6)	5136 (55.0)	4543 (55.2)	4661 (55.3)
	Male	5202 (45.5)	4047 (44.7)	4171 (45.2)	4816 (45.4)	4482 (45.0)	4637 (45.4)	4198 (45.0)	3680 (44.8)	3768 (44.7)
Net Wealth n(%)	High	4483 (39.2)	3590 (39.6)	3628 (39.3)	4156 (39.2)	3923 (39.3)	4044 (39.6)	3672 (39.3)	3262 (39.7)	3352 (39.8)
	Medium	2253 (19.7)	1804 (19.9)	1818 (19.7)	2075 (19.6)	1967 (19.7)	2007 (19.6)	1833 (19.6)	1629 (19.8)	1670 (19.8)
	Low	4491 (39.3)	3546 (39.1)	3549 (38.5)	4100 (38.6)	3870 (38.8)	3951 (38.7)	3605 (38.6)	3216 (39.1)	3268 (38.8)
	missing	199 (1.7)	122 (1.3)	232 (2.5)	281 (2.6)	210 (2.1)	213 (2.1)	224 (2.4)	116 (1.4)	139 (1.6)
Long-term conditions n(%)	0	3186 (27.9)	2054 (22.7)	2144 (23.2)	2559 (24.1)	2054 (20.6)	2139 (20.9)	1878 (20.1)	1414 (17.2)	1679 (19.9)
	1	3663 (32.1)	2711 (29.9)	2687 (29.1)	3061 (28.8)	2729 (27.4)	2731 (26.7)	2361 (25.3)	2006 (24.4)	2035 (24.1)
	2+	4567 (40.0)	4284 (47.3)	4385 (47.5)	4970 (46.8)	5168 (51.8)	5333 (52.2)	5086 (54.5)	4790 (58.3)	4708 (55.9)
	missing	10 (0.1)	13 (0.1)	11 (0.1)	22 (0.2)	19 (0.2)	12 (0.1)	9 (0.1)	13 (0.2)	7 (0.1)
FFM	(mean (SD))	0.17 (0.15)	0.18 (0.14)	0.16 (0.15)	0.16 (0.14)	0.17 (0.15)	0.16 (0.15)	0.16 (0.15)	0.16 (0.15)	0.16 (0.14)
	missing	4	2	0	3	5	0	0	0	0
CASP-12 ca	(mean (SD))	26.96 (5.88)	27.22 (5.91)	25.99 (5.84)	25.96 (5.85)	26.00 (5.96)	25.88 (5.98)	26.59 (5.94)	26.59 (5.95)	26.74 (5.96)
	missing	1790 (15.7)	1769 (19.5)	1744 (18.9)	1965 (18.5)	1483 (14.9)	1959 (19.2)	1799 (19.3)	1498 (18.2)	1525 (18.1)
	1	387 (3.4)	335 (3.7)	190 (2.1)	178 (1.7)	176 (1.8)	291 (2.8)	232 (2.5)	183 (2.2)	225 (2.7)
	2	80 (0.7)	96 (1.1)	52 (0.6)	24 (0.2)	37 (0.4)	66 (0.6)	57 (0.6)	51 (0.6)	45 (0.5)
	3	45 (0.4)	54 (0.6)	14 (0.2)	15 (0.1)	14 (0.1)	18 (0.2)	26 (0.3)	27 (0.3)	24 (0.3)
	4	41 (0.4)	36 (0.4)	8 (0.1)	11 (0.1)	10 (0.1)	17 (0.2)	19 (0.2)	10 (0.1)	10 (0.1)
	5	30 (0.3)	41 (0.5)	9 (0.1)	9 (0.1)	6 (0.1)	12 (0.1)	15 (0.2)	16 (0.2)	8 (0.1)
	6	19 (0.2)	32 (0.4)	7 (0.1)	11 (0.1)	6 (0.1)	10 (0.1)	12 (0.1)	11 (0.1)	15 (0.2)
	7	15 (0.1)	28 (0.3)	4 (0.0)	7 (0.1)	6 (0.1)	12 (0.1)	6 (0.1)	12 (0.1)	8 (0.1)
	8	26 (0.2)	19 (0.2)	10 (0.1)	10 (0.1)	11 (0.1)	14 (0.1)	11 (0.1)	6 (0.1)	3 (0.0)
	9	7 (0.1)	27 (0.3)	7 (0.1)	7 (0.1)	4 (0.0)	3 (0.0)	12 (0.1)	8 (0.1)	6 (0.1)

