The London School of Economics and Political Science

Pathways to Frailty and its Adverse Outcomes: Evidence from the English Longitudinal Study of Ageing

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Declaration

I certify that the thesis I have presented for examination for the MPhil/PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it).

I warrant that this authorization does not, to the best of my belief, infringe the rights of any third party.

I declare that my thesis consists of 91,415 words.

Statement of conjoint work

I confirm that Chapters 8.2, 9.2, and 10.2 are jointly co-authored with Associate Professor Jouni Kuha and Professor Michael Murphy. I contributed approximately 90% of this work.

Abstract

Frailty affects 10% of adults aged 65 years and older. It denotes loss of an individual's body reserves, which increases vulnerability to developing adverse health outcomes such as death, disability, and institutionalization. Consequently, frailty has been described as the most problematic expression of ageing. Having good understanding of specific conditions influencing development of frailty and its effects holds the key to slowing its progression and mitigating its adverse outcomes. To this end, pathways to frailty and its adverse outcomes are the focus of my thesis. I begin with a literature review to assemble evidence on frailty pathways and instruments. Guided by this evidence and using the working framework of the Canadian Initiative on Frailty and Aging as the template, frailty pathways incorporating physical, psychological, and social conditions are conceptualized. Arguing that narrower physical frailty specifications are more suitable for investigating these pathways, I develop them based on the frailty phenotype. In my first two papers, I use data of 4,638 respondents aged 65 to 89 years from the English Longitudinal Study of Ageing to demonstrate construct, concurrent, and predictive validity of two physical frailty specifications. Adopting the specification with three indicators for latent growth curve analysis in my third paper, I show that chronic disease, allostatic load, low physical activity, cognitive impairment, depressive symptoms, poor social support, and poor social integration are predictors, mediators, or moderators on pathways to physical frailty. In my fourth paper, discrete time survival analysis reveals that low physical activity and cognitive impairment are mediators on pathways from physical frailty to death. In my fifth paper, autoregressive cross-lagged analyses demonstrate that these two conditions and depressive symptoms are mediators on pathways from physical frailty to activity limitation. All these conditions represent potentially modifiable targets for population-level interventions to address physical frailty in older people.

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Part One

Frailty Pathways: Defining the Issues and Charting the Course Ahead

1 Background

Most of us have used the word “frail” to describe some older people we know. Although it means different things to different people, frailty is most commonly equated to being old and weak. Indeed, the Oxford Dictionary defines frailty as “the condition of being weak and delicate”.

However, to the scientific community, frailty has two different albeit related meanings. The first has its roots in demography and refers to the unobservable heterogeneity distribution in mathematical models for survival (Hogan, 2003), which have come to be known as frailty models. That these models have been applied to mortality and ageing establishes the common ground it shares with the second meaning, which is the subject of this thesis. Here, frailty denotes the multidimensional loss of an individual’s reserves that occurs with greater probability in the face of advancing age. This loss results in the vulnerability to developing adverse outcomes such as hospitalization, functional dependency, and death (Espinoza & Walston, 2005; Lally & Crome, 2007; Mohandas et al., 2011; Pel-Littel et al., 2009). Within medical circles, frailty is widely considered as a clinical syndrome with an underlying biological basis, and is thought to be a transitional state that lies between robustness and functional decline (P. O. Lang et al., 2009b). A key underlying concept is that multiple body systems are involved (Strawbridge et al., 1998). Historically, frailty was first conceptualized as involving multiple domains by Strawbridge almost two decades ago in his seminal work on older respondents in the Alameda County study. He proposed viewing frailty as a syndrome involving deficiencies in two or more of physical, nutritive, cognitive, and sensory domains (Strawbridge et al., 1998).

Despite the existence of frailty being generally accepted in most quarters, its concept has yet to be widely agreed upon by researchers and practitioners alike. For a long time, a broad consensus on its precise definition was lacking (Bergman et al., 2007; Crome & Lally, 2011). Although many health care professionals encounter frailty among older patients they care for on a daily basis, a single and universally accepted definition for its clinical diagnosis has long remained elusive (Conroy, 2009). Indeed, a well-known Canadian geriatrician declared that for clinicians, “frailty is like pornography: it is hard to define but easy to recognize when seen” (Rockwood & Bergman, 2012). However, a recent conference involving experts representing six major international bodies involved in ageing issues achieved some degree of consensus in conceptualizing frailty. Frailty was defined as "a medical syndrome with multiple causes and contributions that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death". More significantly, it was agreed that the diagnosis of frailty can be made on the basis of existing well-validated models that are operationalized as screening instruments (Morley et al., 2013).

Aside from formal definitions of frailty, knowing its opposite meaning can assist in achieving a better understanding of this seemingly vague concept. In this case, an antonym of frail is “robust”, which has been adopted in the categorization of health states (Fried et al., 2001). Alternatively, “resilience” is at one end of the spectrum of well-being and is characterized by the capacity for adaptation when confronted with challenges, whereas at the opposite end, frailty represents a reduced capacity to respond to these challenges due to loss of physiologic reserves (Kuh, 2007). Finally, the idea of “fitness” has also been used in contrast to frailty (A. Mitnitski et al., 2005; Rockwood et al., 2004).

Not surprisingly, common physical states have often been confused with and mistaken for frailty. Particularly, it is worth highlighting that while there is some degree of overlap of frailty with co-morbidity and disability, all three are distinct concepts (Fried et al., 2004). Co-morbidity refers to the presence of chronic medical illnesses, while disability describes impairments, activity limitations, and participation restrictions (ICF, 2002).

Another key condition related to frailty is sarcopenia. This has been defined as the age-associated loss of skeletal muscle mass and function (Fielding et al., 2011). While frailty and sarcopenia are linked, they are considered as distinct entities, but with overlapping causes (Cooper et al., 2012; Reijnierse et al., 2016). Alternatively, sarcopenia has been viewed as a component of frailty, but that the latter is more multifaceted than sarcopenia alone (Morley et al., 2013). More crucially, I will argue that sarcopenia is the biological process underpinning the concept of physical frailty, which is a key domain of frailty. Beyond this, frailty is the subject of interest in this document and therefore, the focal point for analyses and conclusions that follow.

In investigating frailty, one cannot help but be impressed by the rapid growth of the emerging literature on this condition over the past two decades (Karunananthan, 2009). There are a number of possible reasons for this. Firstly, the size of the problem needs to be considered. Precise estimation of the prevalence of frailty among older adults living in the community is a challenging task due to the lack of a universally accepted definition of frailty (Lally & Crome, 2007). Nevertheless, a laudable attempt at obtaining a weighted average of its prevalence from different studies yielded an estimate of 10.7% among adults aged 65 years and older. The data was drawn from multiple individual studies that contributed prevalence estimates ranging from 4 to 59% (Collard et al., 2012). Given this, we can infer that one out of every 10 community-dwelling older people is likely to be frail. In 2015, the proportion of the population aged 65 years or older in the United Kingdom was 17.8 per cent, or 11.6 million people (ONS, 2016). In other words, frail older people comprised approximately 1.2 million in absolute numbers. Across the world where about 8.3% of the almost 7.4 billion people were aged 65 years or older in that same year (World Bank, 2016), we can expect about 65 million of them to be frail. To say that this is an enormous number of people would still be an understatement. Yet beyond size, its potential consequences bring about its true impact. On this count, there is overwhelming evidence that frailty confers increased risk of adverse health-related outcomes that matter to older people and their families. As mentioned, these include death (Buchman et al., 2009;

Cawthon et al., 2009; Gu et al., 2009; A. B. Mitnitski et al., 2004; Rockwood et al., 2011), disability (Avila-Funes et al., 2008; Romero-Ortuno et al., 2011; Woo et al., 2006), falls (Bilotta et al., 2012a; Samper-Ternent et al., 2012), fractures, cognitive impairment and dementia (Auyeung et al., 2011; Boyle et al., 2010; Woo et al., 2006), lower health-related quality of life (Kanauchi et al., 2008), hospitalization (Bilotta et al., 2012a), greater health services utilization (Rockwood et al., 2011), and institutionalization in long term care facilities (Jones et al., 2005). In view of these consequences, frailty plays a significant role in the well-being of older people at the individual and societal levels, and therefore has major public health importance. Moreover, with the projection of rapid growth in the number of older people across the world, frailty presents a rapidly escalating societal challenge on a global scale (Conroy, 2009). Finally, given its impact, frailty has been summarily described as the most problematic expression of ageing (Clegg et al., 2013).

On a more positive note, there is accumulating evidence suggesting that frailty is an addressable issue from both health and social viewpoints. Using the metaphor of a frail older person as a car running out of petrol, there now appears to be measures that can be applied as it were to "fill up the tank" (Jeffery et al., 2013). Targeted interventions such as exercise have shown promise in reducing incident frailty (Mohandas et al., 2011). Moreover, the adverse outcomes of frailty may be modifiable to a certain extent. In this light, a good understanding of determinants of frailty and factors influencing the development of its adverse outcomes holds the key to its successful management (Bergman et al., 2004; Espinoza & Walston, 2005; Ho et al., 2011; Walston et al., 2006). With this knowledge, appropriate solutions can be better formulated and implemented in rational, effective, and efficient ways. To this end, pathways to frailty and from frailty to its adverse outcomes will be the focus of this thesis.