	10	13 (0.1)	21 (0.2)	6 (0.1)	12 (0.1)	5 (0.1)	12 (0.1)	13 (0.1)	7 (0.1)	7 (0.1)
	11	16 (0.1)	24 (0.3)	5 (0.1)	6 (0.1)	9 (0.1)	18 (0.2)	13 (0.1)	7 (0.1)	9 (0.1)

Table c3: 12 items of CASP12 and its four domains

Item (number)	**Domain**
My age prevents me from doing the things I would like to do (*C1*)	Control
I feel that what happens to me is beyond my control (*C2*)	
I feel left out of things (*C3*)	
I can do the things I want to do (*A1*)	Autonomy
I feel that I can please myself what I do (*A2*)	
A lack of money stops me from doing things I want to do (*A3*)	
I look forward to each day (*P1*)	Pleasure
I feel that my life has meaning (*P2*)	
I enjoy the things that I do (*P3*)	
I feel full of energy these days (*S1*)	Self-realisation
I feel that life is full of opportunities (*S2*)	
I feel that the future looks good for me (*S3*)	

Table c4: 44 deficits of the functional frailty measure (FFM)

Domain		Item	Domain		Item
Mobility	1	difficulty walking 100 yards	Psychology	24	Whether felt depressed much of the time during the past week
	2	difficulty sitting 2 hours		25	Whether felt everything they did during the past week was an effort
	3	difficulty getting up from a chair after sitting long periods		26	felt their sleep was restless during the past week
	4	difficulty climbing several flights of stairs without resting		27	Whether was happy much of the time during the past week
	5	difficulty climbing one flight stairs without resting		28	Whether felt lonely much of the time during the past week
	6	difficulty stooping, kneeling or crouching		29	Whether enjoyed life much of the time during the past week
	7	difficulty reaching or extending arms above shoulder level		30	Whether felt sad much of the time during the past week
	8	difficulty pulling or pushing large objects		31	Whether could not get going much of the time during the past week
	9	difficulty lifting or carrying weights over 10 pounds	self-reported and operation	32	Self-reported eyesight
	10	difficulty picking up 5p coin from the table		33	Self-reported general health
	11	difficulty dressing, including putting on shoes and socks		34	Self-reported hearing
	12	difficulty walking across a room		35	Fallen down
	13	difficulty bathing or showering		36	fractured hip
	14	difficulty eating, such as cutting up food		37	had joint replacement
	15	difficulty getting in and out of bed		38	had pain whilst walking
	16	difficulty using the toilet, including getting up or down	memory test	39	correct day of month given
	17	difficulty using a map to figure out how to get around a strange place		40	correct month given
	18	preparing a hot meal		41	correct year given

Domain		Item	Domain		Item
	19	shopping for groceries		42	correct day given
	20	making telephone calls		43	Number of words recalled immediately
	21	taking medications		44	Number of words recalled after a delay
	22	doing work around the house or garden			
	23	managing money, such as bills and expenses			

Table c5: Summary statistics for participants with and without missing data in CASP-12.

CASP-12 items		Complete observations	Missing observations	
		68021	3663	
Age (mean (SD))		66.17 (9.19)	72.11 (9.55)	<0.001
gender (%)	Female	37428 (55.0)	2373 (64.8)	<0.001
	Male	30593 (45.0)	1290 (35.2)	
Net Wealth (%)	RR	28838 (42.4)	914 (25.0)	<0.001
	AA	13748 (20.2)	780 (21.3)	
	PP	24401 (35.9)	1914 (52.3)	
	NA	1034 (1.5)	55 (1.5)	
LTCs (mean (SD))	0	15095 (22.2)	491 (13.4)	<0.001
	1	19282 (28.3)	868 (23.7)	
	2	33608 (49.4)	2297 (62.7)	
	NA	36 (0.1)	7 (0.2)	
FI44 (mean (SD))		0.15 (0.13)	0.22 (0.15)	<0.001
CASP-12		26.45 (5.91)	24.29 (6.69)	<0.001

Table c6: Pairwise correlations and reliability estimates for the FMM and CASP-12 scores across the nine waves.