With these in mind, the overarching research aim is to achieve a good understanding of the physical, psychological, and social conditions influencing the development of frailty and its adverse outcomes.

A brief outline of this document is as follows:

1) Literature review: A critical review will assemble current evidence, discuss its implications, and identify important gaps in the understanding of the predictors of frailty and its effects. The definition of frailty and instruments for its identification will be the secondary focus.
2) Research plan: Based on evidence gathered from the literature review, further research will be proposed to address important knowledge gaps and gather additional evidence that can inform the development of interventions and policies aimed at improving the health and well-being of older people.
3) Data: A brief discussion on the choice of secondary data set and its feasibility for the proposed research will follow.
4) First paper: I will discuss the process of selecting suitable frailty specifications for investigating frailty pathways, which specify relationships between frailty and its

multidimensional predictors, as well as its outcomes. I will argue that a narrower physical frailty specification is more suitable for this task. Evaluation of construct and concurrent validity of candidate physical frailty specifications will be the focus.

5) Second paper: I will complete the selection of candidate physical frailty specifications by evaluating their predictive validity with respect to key outcomes relevant to older people.
6) Third paper: I will proceed with implementing one of these candidate physical frailty specifications in examining pathways to physical frailty.
7) Fourth paper: I will shift the focus to examining pathways from physical frailty to death.
8) Fifth paper: Finally, I will explore pathways from physical frailty to activity limitation.
9) Closing discussion and final conclusions: I will summarize the key findings of my thesis, and then suggest directions for further work.

The five papers (found in sections 5.2, 6.2, 8.2, 9.2, and 10.2) are written in the format required for submission to peer-reviewed journals that impose word limits. Thus, they are necessarily brief in keeping with length restrictions for original research articles, which are typically in the range of 6000 to 8000 words. Furthermore, this document is written in United States English to maintain consistency throughout, and to keep in mind the submission to journals. Given that these papers are self-contained articles, their texts inevitably contain repetitions of points made elsewhere in the thesis. Finally, the specific references for the five papers are listed near their end just before their respective Supplementary Materials sections. On the other hand, references for the rest of the document are compiled at the end of the thesis (pages 226 to 243) just before the Appendix.

2 Literature Review: Pathways to Frailty and its Adverse Outcomes in Older People

2.1 Abstract

Pathways to frailty and to its adverse outcomes hold the key to the translation of research on frailty into successful health and social care strategies for older people. Physical, psychological, and social conditions that operate as individual determinants of frailty or as mediators and moderators of its effects are best integrated in a framework of pathways that takes into account their inter-relationships. A suitable frailty specification is needed at the heart of this framework.

In view of these points, the primary aim of this critical review is to identify conditions on pathways to frailty and to its adverse outcomes. The secondary aim is to identify frailty specifications that could be suitable to be operationalized in the investigation of these pathways. This review focuses on conceptual development, and then develops hypotheses for further research. Sources of literature include electronic databases and hand searched documents. Papers are selected on the basis of their relevance and contribution. The narrative form of synthesis is adopted rather than attempting a systematic review.

Conditions on pathways to frailty are largely those in the physical domain. They include older age, female gender, genetic influences, chronic disease, taking multiple medications, health events requiring hospitalization or activity restriction, allostatic load or physiological dysregulation, chronic systemic inflammation, physical inactivity, being underweight or overweight, specific diet compositions, smoking, and heavy drinking. Conditions in the psychological domain are impaired cognition and depression. The social domain is represented by less education, lower income, living alone, and social isolation. A number of exposures on pathways from frailty to its adverse outcomes decrease the risk of adverse outcomes such as hospitalization, functional dependency, and death. They are largely in the physical domain and include exercise, protein-energy supplementation, multidimensional intervention programs, and somewhat unexpectedly, being overweight. Conversely, low blood vitamin D levels increase this risk. To integrate the multiple physical, psychological, and social conditions on frailty pathways, the working framework of the Canadian Initiative for Frailty and Aging provides a useful frame of reference to build on.

A wide array of frailty identifiers are available and they reflect different, albeit overlapping constructs. Given that key conditions on frailty pathways include those in the psychological and social domains, narrower physical frailty specifications may be more suitable for investigation of these pathways. The Cardiovascular Health Study (CHS) frailty phenotype is the prototype for physical frailty. It has five components, namely slowness, weakness, exhaustion, weight loss, and low physical activity. In developing physical frailty specifications to investigate frailty pathways based on the CHS frailty phenotype, the item on low physical inactivity should ideally be omitted from the list of indicators since it is a predictor of frailty. Since exhaustion might also be a manifestation of depression, which is in the psychological domain and also a predictor of

frailty, omitting this component may need to be considered. Therefore, candidate physical frailty specifications could be based on the CHS frailty phenotype, but exclude the component of physical inactivity and perhaps, exhaustion. The feasibility and validity of these specifications will need to be evaluated.

The findings of this literature review offer guidance for further research on candidate frailty specifications and effects of physical, psychological, and social conditions on frailty pathways. They also provide a useful conceptual framework for understanding how these conditions may be related to frailty.

2.2 Introduction

To begin with, it is worth reiterating the key features of frailty that explain the amount of attention it has received in recent years, and which also constitute the basis for its choice as the subject for this research. Firstly, frailty is a common problem for older people, which is set to grow rapidly in terms of numbers affected. Secondly, frailty bears adverse consequences, which are significant at both the individual and societal levels. Finally, frailty may be prevented or have its adverse impact mitigated at least in part by appropriate interventions.

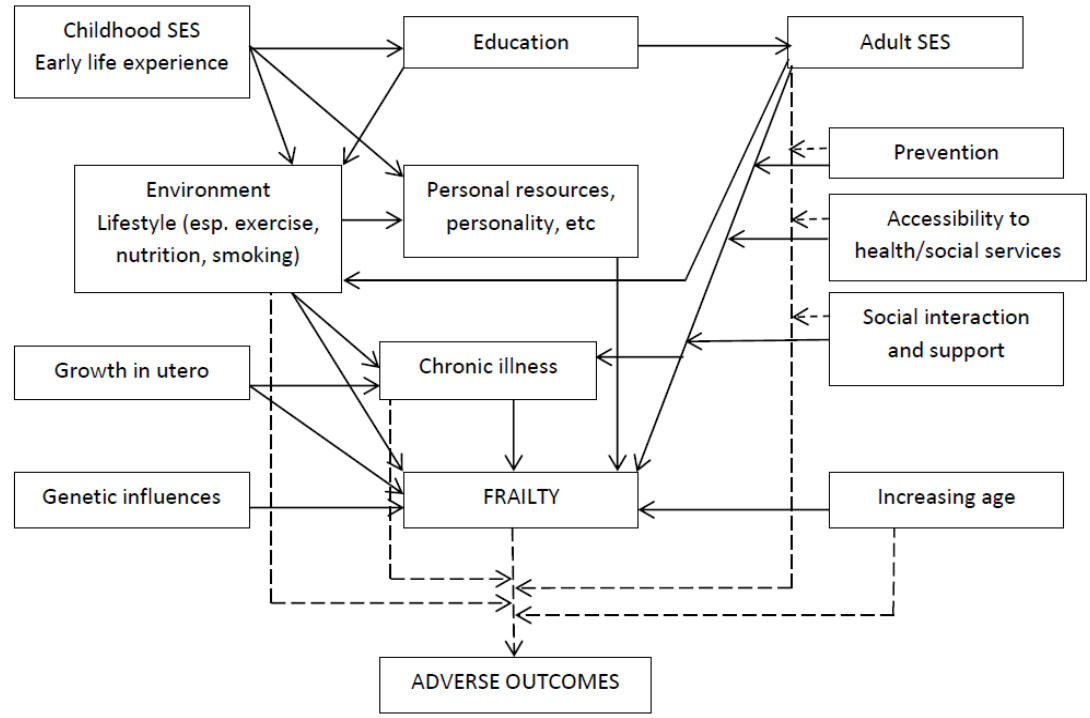
Given that the ultimate purpose for studying frailty is to understand how we may influence its development and effects, a detailed examination of its pathways is an essential step. Early attempts to create graphical representations focused largely on biological pathways. Fried proposed a cycle of frailty that assembles physiological and clinical factors in a feedback loop (Fried et al., 2001). The effects of ageing, disease, and under-nutrition are linked to loss of muscle mass known as sarcopenia. This in turn manifests as decreased strength, physical inactivity, and low energy expenditure, which then leads back to under-nutrition. The cycle is then repeated as a feedback loop.

Subsequently, a life course epidemiological approach was proposed to offer a more comprehensive framework for investigating predictors and effects of frailty in older people. Life course epidemiology can be best understood as the study of longer term physical and social exposures on health across life stages. It attempts to integrate rather than dichotomize biological and social risk factors for a given condition (Kuh et al., 2003). In doing so, this approach can be valuable in conceptualizing multiple predictors that exert their dynamic effects across different time periods (Kuh, 2007). Typically, there is explicit temporal ordering of exposures with inter-relationships among themselves. Their links with outcomes are either direct or indirectly through intermediate conditions known as a mediators (Ben-Shlomo & Kuh, 2002). A tangible and desirable output is the diagrammatic representation of these factors that serves as a suitable framework for the application of statistical modeling techniques such as path analysis and structural equation modeling (Ben-Shlomo & Kuh, 2002). Kuh argues that the ability to study lifetime determinants of frailty including its early life origins is an advantage of adopting this approach. Moreover, it affords opportunities to examine separate components of

the frailty syndrome prior to their clustering, dynamic relationships between different domains of frailty, and conditions promoting resilience in contrast to frailty (Kuh, 2007).

Adopting this line of thought, Bergman used the life-course approach for chronic disease (Ben-Shlomo & Kuh, 2002) to develop the working framework of the Canadian Initiative on Frailty and Aging. A graphical representation of biological and social exposures across the life span with their explicit relationship with frailty and its adverse outcomes is constructed (Bergman et al., 2004). An adapted version of these relationships across the life course is shown in Figure 2.1.

Figure 2.1. A life course approach to exposures in relation to frailty and its adverse outcomes by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) (adapted)



Here, conditions on pathways to frailty include increasing age, genetic influences, pre-birth growth, chronic diseases, environment influences, lifestyle habits, education, socioeconomic status, personal resources, social interaction and support, preventative measures, and access to medical and social services. While some of these conditions may have direct effects on frailty, others have their effects filtered through mediators on alternative pathways. Yet some others influence pathways from frailty to its adverse outcomes as moderators (Hendricks, 2012)

by increasing or decreasing the strength of relationships between frailty and these conditions. For simplicity, possible feedback loops are not illustrated. Individual conditions in the framework were selected on the basis of empirical evidence, theoretical grounds, or expert opinion.

The relationship between frailty and adverse outcomes has attracted increasing interest in recent years. Indeed, the consistent ability of frailty to predict adverse outcomes is perhaps the most prominent finding in this area of research. A wide array of instruments to identify frailty have been developed and validated over the past decade (Pialoux et al., 2012), with different tools probably best suited for different purposes (Martin & Brighton, 2008). Direct comparative studies of several of these instruments have demonstrated largely equivalent predictive ability (Pilotto et al., 2012). However, beyond mere prediction, it is important to explain how frailty actually leads to these outcomes. In other words, a more precise understanding of pathways from frailty to these outcomes is desirable. This requires the unpacking of the "black box" of these pathways since underlying mechanisms offer plausibility for interventions designed to modify the adverse effects of frailty. More specifically, conditions along these pathways represent potential points for effective interventions (Rockwood et al., 2011).

Thus, pathways from predictors to frailty and from frailty to its adverse outcomes hold the key to the translation of frailty research into effective health and social care interventions. Questions on what multidimensional conditions operate as predictors of frailty or as mediators and moderators of its effects, and how they relate to each other and to frailty are of interest. In addition, the direct and indirect pathways to adverse outcomes need to be understood better. Furthermore, knowledge of how individual conditions may be integrated in a common set of pathways that considers their inter-relationships is needed.

For the study of these pathways, it is essential to have a suitable specification of frailty. However, deciding on the definition of frailty is challenging given that this condition is not directly observed (Kamaruzzaman et al., 2010). Moreover, the absence of universal agreement among researchers on one dominant frailty construct, and the resulting multitude of instruments developed for its identification (Pialoux et al., 2012) makes this task a most challenging and at the same time, an intriguing one (Heuberger, 2011). In fact, the search for an optimal definition of frailty has been likened to the holy grail of geriatric medicine (Conroy, 2009). Meaningful specifications of frailty for the purpose of investigating pathways are needed. A key emerging question is whether a narrower definition such as physical frailty would be more suitable given that important psychological and social conditions that are possible frailty indicators may already be represented along these frailty pathways.

With all these questions in mind, the aims of this literature review are twofold. Firstly, it seeks to identify multidimensional conditions on pathways to frailty and to its adverse outcomes. Secondly, it attempts to review available frailty specifications and then propose one or more of these as candidates for implementation in the investigation of frailty pathways.

Therefore, the objectives of this review are:

1) To examine pathways to frailty and its adverse outcomes, which include physical, psychological, and social conditions that operate as direct agents, mediators, and moderators.
2) To identify frailty specifications that have a more parsimonious set of indicators, while retaining good predictive ability with respect to adverse outcomes of frailty.

2.3 Methods

2.3.1 Strategy

The underlying approach I will adopt is that of a critical review, according to terminology proposed in the recent past (Grant & Booth, 2009). This type of review starts with wide search, analysis, and synthesis of the literature, progresses on to conceptual development, and then arrives at hypotheses or models as its end. While a systematic approach to search, appraisal, synthesis and analysis is utilized, this is nevertheless not a systematic review. The latter constitutes a secondary analysis that focuses on the collation of all empirical evidence that fits pre-specified criteria to answer a specific research question, and uses explicit and reproducible methods to minimize bias (Higgins & Green, 2011). Nevertheless, this review will have an aggregative intent in the sense that the principal focus is on the average overall result (Booth et al., 2012).

2.3.2 Scope

The scope of this review is defined by the research question, which has two parts:

1) For community-dwelling older adults:
    a) What conditions are physical, psychological, and social predictors of frailty?
    b) Which of these conditions influence the progression from frailty to its adverse health-related outcomes?
2) For the purpose of examining the relationship of frailty with its predictors and outcomes, what are suitable specifications of frailty?

2.3.3 Search

Two separate sets of search strategies and terms for the two parts of the research question are used. The sources of literature include electronic databases such as MEDLINE and hand searched documents. The search strategies and list of these sources are provided in the Appendix (pages 244 and 245). The final search was conducted on 2 June 2016.

2.3.4 Selection

Rather than focusing on quality of evidence, I evaluate and select papers on the basis of their relevance and contribution to answering the research question. To do this, I employ a two-stage approach. Firstly, titles of papers are screened for short-listing. Then from these, abstracts are examined to decide on the final list of papers for inclusion. This sequential strategy was previously found to be more efficient than the combined titles and abstract screening approach (Mateen et al., 2013).

2.3.5 Synthesis

I adopt the narrative form of synthesis. The purpose is to identify conceptual contribution towards suitable frailty specifications and theoretical frameworks that define pathways to frailty and its adverse outcomes.

2.4 Results

2.4.1 Search

Using the search strategy for frailty identifiers through MEDLINE with PubMed, 3,157 papers are found. Similarly, for frailty pathways, 2,995 papers are identified. From Web of Science, 2,485 and 1,220 titles including journal articles and conference proceedings are found for frailty indicators and pathways respectively. From the Cochrane Library, use of the title, abstract, and keywords search term “frailty” yields 4 reviews. No relevant papers are identified in title and keywords search term “frailty” of the Campbell Library.

2.4.2 Selection

From MEDLINE with PubMed and Web of Science, 209 papers on frailty identifiers and 283 for frailty pathways are selected from sequential screening of titles and abstracts. Of the systematic reviews identified in the Cochrane Library, no reviews are selected on account of relevance.

2.4.3 Synthesis

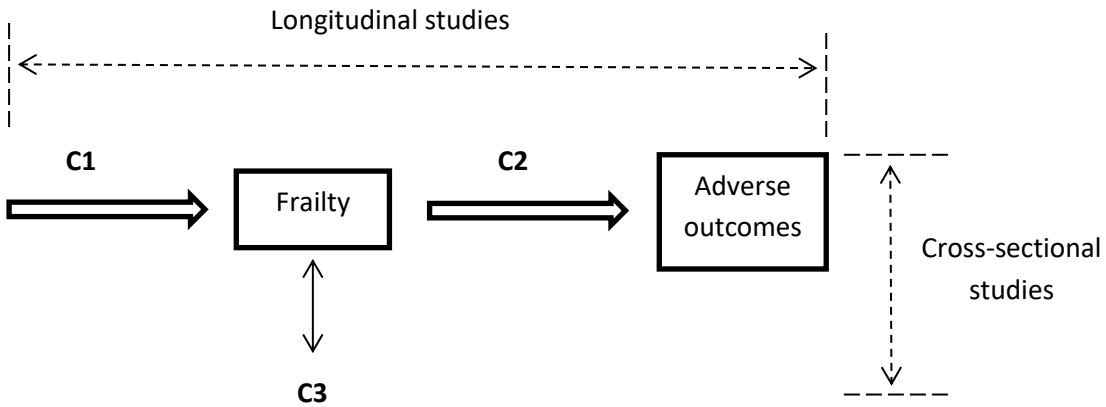
Frailty pathways

Concerning the literature on pathways to frailty and from frailty to adverse outcomes, most available evidence has been generated in the past two decades. Much of the empirical work has focused on investigation of the relationship between single conditions and frailty. However,

conceptual frameworks that take into account the simultaneous and sequential effects of a range of individual health and social conditions have also been proposed. These frameworks provide a more complete picture of predictors and effects of frailty. Nevertheless, it is the evidence on individual conditions that constitute the building blocks for the construction of these frameworks, and offers plausibility for the existence of these pathways in the first place. It is worth noting that different studies use different definitions of frailty. While this may have implications on understanding pathways, I will put this issue aside for the moment in the bid to maintain focus on conditions related to frailty.