	FFM_{W1}	FFM_{W2}	FFM_{W3}	FFM_{W4}	FFM_{W5}	FFM_{W6}	FFM_{W7}	FFM_{W8}	FFM_{W9}	$CASP_{W1}$	$CASP_{W2}$	$CASP_{W3}$	$CASP_{W4}$	$CASP_{W5}$	$CASP_{W6}$	$CASP_{W7}$	$CASP_{W8}$	$CASP_{W9}$
FFM_{W1}	(0.91)	0.794	0.755	0.707	0.686	0.664	0.630	0.608	0.565	-0.596	-0.537	-0.495	-0.472	-0.474	-0.456	-0.408	-0.410	-0.376
FFM_{W2}	--	(0.91)	0.813	0.760	0.730	0.694	0.654	0.637	0.574	-0.538	-0.597	-0.533	-0.507	-0.497	-0.473	-0.430	-0.426	-0.391
FFM_{W3}	--	--	(0.91)	0.796	0.750	0.726	0.672	0.645	0.586	-0.512	-0.535	-0.568	-0.514	-0.510	-0.477	-0.422	-0.446	-0.423
FFM_{W4}	--	--	--	(0.90)	0.815	0.773	0.734	0.705	0.651	-0.450	-0.482	-0.506	-0.577	-0.542	-0.503	-0.467	-0.463	-0.440
FFM_{W5}	--	--	--	--	(0.91)	0.818	0.766	0.740	0.689	-0.450	-0.478	-0.481	-0.524	-0.600	-0.546	-0.505	-0.500	-0.489
FFM_{W6}	--	--	--	--	--	(0.91)	0.824	0.783	0.726	-0.407	-0.424	-0.454	-0.489	-0.529	-0.579	-0.521	-0.517	-0.504
FFM_{W7}	--	--	--	--	--	--	(0.91)	0.820	0.756	-0.395	-0.405	-0.408	-0.460	-0.490	-0.519	-0.563	-0.528	-0.513
FFM_{W8}	--	--	--	--	--	--	--	(0.90)	0.801	-0.357	-0.385	-0.397	-0.440	-0.476	-0.494	-0.514	-0.583	-0.554
FFM_{W9}	--	--	--	--	--	--	--	--	(0.91)	-0.328	-0.361	-0.364	-0.389	-0.433	-0.449	-0.469	-0.520	-0.583
$CASP_{W1}$	--	--	--	--	--	--	--	--	--	(0.88)	0.704	0.661	0.616	0.598	0.558	0.537	0.512	0.507
$CASP_{W2}$	--	--	--	--	--	--	--	--	--	--	(0.89)	0.729	0.681	0.651	0.617	0.580	0.564	0.542
$CASP_{W3}$	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.764	0.722	0.682	0.651	0.623	0.591
$CASP_{W4}$	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.765	0.718	0.683	0.652	0.613
$CASP_{W5}$	--	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.768	0.722	0.682	0.661
$CASP_{W6}$	--	--	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.758	0.718	0.685
$CASP_{W7}$	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.761	0.724
$CASP_{W8}$	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)	0.768
$CASP_{W9}$	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	(0.89)

CASP here means CASP-12; Reliability estimates based on tetrachoric correlations are reported in the diagonal and marked with coefficient ω in parenthesis.

Table c7: Fit statistics of two LCM-SR models (Complete cases in FFM or CASP-12); N= 17115

Model	Chi-s	df	RTLI	RCFI	RRMSEA
A	3037.01*	160	0.968	0.967	0.068 (0.065 - 0.070)
B	1570.48*	151	0.985	0.985	0.047 (0.044- 0.050)

Model A: random intercept (RI) factors are added for both the CASP-12 and FFM; Model B random slope factors were added for CASP-12 and FFM to the model A. *p-value<0.01.