For clarity, individual conditions may be classified into those on pathways to frailty, and others on pathways from frailty to its adverse outcomes. Evidence on these conditions emanate from longitudinal studies, which may have randomized controlled trial (RCT) or cohort designs. RCTs provide stronger evidence than cohort studies do. Conditions only found to be associated with frailty in cross-sectional studies offer additional evidence albeit with uncertain direction of effect. The relative positions of these categories of conditions in a conceptual framework of frailty are illustrated in Figure 2.2.

Figure 2.2. Conditions along pathways to frailty (C1), and from frailty to adverse outcomes (C2) based on evidence from longitudinal studies and those only found to be associated with frailty (C3) from cross-sectional studies



These categories can be further sub-divided into conditions in the physical, psychological, and social domains. In this classification, no distinction is made on whether these conditions operate as effects, mediators, or moderators.

Conditions on pathways to frailty

There are multiple conditions (Levers et al., 2006; Strawbridge et al., 1998) on pathways to frailty, and they are represented by C1 in Figure 2.2. Most of the available evidence concerns those of the physical domain. Both older age (Fallah et al., 2011; Ottenbacher et al., 2009) and female gender increase the likelihood of frailty (Etman et al., 2012; Peek et al., 2012; Woods et al., 2005). That frailty is attributable in part to genetic influences is expected. Data from multi-generational families suggest that for frailty, the variance components due to genetic and shared environmental influences are comparable (Garibotti et al., 2006). Chronic disease has also been found to be a predictor of frailty (Ottenbacher et al., 2009; Strawbridge et al., 1998; Syddall et al., 2010; Woods et al., 2005). Cardiovascular risk scores were associated with higher risk of developing frailty (Bouillon et al., 2013a). Polypharmacy defined as the concurrent prescription of five or more medications has also been shown to increase the likelihood of incident frailty (Gnjidic et al., 2012). Heath events such as illness requiring hospitalization or restriction of activities also increased this risk (Peek et al., 2012). Poorer mobility measured by walking speed was also associated with development of frailty (Fallah et al., 2011). Sleep disturbances were independently associated with higher future odds of frailty (Ensrud et al., 2012).

Allostatic load or multiple physiological dysregulation is a more complex physical condition. This entity refers to alterations in the molecular, cellular, and physiological mechanisms of cardiovascular, neuroendocrine, metabolic, immune, and nervous systems (Gruenewald et al., 2009). Typically, multiple biomarkers are employed to assess and measure allostatic load. In a study of 803 adults aged 70 years and older, Gruenewald and co-investigators assigned a value of one for each of 13 selected biomarkers when their scores fell into the quartile of highest clinical risk, thus obtaining total scores ranging from 0 to 13. They demonstrated that for each one-unit increase in the allostatic load score at baseline, there was 10% increase in the likelihood of frailty at 3 years (Gruenewald et al., 2009).

Chronic systemic inflammation is also an important underlying mechanism for the development of frailty. Higher blood levels of C-reactive protein (CRP) (Puts et al., 2005), a marker of inflammation were associated with incident frailty in a sub-cohort of participants of the Cardiovascular Health Study (Barzilay et al., 2007). Similarly, immune-endocrine biomarkers predicted development of frailty. Lower baseline blood levels of insulin-like growth factor-1 (IGF-1) predicted new-onset frailty (Yeap et al., 2013). Higher baseline white blood cell count and lower levels of dehydroepiandrosterone (DHEAS) were associated with increased odds of incident frailty (Baylis et al., 2013). Lower blood testosterone levels were associated with incident frailty (Cawthon et al., 2009; Hyde et al., 2010). Finally, low vitamin D levels (Puts et al., 2005; Shardell et al., 2012; Y. Y. Wong et al., 2013b) also increase the risk of frailty.

Exercise is by far the most prominent factor shown to prevent or minimize frailty. Convincing evidence comes from randomized controlled trials and observational studies of exercise

programs in community-dwelling frail older adults (Brown et al., 2000b; Faber et al., 2006; Yamada et al., 2012). Moreover, higher midlife leisure time physical activity was associated with lower prevalence of frailty in old age among Finnish men (Savela et al., 2013). Similarly, participation in self-selected exercise by frail older people was associated with delay in onset and progression of frailty (Peterson et al., 2009). Sedentary individuals had higher odds of developing frailty compared with the exercise active participants in the Health, Aging and Body Composition (ABC) study (Peterson et al., 2009). Poor mobility (Fallah et al., 2011), physical inactivity (Strawbridge et al., 1998), and life-space restriction (Xue et al., 2008b) are predictors of frailty.

In nutrition, findings from the Women's Health Initiative Observational Study indicate that being underweight, overweight, or obese are positively associated with incident frailty compared with having normal weight (Woods et al., 2005). In older men, weight loss was associated with incident frailty, compared with normal weight (Strandberg et al., 2013). On the other hand, midlife obesity and overweight state was associated with higher risk of developing frailty in old age among Finnish adults (Stenholm et al., 2014; Strandberg et al., 2012). In contrast, higher dietary protein intake (Beasley et al., 2010) and greater adherence to a Mediterranean-style diet led to reduced risk of developing frailty (Talegawkar et al., 2012). Among other lifestyle habits, smoking (Ottenbacher et al., 2009; Woods et al., 2005) and heavy drinking (Strawbridge et al., 1998) are positively associated with incident frailty, while moderate drinking has a negative association (Woods et al., 2005).

In the psychological domain, poorer cognition such as indicated by lower Mini-Mental State Examination (MMSE) scores confers higher risk of developing frailty (Ottenbacher et al., 2009; Raji et al., 2010). Similarly, depression is associated with higher risk of incident frailty (Lakey et al., 2012; Ottenbacher et al., 2009; Park-Lee et al., 2009; Strawbridge et al., 1998; Woods et al., 2005). Conversely, having positive affect was protective against the risk of developing frailty (Ostir et al., 2004).

In the social domain, having less education (Alvarado et al., 2008), lower income, non-white collar occupation (Alvarado et al., 2008), living alone, and being social isolated are associated with higher risk of developing frailty or worsening of frailty (Etman et al., 2012; Peek et al., 2012; Strawbridge et al., 1998; Syddall et al., 2010; Woods et al., 2005). Financial strain also increases this risk (Alvarado et al., 2008; Peek et al., 2012). These findings are likely to reflect the effect of chronic stressors on older people. From a life course perspective, poor social conditions in childhood in the form of experiencing hunger and having challenging socioeconomic circumstances was also associated with developing frailty in older persons (Alvarado et al., 2008). On the other hand, social support characterized by perceived emotional support from family or friends protects against increasing degrees of frailty (Peek et al., 2012). Risk of incident frailty was also lower for older persons who participated in group cultural activities (Fushiki et al., 2012).

Finally, multidimensional interventional programs can influence frailty. In a randomized controlled trial (RCT) of frail community-dwelling older adults in Australia, the intervention group received multi-factorial, inter-disciplinary measures, which included a home exercise program focusing on mobility and coordinated management of medical and psychological conditions. Frailty was reduced in them compared with the control group (Cameron et al., 2013).

Conditions on pathways from frailty to its adverse outcomes

Conditions on pathways from frailty to its adverse outcomes are represented by C2 in Figure 2.2 (page 25). These influence outcomes of older people who are already frail. It is worth noting that these conditions operate either as moderators, mediators, or both. To a large extent, existing theory will inform the appropriate categorization of the effect of individual conditions into one of these three possible roles.

Here again, most conditions are in the physical domain. Exercise is the most prominent among them. An RCT of exercise training yielded improved physical performance measures and functional status among participants (Binder et al., 2002). Similarly, an RCT on Tai Chi training demonstrated improved physical performance and reduced fall occurrence (Wolf et al., 2006). Another RCT on functional circuit training improved basic activities of daily living (BADL) among frail older people (Gine-Garriga et al., 2010). On a broader scale, the findings of a systematic review of 20 selected studies on physical exercise training suggested that older people with varying degrees of frailty can still improve their functional performance with regular exercise training programs. The majority of these programs studied were facility-based and based on group exercise of 45 to 60 minutes in duration performed 3 times per week (Chin et al., 2008). Yet another systematic review found that long-lasting and high-intensive multi-component exercise programs had a positive effect on ability in activities of daily living (ADL) in moderately frail community-dwelling older people (Daniels et al., 2008). Then, a meta-analysis of studies on exercise in frail older adults revealed that performance in ADL was improved in addition to better physical performance (Chou et al., 2012). However, the clearest indication on the benefits of exercise at the population level comes from the Canadian Study of Health and Aging. Death rates for those aged over 75 years who exercised were similar to those aged from 65 to 75 years who did not exercise. This effect was seen across gender and different degrees of frailty. Of note, the largest health benefits of exercise were found among those participants who were more frail at baseline (Hubbard et al., 2009a). In another study, exercise training improved physical capacity (functional capacities and physical endurance), cognitive performance, and quality of life in frail older people (Langlois et al., 2013). Overall, several studies on exercise intervention composed of strength, endurance and balance training reduced falls, enhanced gait ability and balance, and increased muscle strength among physically frail older people (Cadore et al., 2013).

Other physical conditions on these pathways include those related to nutrition. In an RCT examining the effect of protein-energy supplementation for frail older adults with low socioeconomic status, the intervention group had reduced progression of functional decline measured by physical performance measures (Kim & Lee, 2013). In another RCT, combined amino acid supplementation and a self-administered exercise program under the supervision of home helpers resulted in less worsening of instrumental activities of daily living (IADL) of older persons at risk for frailty (Bonnefoy et al., 2012). Quite unexpectedly, frail overweight and obese respondents have reduced rate of functional limitations and disability in the Health and Retirement Study (Bowen, 2012). While suggesting that some excess body weight may be beneficial, these findings appear to contradict those of studies mentioned earlier where being overweight or obese was associated with the development of frailty. Finally, low vitamin D levels conferred added risk of mortality among frail non-institutionalized older people (Smit et al., 2012).

Among psychological conditions, only cognitive impairment was found to increase the likelihood of incident disability among frail older persons (Avila-Funes et al., 2009).

Yet again, multidimensional interventional programs influence the outcomes in frail older people. Three RCT's provide supporting evidence. The first involved frail community-dwelling older adults in Australia that was mentioned earlier. The intervention group received measures that included a home exercise program focusing on mobility and coordinated management of medical and psychological conditions. At 12 months, benefit was seen in the attainment of individualized goals on participation and in mobility measured by Life Space Assessment among those who received the intervention compared with controls (Fairhall et al., 2012). The second is the Elderly Persons in the Risk Zone study conducted in Sweden where the intervention was either a preventative home visit or four-weekly multi-professional senior group meetings with one follow-up home visit. Compared with the control group, both these health-promoting interventions delayed deterioration in self-rated health and dependence in activities of daily living (ADL) at three months among adults aged 80 years or older (Gustafsson et al., 2012). The third implemented a six-month program that included measures focused on improving physical function impairments in moderately physically frail older people living in their homes in the United States of America. The intervention group had reduced functional decline compared with those in the control group. However, this benefit was not observed in those with severe frailty (Gill et al., 2002).

Conditions associated with frailty but with uncertain position on pathways

There are a host of conditions associated with frailty where the evidence is from cross-sectional studies. These conditions are represented as C3 in Figure 2.2. Lack of temporal ordering of conditions and outcomes imposes limits in the confidence we can have in placing them on frailty pathways, since the direction of effect would be uncertain. Nevertheless, most of them

have also been studied in longitudinal studies and are already categorized as belonging to C1, C2, or both.

Among these conditions in the physical domain are older age (Avila-Funes et al., 2008; Cramm & Nieboer, 2013; A. B. Mitnitski et al., 2004), chronic co-morbidity (Chen et al., 2010) especially cardiovascular disease (Danon-Hersch et al., 2012) and multi-morbidity (Avila-Funes et al., 2008; Gobbens et al., 2010c), cardio-metabolic disorders (Tang et al., 2013), higher blood pressure and other cardiovascular risk factors (Bastos-Barbosa et al., 2012), inflammatory-related disease (S. S. Chang et al., 2012), disability such as impairment in performing BADL and instrumental activities of daily living (IADL) (Bilotta et al., 2010; Chen et al., 2010; C. H. Wong et al., 2010), falls (Fhon et al., 2013), walking impairment (Nishi et al., 2012), urinary incontinence (Bilotta et al., 2010; Nishi et al., 2012), hearing impairment (Nishi et al., 2012), poor visual function (Klein et al., 2003), sleep disturbances (Ensrud et al., 2009; Vaz Fragoso et al., 2009), specific medications, and unhealthy lifestyle that includes smoking and alcohol use (Gobbens et al., 2010c; Woo et al., 2010). Constricted life space manifesting as leaving the neighborhood less frequently was associated with frailty (Xue et al., 2008b).

In addition, inflammatory markers were associated with frailty. Among these, higher levels of blood protein biomarkers such as transferrin, fibrinogen, and interleukin-6 are associated with frailty even after adjustment for age and sex (Darvin et al., 2014). In addition, blood levels of interleukin-6 (IL-6) (Leng et al., 2007), tumor necrosis factor alpha (TNF-alpha), C-reactive protein (CRP) (Walston et al., 2002) were associated with frailty in very old people (Collerton et al., 2012; Hubbard et al., 2009b) as were neutrophils (Collerton et al., 2012; Leng et al., 2007) and albumin (Hubbard et al., 2009b). Interestingly, the combination of elevated white blood cell (WBC) counts and low insulin-like growth factor-1 (IGF-1) is associated with frailty (Leng et al., 2009). Higher D-dimer and tissue plasminogen activator (t-PA) levels in the blood were also associated with frailty (Reiner et al., 2009). Similarly, higher blood adiponectin levels were associated with increasing number of frailty components (Tsai et al., 2013). Higher blood neopterin levels were associated with frailty (Leng et al., 2011). Lower levels of vitamin D were associated with frailty (C. I. Chang et al., 2010; Hirani et al., 2013; Tajar et al., 2013; Wilhelm-Leen et al., 2010) with one study showing this relationship in men, but not in women (Shardell et al., 2009). Higher levels of blood cystatin C, a precise marker of kidney function were associated with greater odds of being frail rather than robust in older men (Hart et al., 2013). Higher levels of blood homocysteine levels were associated with frailty (Y. Y. Wong et al., 2013a), as were higher estrogen levels (Carcaillon et al., 2012). On the other hand, low blood testosterone (Wu et al., 2010) and dehydroepiandosterone (DHEAS) levels (Voznesensky et al., 2009) were associated with frailty. Another interesting observation is that absolute burden of hormonal deficiencies manifested as low levels of two or more of IGF-1, DHEAS, and testosterone has a much stronger association with being frail than the individual hormonal deficiency. This suggests that a more generalized hormonal disorder is involved in frailty (Cappola et al., 2009). Moreover, frailty was also associated with higher blood inflammatory markers and lower blood esterase activity (Hubbard et al., 2008). Low levels of vitamin E, which

is a component of the human anti-oxidant system, was associated with frailty (Ble et al., 2006). Finally, heavier allostatic load was associated with increasing degrees of frailty (Szanton et al., 2009).

Among other conditions in the physical domain, common brain abnormalities such as those of Alzheimer's Disease at autopsy showed association with more rapid progression of frailty beyond that explained by demographic factors (Buchman et al., 2008). Further, malnutrition risk using anthropometric and dietary measures was associated with frailty in community dwelling older adults (Bollwein et al., 2013b). The Mediterranean-type of diet was associated with reduced frailty (Bollwein et al., 2013a). Smoking was associated with presence of frailty (Hubbard et al., 2009c; Wang et al., 2013).

Among conditions in the psychological domain, mild cognitive impairment was associated with higher odds of being frail (Nishi et al., 2012; Shimada et al., 2013). Depression was also associated with frailty (Bilotta et al., 2010; Nishi et al., 2012) as were mere depressive symptoms (Chen et al., 2010; Ni Mhaolain et al., 2012a; Ni Mhaolain et al., 2012b; St John et al., 2013). Higher emotional reliance on another person and less self-efficacy were found among frail older people compared with those who were not frail (Imuta et al., 2001). In addition, lower levels of psychological well-being were also associated with frailty (Andrew et al., 2012).

Concerning conditions in the social domain, singlehood (Chen et al., 2010; Cramm & Nieboer, 2013), less education (Avila-Funes et al., 2008; Chen et al., 2010; Szanton et al., 2010), lower income (Avila-Funes et al., 2008; Szanton et al., 2010), non-white collar occupation (Woo et al., 2005), low social participation (Woo et al., 2005), living alone (Bilotta et al., 2010), social vulnerability (Andrew et al., 2008), and neighborhood deprivation (I. A. Lang et al., 2009a) were all associated with frailty. On the other hand, stronger sense of social cohesion and neighborhood belonging was associated with reduced frailty (Cramm & Nieboer, 2013).

A summary of the evidence on conditions on pathways to frailty (C1) and from frailty to its adverse outcomes (C2), or merely associated with frailty (C3) is presented in Table 2.1. It is again clear that there is much more evidence available on pathways to frailty (first column) than from frailty to adverse outcomes (second column).