Table c8: Standardized parameters for Models A and B (Complete cases in FFM or CASP-12)

Model	A	B
Random effect: Means		
CASP-12 intercept** ×36	0.721* 25.96	0.741* 26.68
FFM intercept**	0.162*	0.148*
CASP-12 slope** ×36	--	-0.006* -0.22
FFM slope**	--	0.004*
Random effect: Correlation		
CASP-12 intercept vs FFM Intercept	-0.699*	*-0.700**
CASP-12 intercept vs CASP-12 slope	--	-0.118*
CASP-12 intercept vs FFM slope	--	0.130*
FFM intercept vs CASP-12 slope	--	-0.032
FFM intercept & FFM slope	--	0.090*
CASP-12 slope & FFM slope	--	*-0.766**
Autoregressive CASP-12 to CASP-12		
Wave 2	0.324*	0.197*
Wave 3	0.323*	0.207*
Wave 4	0.310*	0.201*
Wave 5	0.303*	0.199*
Wave 6	0.293*	0.191*
Wave 7	0.301*	0.198*
Wave 8	0.297*	0.195*
Wave 9	0.303*	0.203*
Autoregressive FFM to FFM		
Wave 2	0.409*	0.234*
Wave 3	0.393*	0.222*
Wave 4	0.397*	0.232*
Wave 5	0.379*	0.219*
Wave 6	0.380*	0.224*
Wave 7	0.383*	0.226*
Wave 8	0.371*	0.218*
Wave 9	0.366*	0.212*
Cross-lagged CASP-12 to FFM		
Wave 2	-0.118*	-0.032*
Wave 3	-0.113*	-0.032*
Wave 4	-0.109*	-0.032*
Wave 5	-0.105*	-0.031*
Wave 6	-0.104*	-0.030*
Wave 7	-0.107*	-0.032*
Wave 8	-0.105*	-0.031*

Model	A	B
Wave 9	-0.102*	-0.030*
Cross-lagged FFM to CASP-12		
Wave 2	-0.146*	-0.045*
Wave 3	-0.146*	-0.045*
Wave 4	-0.146*	-0.046*
Wave 5	-0.142*	-0.045*
Wave 6	-0.139*	-0.044*
Wave 7	-0.139*	-0.044*
Wave 8	-0.136*	-0.043*
Wave 9	-0.141*	-0.045*
Association within-wave		
Wave 1	-0.478*	-0.294*
Wave 2	-0.330*	-0.215*
Wave 3	-0.322*	-0.214*
Wave 4	-0.321*	-0.215*
Wave 5	-0.317*	-0.214*
Wave 6	-0.315*	-0.214*
Wave 7	-0.317*	-0.214*
Wave 8	-0.314*	-0.214*
Wave 9	-0.313*	-0.214*

** unstandardized ; *p<0.001;

Table *c9*: Model fit statistics of B model for multi-group (age, net wealth and LTCs)

	N	Chi-s	df	RTLI	RCFI	R-RMSEA
Gender						
Male	8007	695.024*	151	0.986	0.986	0.044 (0.040-0.049)
Female	9527	1042.820*	151	0.985	0.985	0.047 (0.043-0.050)
Age						
50-69	13570	1043.626*	151	0.984	0.984	0.047 (0.043-0.051)
70-90	8337	634.338	151	0.985	0.985	0.044 (0.038-0.049)
Net wealth						
High	8409	818.510*	151	0.982	0.982	0.048 (0.044-0.052)
Average	6315	419.212*	151	0.988	0.988	0.038 (0.026-0.050)
Low	9559	586.923*	151	0.988	0.988	0.039 (0.034-0.044)
Multimorbidity						
Non-multimorbid	11475	875.734	151	0.977	0.977	0.052 (0.047-0.057)
multimorbid	9831	806.335	151	0.986	0.986	0.043 (0.039-0.047)

(Model B) the random slope factors were added to the model A.

Table *c10*: Standardized parameters for Model B in three group variables; gender, two age groups and three net wealth groups