Table 2.1. Summary of evidence on conditions on pathways related to frailty

Condition	Pathways to frailty (C1)	Pathways from frailty to adverse outcomes (C2)	Uncertain position on pathways (C3)
Physical:			
Older age	+		
Female gender	+		
Singlehood			+
Non-white collar occupation			+
Less education	+		
Genetic factors	+/-		
Chronic disease	+		
Polypharmacy (>=5 concurrent medications)	+		
Health-related events	+		
Allostatic load	+		
Chronic systemic inflammation	+		
Low blood vitamin D level	+	+	
Low blood vitamin E level			+
Low blood estrogens level			+
Low blood testosterone level	+		
Overweight	+	-	
Underweight	+		
Disability in activities of daily living (ADL)			+
Sleep disturbances	+		
Impaired mobility	+		
Urinary incontinence			+
Impaired vision			+
Impaired hearing			+
Lifestyle factors			
Exercise (or physical activity)	-	-	
Smoking	+		
Increased protein /amino acid in diet	-	-	
Mediterranean-type diet	-		
Heavy drinking	+		
Moderate drinking	-		

Table 2.1 (continued). Summary of evidence on conditions on pathways related frailty

Condition	Pathways to frailty (C1)	Pathways from frailty to adverse outcomes (C2)	Uncertain position on pathways (C3)
Psychological:			
Poor cognition	+	+	
Depression	+		
High emotional reliance			+
Less self-efficacy			+
Lower psychological well-being			+
Social:			
Lower education	+		
Non-white collar occupation	+		
Lower income	+		
Financial strain	+		
Living alone	+		
Social isolation	+		
Social support	-		
Low social participation	+		
Social vulnerability			+
Neighborhood deprivation			+
Stronger social cohesion			-
Poor social conditions in childhood	+		
Multidimensional:			
Interdisciplinary intervention program	-	-	

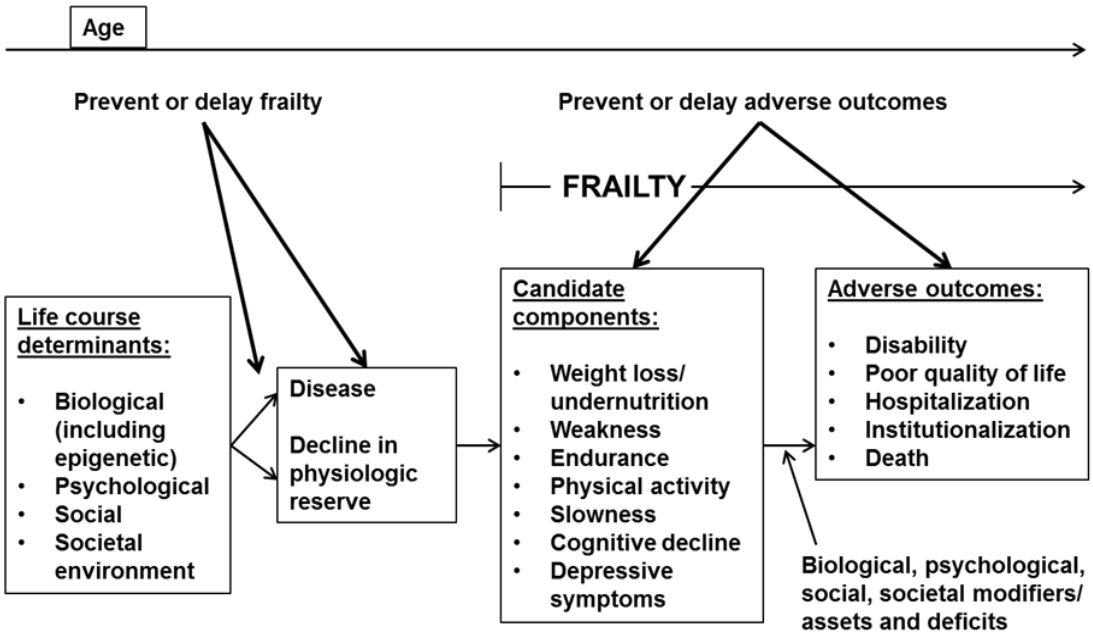
Note: + positive effect; - negative effect;

Frailty frameworks

Conceptual frameworks that integrate multidimensional conditions and define their relationship with frailty and with each other have been proposed and reported in the literature by several research groups. However, empirical studies of such frameworks are not identified. Nevertheless, examination of these frameworks is worthwhile as they provide the basis for construction of frailty models for further research.

The best known frailty framework is that proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004). This is shown in Figure 2.3. It acknowledges the influence of advancing age on transitions from pre-frailty to frailty. Life-course conditions from the biological, psychological, social, and societal spheres influence age-related declines in physiological reserves and disease. These in turn promote the onset of frailty in later life. Frailty leads to adverse outcomes ranging from disability to hospitalization and death. Its effects are modified by the same conditions. Emphasis on multidimensional conditions and the distinction it makes between pathways leading to frailty, and those from frailty to adverse outcomes are valuable features of this framework.

Figure 2.3. Working framework of the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) (adapted with modifications)



This working framework was adapted and modified in the development of the integral conceptual model of frailty (Gobbens et al., 2010b). While most elements are retained, this model accommodates physical, psychological, and social components of frailty rather than the

original seven candidate components. For physical frailty, its components are decline in nutrition, mobility, physical activity, strength, endurance, balance, and sensory functions. For psychological frailty, decline in cognition, mood, and coping are specified, while for social frailty, decline in social relations and social support are included as components.

While other frailty models have been proposed, most are restricted to biological aspects or have a heavy mathematical emphasis. Given that these do not contribute to a multidimensional approach to frailty, they will not be discussed.

Frailty identifiers

For the study of frailty pathways, an appropriate specification of frailty is needed. The wide array of screening instruments developed and validated over the past decade (Pialoux et al., 2012) attests to the absence of a universally accepted definition of frailty (Rodriguez-Manas et al., 2013). Closer examination reveals that these instruments reflect different yet overlapping concepts of frailty. What is strikingly common among these concepts is their consistent ability to predict adverse outcomes such as mortality, disability, falls, hospitalization, and nursing home placement (Ensrud et al., 2008; Jones et al., 2005; Kiely et al., 2009; Woo et al., 2012). The purpose of this section is to survey these various frailty concepts and to compare them. At the close, one or more candidate frailty specifications judged to be more suitable for the study of frailty pathways will be discussed.

To start with, the Cardiovascular Health Study (CHS) frailty phenotype proposed by Fried is arguably the most widely adopted among existing concepts (Bouillon et al., 2013b). It conceptualizes frailty as being a geriatric syndrome resulting from decline in multiple physiologic systems and operationalized by requiring the presence of *at least three of its five components*:

1) Shrinking: unintentional weight loss of at least 10 pounds or 5% in the prior year
2) Weakness: hand grip strength in the lowest quintile adjusting for gender and body mass index
3) Poor endurance and energy: self-reported exhaustion
4) Slowness: slowest quintile of the population based on 15-feet walk adjusting for gender and standing height
5) Low physical activity level: lowest gender-specific quintile of weighted score of kilocalories expended per week based on self-report

This specification of frailty predicted mortality at three years with an adjusted hazard ratio (HR) of 2.24. Worsening activities of daily living disability and falls over three years could also be predicted with adjusted HR of 1.98 and 1.29 respectively (Fried et al., 2001). The frailty phenotype has subsequently been adapted to measure frailty in specific populations (Avila-Funes et al., 2009; Avila-Funes et al., 2008; Graham et al., 2009; Woods et al., 2005; Xue et al., 2008a). In addition, it has also been modified while retaining the same phenotypic concept,

and then applied using the data of specific populations (Romero-Ortuno, 2013; Romero-Ortuno et al., 2010; Santos-Eggimann et al., 2009). A variant of the original definition used sarcopenia (low skeletal muscle mass) in place of hand grip strength (Cawthon et al., 2007). Yet another modification of the frailty phenotype developed by Buchman has four of the five components represented. It omitted physical activity and replaced weight loss with body mass index. Of note, this frailty specification retained the ability to predict death, dementia, and disability in the future (Boyle et al., 2010; Buchman et al., 2007; Buchman et al., 2011; Buchman et al., 2009).

In the aforementioned working framework of the Canadian Initiative on Frailty and Aging, frailty is defined by seven components. Of these, five items are of the CHS frailty phenotype with cognitive decline and depressive symptoms as additional ones (Bergman et al., 2004). Of these, slow walking speed, low physical activity, weight loss, and cognitive impairment were individually associated with mortality, disability, and nursing home residence over the following 7.5 years with HR ranging from 1.4 to 3.9 controlling for other frailty components (Rothman et al., 2008).

As mentioned, the integral conceptual model of frailty builds on the Canadian framework and explicitly recognizes its multidimensional nature (Gobbens et al., 2012a). Here, frailty is defined by losses in one of more of the physical, psychological and social domains of functioning (Gobbens et al., 2010a). Based on this model, the Tilburg Frailty Indicator (TFI) comprising 15 items representing the three domains was developed (Gobbens et al., 2010d). The TFI predicted disability, higher health care utilization including hospitalization and use of residential care facilities, as well as poorer quality of life at two years. Using Cohen's f^2 for continuous outcomes, all effect sizes were categorized as small to medium (f^2 between 0.02 and 0.15) (Gobbens et al., 2012b).

Next, the Frailty Index (FI) based on a deficit accumulation approach proposed by Rockwood is arguably the second most widely adopted concept for the measurement of frailty (Bouillon et al., 2013b; Rockwood & Mitnitski, 2007). The FI is constructed by taking a simple count of deficits, which are a collection of symptoms, signs, diseases, disabilities, or test abnormalities. The simple idea is that increasing number of deficits increased the likelihood of being frail. The FI is expressed as the ratio of actual deficits to total possible number of deficits, and is therefore a scalar measure from 0 to 1. Typically, at least 30 variables reflecting a wide range of deficits are used to construct the FI (Searle et al., 2008). Indicators used varied across studies. When FI was dichotomized to scores less than 0.25 (robust group) and scores equal to or higher than 0.25 (frail group), Kaplan-Meier 5-year survival curves indicated that probabilities of survival and institutional care avoidance were significantly higher for the robust group (Rockwood et al., 2007). The FI also identified frail people at risk of death and institutionalization over the following 10 years (Song et al., 2010). When the FI was based on elements of clinical examination that were part of a standard comprehensive geriatric assessment (CGA) of older people, it was designated as FI-CGA (Jones et al., 2005). Aside from this, the FI has been applied populations around the world using locally available data to

construct its required set of variables (Garcia-Gonzalez et al., 2009; Romero-Ortuno et al., 2011; Woo et al., 2006; Yu et al., 2012). In fact, the anthropological approach to operationalize the FI by using deficits selected at the local level was advocated in contrast to prevailing efforts to obtain a standardized version to be applied across different populations (de Souto Barreto, 2011). The FI has also been applied in specific settings such as primary health care (Drubbel et al., 2013). An interesting variant of the FI uses the deficit accumulation approach to define disability-free physical frailty phenotype (PFP), mental frailty phenotype (MFP), and social frailty phenotype (SFP). The combination of these three deficit-defined entities was able to predict mortality (Garre-Olmo et al., 2013).

An emerging frailty identifier is the five-item FRAIL scale, which assesses **f**atigue, **r**esistance, **a**mbulation, **i**llness, and **l**oss of weight. (Abellan van Kan et al., 2010; Morley et al., 2012). This instrument relies solely on self-report. It was listed as one of a few suitable tools to screen for frailty at the recent landmark consensus meeting on frailty (Morley et al., 2013).

Other frailty indicators described in the literature comprise an extremely lengthy list. In a review of the definition and measurement of the frailty concept, existing instruments were categorized as either multi-component or single component (Pel-Littel et al., 2009). It is worth highlighting that frailty instruments reviewed so far are multi-component with most being multidimensional as well. Others in this category but not mentioned yet include two related instruments, the Frailty Scale, which is based on the Geriatric Status Scale (GSS) that focused on several functional domains (Rockwood et al., 1999), and Canadian Study of Health and Aging (CSHA) Clinical Frailty Index, which is a seven-point scale based on activity and illness (Rockwood et al., 2005). Going further back in time, the Frailty Measure proposed by Strawbridge was the earliest of multidimensional instruments. It is a 16-item tool that defined frailty based on features in at least two out of four domains, which are physical function, nutritional status, cognition, and sensory function (Matthews et al., 2004; Strawbridge et al., 1998). The Groningen Frailty Indicator (GFI) identifies loss of function in four domains, namely physical, cognitive, social, and mental, using a total of 15 questions (Steverink, 2001). It feasibility, reliability, and validity were demonstrated (Peters et al., 2012). Others that make the list include the Edmonton Frail Scale (EFS), which samples 10 domains (cognition, balance and mobility, mood, functional independence, medication use, social support, nutrition, general health, continence, and burden of medical illness) (Rolfson et al., 2006), Study of Osteoporotic Fractures (SOF) frailty index, which consists of three items (weight loss, chair rise inability, and reduced energy) (Bilotta et al., 2012a; Bilotta et al., 2012b; Ensrud et al., 2008) , and Sherbrooke Postal Questionnaire (SPQ), which has six items that cover the physical, cognitive, and social domains (Hebert, 1996). As expected, these instruments have demonstrated similar ability to predict a range of adverse outcomes.

Meanwhile, other multi-component instruments have continued to be developed and proposed for various settings. These include the Gerontopole Frailty Screening Tool (GFST) which is designed for general practitioners and consists of two sections. The first is an initial

questionnaire to detect symptoms and signs suggestive of frailty, whereas the second allows the practitioner to exercise clinical judgment on the presence or otherwise of frailty (Vellas et al., 2013). The Comprehensive Frailty Assessment Instrument (CFAI) is a self-reporting instrument that includes physical, psychological, social, and environmental domains (De Witte et al., 2013). The frailty identifier derived from data of the Beaver Dam Eye Study uses frailty markers that included walking time, handgrip strength, peak respiratory flow rate, ability to stand from a sitting position without using arms, and best corrected visual acuity (Klein et al., 2003, 2005). The Conselice Study of Brain Aging Score (CSBAS) consists of seven variables was also used as a frailty measure (Lucicesare et al., 2010). The Identification of Seniors at Risk (ISAR) screening tool utilizes a comprehensive geriatric assessment based approach to define frailty and risk of adverse outcomes, albeit in older people after an Emergence Department (ED) visit (Salvi et al., 2012). Definition of frailty using four items based on information from the RAND-36/SF-36 tool was also proposed and used in a Finnish population of older men (Sirola et al., 2011). The combination of five frailty markers concerning physical activity, strength, cognition, energy, and mobility has been investigated (Au et al., 2011). Frailty was also operationalized using four criteria, namely low body mass index (BMI), low physical activity level, and dissatisfaction with both muscle strength and endurance, which was based on self-report in a French population (Barreto et al., 2012). The "Kihon Checklist" and "Kaigo-Yobo Checklist" were developed and validated for use in the Japanese population (Ogawa et al., 2011; Shinkai et al., 2010). The Elders Risk Assessment (ERS) index based on information gleaned from electronic medical records was developed to measure frailty and future risk of hip fracture (Albaba et al., 2012). The Evaluative Frailty Index for Physical Activity (EFIP) was based on deficit accumulation and designed to evaluate the effect of physical activity on frailty (de Vries et al., 2013). Weight loss and physical activity were proposed as effective criteria to identify frail older people (Chin et al., 2003). In a similar vein, two self-report measures on self-perception of one`s health and whether health troubles prevent one from doing things were used to predict frailty (Gutman et al., 2001). The Short Physical Performance Battery (SPPB) is an assessment tool that evaluates physical performance and frailty (Berkova et al., 2013). The Vienna Frailty Questionnaire for Persons with Intellectual Disabilities (VFQ-ID) and its revised version (VFQ-ID-R) were developed specifically to assess frailty in persons with existing intellectual disabilities (Brehmer-Rinderer et al., 2013).

The long list of single component instruments includes functional measures such as ADL and IADL scales (Chin et al., 1999; Weiner, 1992), individual tests of musculoskeletal function such as grip strength (Syddall et al., 2003), and 30-second chair stand test (Millor et al., 2013), mobility tests such as the walking speed (Abellan van Kan et al., 2009; Brown et al., 2000a; Chin et al., 1999) and Timed Up and Go (TUG) test (Savva et al., 2013), balance tests such as functional reach (Weiner, 1992) and Berg balance test (Brown et al., 2000a), and tests of cognitive function such as the Mini-Mental State Examination (MMSE) (Chin et al., 1999). The Adjusted Clinical Groups (ACG) frailty tag extracted from the ACG-diagnoses based computerized predictive model (ACG-DX-PM) suite for administrative data was able to identify older people who were frail (Sternberg et al., 2012). Generally, most single component

instruments are not likely to be suitable for the identification of frailty when used alone. Nevertheless, an interesting instrument that could show promise in predicting frailty is the Walking While Talking Test (WWT). This is a performed mobility stress test that utilizes dual-tasking ability. Its predictive validity with respect to disability and death was demonstrated (Verghese et al., 2012). Another potentially promising tool for identifying frailty was gait variability. Walking stride time variability under fast walking conditions was prominently associated with frailty (Montero-Odasso et al., 2011). Further development of these two measures is awaited.