	Gender		Age		Net wealth		
Parameter	Male	Female	50-69	70-90	High	Average	Low
Random effect: Means							
CASP-12 intercept** ×36	0.733* 26.39	0.743* 26.75	0.743* 26.75	0.739* 26.60	0.784* 28.22	0.749* 26.96	0.696* 25.10
FFM intercept**	0.139*	0.160*	0.139*	0.170*	0.112*	0.141	0.187*
CASP-12 slope** ×36	-0.006* -0.22	-0.007* -0.25	-0.002* -0.07	-0.01* -0.36	-0.005* -0.18	-0.005* -0.18	-0.005* -0.18
FFM slope**	0.004*	0.005*	0.001*	0.007*	0.004*	0.003*	0.004*
Random effect: Correlation							
CASP-12 intercept vs FFM Intercept	-0.722*	-0.710*	-0.683*	-0.755*	-0.635*	-0.601*	-0.727*
CASP-12 intercept vs CASP-12 slope	-0.092*	-0.119*	-0.095^	-0.118^	-0.069	-0.203*	-0.193*
CASP-12 intercept vs FFM slope	0.189*	0.108*	0.137*	0.150*	0.143*	0.199*	0.237*
FFM intercept vs CASP-12 slope	0.021	-0.048	-0.016	0.183*	-0.163*	-0.049	0.185*
FFM intercept & FFM slope	--0.188*	-0.040	-0.217*	-0.248*	-0.078	-0.245*	-0.247*
CASP12 slope & FFM slope	-0.818*	-0.783*	-0.630*	-0.846*	-0.703*	-0.644*	-0.888*
Autoregressive CASP-12 to CASP-12							
Wave 2	0.192*	0.208*	0.208*	0.201*	0.184*	0.174*	0.226*
Wave 3	0.211*	0.230*	0.218*	0.239*	0.204*	0.186*	0.259*
Wave 4	0.197*	0.222*	0.223*	0.206*	0.198*	0.185*	0.231*
Wave 5	0.198*	0.215*	0.217*	0.202*	0.189*	0.182*	0.241*
Wave 6	0.184*	0.207*	0.201*	0.204*	0.186*	0.181*	0.215*
Wave 7	0.196*	0.214*	0.224*	0.189*	0.189*	0.170*	0.237*
Wave 8	0.191*	0.213*	0.208*	0.207*	0.188*	0.195*	0.226*
Wave 9	0.203*	0.218*	0.216*	0.211*	0.203*	0.177*	0.239*
Autoregressive FFM to FFM							

	Gender		Age		Net wealth		
Parameter	Male	Female	50-69	70-90	High	Average	Low
Wave 2	0.261*	0.202*	0.194*	0.286*	0.180*	0.203*	0.249*
Wave 3	0.262*	0.197*	0.196*	0.285*	0.194*	0.219*	0.232*
Wave 4	0.259*	0.207*	0.207*	0.271*	0.200*	0.222*	0.236*
Wave 5	0.253*	0.192*	0.190*	0.273*	0.185*	0.206*	0.233*
Wave 6	0.246*	0.200*	0.192*	0.275*	0.199*	0.207*	0.228*
Wave 7	0.272*	0.192*	0.205*	0.270*	0.187*	0.228*	0.237*
Wave 8	0.231*	0.200*	0.183*	0.280*	0.186*	0.203*	0.218*
Wave 9	0.257*	0.180*	0.193*	0.253*	0.178*	0.213*	0.227*
Cross-lagged CASP-12 to FFM							
Wave 2	-0.031*	-0.039*	-0.020*	-0.072*	-0.025*	-0.065*	-0.035*
Wave 3	-0.032*	-0.040*	-0.021*	-0.077*	-0.027*	-0.068*	-0.036*
Wave 4	-0.030*	-0.040*	-0.022*	-0.065*	-0.026*	-0.071*	-0.033*
Wave 5	-0.030*	-0.038*	-0.020*	-0.064*	-0.025*	-0.064*	-0.033*
Wave 6	-0.028*	-0.039*	-0.020*	-0.065*	-0.026*	-0.066*	-0.032*
Wave 7	-0.031*	-0.039*	-0.023*	-0.064*	-0.026*	-0.068*	-0.035*
Wave 8	-0.028*	-0.040*	-0.020*	-0.071*	-0.026*	-0.069*	-0.032*
Wave 9	-0.029*	-0.037*	-0.021*	-0.065*	-0.024*	-0.065*	-0.033*
Cross-lagged FFM to CASP-12							
Wave 2	-0.032*	-0.046*	-0.032*	-0.064*	-0.038*	-0.058*	-0.028*
Wave 3	-0.034*	-0.048*	-0.033*	-0.072*	-0.043*	-0.062*	-0.029*
Wave 4	-0.033*	-0.049*	-0.034*	-0.070*	-0.044*	-0.063*	-0.028*
Wave 5	-0.033*	-0.047*	-0.032*	-0.070*	-0.042*	-0.060*	-0.029*
Wave 6	-0.032*	-0.046*	-0.031*	-0.070*	-0.042*	-0.057*	-0.027*
Wave 7	-0.033*	-0.045*	-0.033*	-0.064*	-0.040*	-0.061*	-0.028*
Wave 8	-0.031*	-0.045*	-0.030*	-0.066*	-0.040*	-0.063*	-0.026*
Wave 9	-0.036*	-0.045*	-0.032*	-0.067*	-0.043*	-0.064*	-0.029*
Association within-wave							

	Gender		Age		Net wealth		
Parameter	Male	Female	50-69	70-90	High	Average	Low
Wave 1	-0.261*	-0.283*	-0.311*	-0.281*	-0.241*	-0.304*	-0.306*
Wave 2	-0.191*	-0.211*	-0.205*	-0.204*	-0.164*	-0.235*	-0.224*
Wave 3	-0.192*	-0.212*	-0.205*	-0.206*	-0.166*	-0.236*	0.225*
Wave 4	-0.191*	-0.212*	-0.206*	-0.203*	-0.166*	-0.236*	0.224*
Wave 5	-0.191*	-0.211*	-0.205*	-0.203*	-0.170*	-0.235*	0.224*
Wave 6	-0.190*	-0.211*	-0.204*	-0.203*	-0.165*	-0.235*	0.222*
Wave 7	-0.192*	-0.211*	-0.206*	-0.202*	-0.165*	-0.236*	0.224*
Wave 8	-0.190*	-0.211*	-0.204*	-0.204*	-0.165*	-0.236*	0.222*
Wave 9	-0.191*	-0.210*	-0.205*	-0.202*	-0.165*	-0.235*	0.224*

** unstandardized ;*p<0.001; ^p<0.05

Table *c11*: Standardized parameters for Model B (two long-term conditions samples)

Parameter	Non-multimorbid	Multimorbid
N		
Random effect: Means		
CASP-12 intercept** ×36	0.770* 27.72	0.699* 25.16
FFM intercept**	0.114*	0.200
CASP-12 slope** ×36	-0.004* -0.14	-0.006* -0.22
FFM slope**	0.001*	0.004*
Random effect: Correlation		
CASP-12 intercept vs FFM Intercept	-0.612*	-0.719*
CASP-12 intercept vs CASP-12 slope	-0.006	-0.234*
CASP-12 intercept vs FFM slope	0.251*	0.264*
FFM intercept vs CASP-12 slope	-0.198*	0.135*
FFM intercept & FFM slope	-0.269*	-0.301*
CASP-12 slope & FFM slope	-0.564*	-0.794*
Autoregressive MCASP12 to MCASP12		
Wave 2	0.208*	0.219*
Wave 3	0.231*	0.238*
Wave 4	0.219*	0.224*
Wave 5	0.223*	0.216*
Wave 6	0.203*	0.212*
Wave 7	0.218*	0.214*
Wave 8	0.209*	0.219*
Wave 9	0.230*	0.217*
Autoregressive FFM to FFM		
Wave 2	0.192*	0.227*
Wave 3	0.181*	0.213*
Wave 4	0.178*	0.220*
Wave 5	0.179*	0.208*
Wave 6	0.174*	0.212*
Wave 7	0.186*	0.214*
Wave 8	0.174*	0.207*
Wave 9	0.178*	0.201*
Cross-lagged CASP-12 to FFM		
Wave 2	-0.036*	-0.059*
Wave 3	-0.039*	-0.059*
Wave 4	-0.037*	-0.056*
Wave 5	-0.037*	-0.053*
Wave 6	-0.035*	-0.054*
Wave 7	-0.039*	-0.055*
Wave 8	-0.038*	-0.055*
Wave 9	-0.040*	-0.052*
Cross-lagged FFM to CASP-12		

Parameter	Non-multimorbid	Multimorbid
Wave 2	-0.054*	-0.040*
Wave 3	-0.053*	-0.041*
Wave 4	-0.053*	-0.042*
Wave 5	-0.054*	-0.040*
Wave 6	-0.050*	-0.040*
Wave 7	-0.051*	-0.039*
Wave 8	-0.047*	-0.039*
Wave 9	-0.051*	-0.040*
Association within-wave		
Wave 1	-0.265*	-0.312*
Wave 2	-0.173*	-0.225*
Wave 3	0.174*	-0.225*
Wave 4	0.173*	-0.225*
Wave 5	0.173*	-0.223*
Wave 6	0.172*	-0.223*
Wave 7	0.173*	-0.224*
Wave 8	0.173*	-0.224*
Wave 9	0.174*	-0.223*

** unstandardized ;*p<0.01