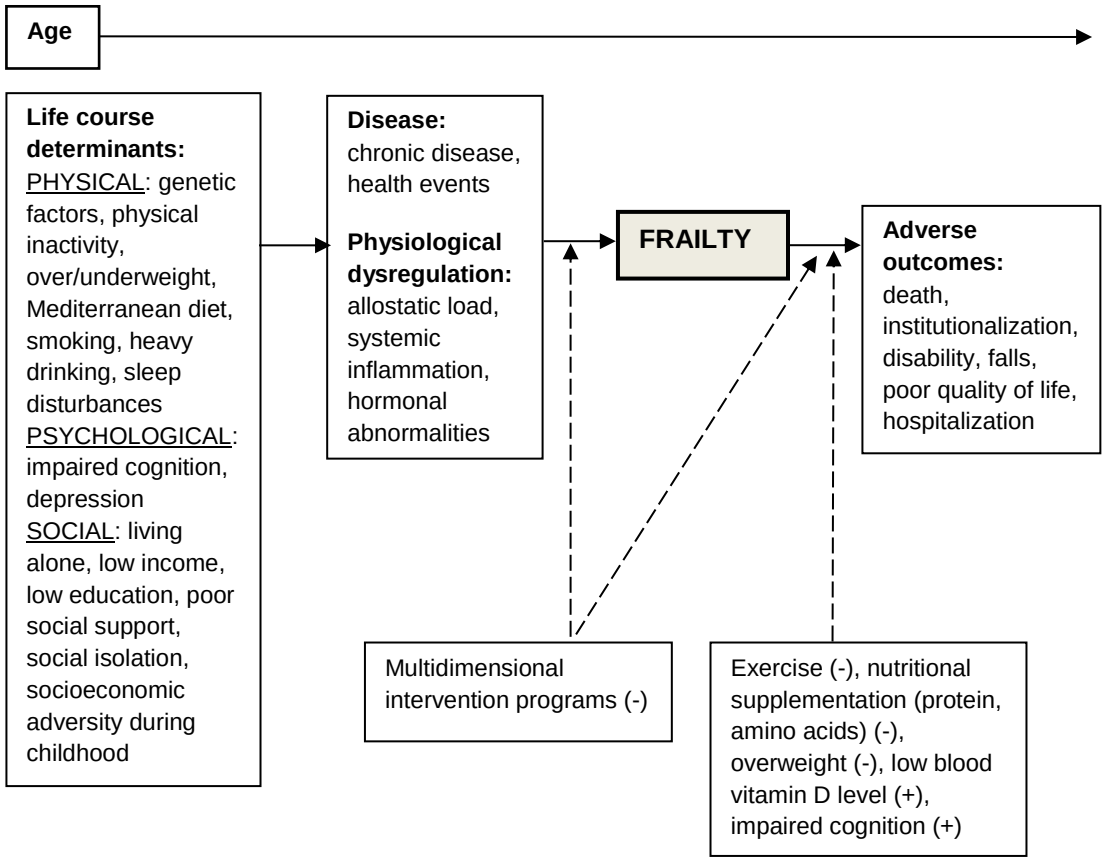
Finally, other practice-based tools for identifying older people with frailty have been developed and reported. These include the EASY-Care Two-step Older Persons Screening (EASY-Care TOS) (van Kempen et al., 2013; van Kempen et al., 2014). The Clinical Global Impression of Change in Physical Frailty (CGIC-PF) instrument includes six intrinsic domains (mobility, balance, strength, endurance, nutrition, and neuromuscular performance) as well as seven consequence domains (medical complexity, healthcare utilization, appearance, self-perceived health, activities of daily living, emotional status, and social status). Each of these domains had two to four clinical indicators scored on a seven-point scale (Studenski et al., 2004). Although announced as having strong face validity, and being reliable and feasible, its subsequent application has been limited.

Developers of individual instruments tend also to be their strongest proponents. Consequently, reasonably objective reviews are few and far between. In a systematic review that possibly possesses this attribute, the CHS frailty phenotype was acknowledged as having attracted the most attention from researchers, given the appeal of its physiological basis and semi-quantifiable components. However, the intuitive feeling was that this definition does an incomplete job in describing frailty. The authors note that in response, more recent studies have added mood and cognition to augment the Fried components. They also offer their opinion that walking speed as a single item may in the future prove to be a feasible early identifier of frailty among non-disabled older people. Nevertheless, they conclude that the choice of instrument is best determined by the purpose at hand. For researchers who desire a biologically plausible model may want to consider the CHS frailty phenotype. Others such as policy makers and administrators whose focus is on planning health services may opt for the Frailty Index given that information on its deficit items may be extracted from administrative databases and clinical records (Sternberg et al., 2011). In another yet more recent systematic review of frailty assessment instruments, the authors recommend careful selection of instrument based on its intended purpose, domains captured, and past use (Buta et al., 2016).

2.5 Discussion

From this literature review, I found a rewarding amount of evidence concerning individual conditions on pathways to frailty. These span the physical, psychological, and social domains, and include relevant medical illnesses and other life course determinants. However, I found less evidence concerning conditions on pathways from frailty to adverse outcomes. Although several conditions were found to be associated with frailty in cross-sectional studies, the direction of these relationships are unclear, particularly when they are not also represented in longitudinal studies. To provide a summary of these factors, the working framework of the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) provides an excellent template to position these individual pieces of evidence on in the attempt to construct the whole picture. Figure 2.4 illustrates how the available evidence from the literature review relates to this framework.

Figure 2.4. Evidence on frailty pathways using the working framework of the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) as the template



(+) positive moderating effect

(-) negative moderating effect

It is important to note that age is designated as having effect on frailty and its adverse outcomes apart from or in combination with the other sets of conditions. It is also worth pointing out that the sequential relationship between life course determinants and both disease and physiological dysregulation may be more complex than represented in this graph. Life course determinants would have direct effects on frailty that are not mediated by the latter two conditions. Moreover, disease and physiological dysregulation may have a bidirectional relationship.

Similarly, the graph implies that multidimensional interventional programs, exercise, nutritional supplementation, and other factors listed have moderating effects. However, it might be possible that these factors, particularly low blood vitamin D levels and impaired cognition may operate as mediators in the relationship between frailty and its adverse outcomes. Nevertheless, this simplified framework of evidence constitutes a reasonable foundation on to build more complex hypothesized pathways for frailty in further work.

Continuing the focus on the relationship between frailty and its adverse outcomes, I note that the working framework of the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) hypothesizes that biological, psychological, social, and societal conditions may have moderating effects on them. However, there is paucity of available evidence on these possible conditions from the literature review, particularly those in non-physical domains. Clearly, it is a subject that requires further investigation given the implications on the search for effective interventions and policies for frail older people. It would be important to investigate whether other medical-related conditions, depression, and social support have their effects on these pathways either as moderators, mediators, or both. The likelihood that frailty pathways may be more complex than is apparent on the surface could also explain in part the apparently contradictory findings that being overweight increases risk of incident frailty, but conversely reduces risk of some adverse outcomes among older people who are already frail.

Moving on to frailty identifiers, the striking picture arising from the literature review is the plethora of instruments which have been developed, applied, and in some cases validated over time. It is also clear that there is significant overlap of the underlying constructs of many of them. For the purpose of selecting a suitable frailty specification for investigation of frailty pathways, the list of potential candidates will be shortened.

The most important consideration is whether a suitable frailty specification should be limited to a single dimension such as the physical domain, or should include multiple dimensions such as also incorporating the psychological and social domains. The concept that frailty represents a multidimensional entity was first mooted by Strawbridge (Strawbridge et al., 1998). Since then, the definition of frailty has been dominated by the CHS frailty phenotype, which is limited to representing its physical domain, and the FI, which attempts to represent more than one domain. Further along the way, the multidimensional construct has been reemphasized by the

integral conceptual model of frailty, which makes reference to physical, psychological, and social frailty (Gobbens et al., 2010b), with these dimensions represented as items in the Tilburg Frailty Indicator (TFI) (Metzelthin, 2010). Moreover, the concept of frailty proposed in the working framework of the Canadian Initiative on Frailty and Aging encompasses the physical domain by including components of the CHS frailty phenotype, and the psychological domain by also incorporating cognitive impairment and depression to complete the set of candidate components (Bergman et al., 2004). Indeed, in the recent frailty consensus conference mentioned earlier, frailty was described as either physical, psychological, or a combination of the two components, at least in concept. However, the collective discourse proceeded to focus on physical frailty and screening for this entity with recommended instruments (Morley et al., 2013). It is important to note that the purpose of that consensus conference was to propose ways of identifying frail older people and offer effective interventions to them. For that purpose, limiting the frailty concept to its physical dimension seems justified. This brings me back to the aforementioned assertion that different frailty instruments best serve different purposes (Martin & Brighton, 2008). In this spirit, I return to the purpose of selecting frailty identifiers for the investigation of frailty pathways that I had set out with.

If the framework in Figure 2.4 is adopted as the conceptual model for investigating the relationship between frailty and the multiple multidimensional conditions, then it is clear that some key components of the multidimensional concept of frailty would be represented on pathways to frailty itself, and from frailty to its adverse outcomes. The theoretical argument on which conditions are predictors or effects, and which conditions should rightfully be considered integral components of the frailty construct is beyond the scope of this review. Rather, I will take the pragmatic view that key conditions which appear to operate as key predictors or effects with respect to frailty are best excluded from its definition when investigating frailty pathways. This will be the general approach adopted in formulating hypotheses on frailty pathways in this review and further research that follows.

In doing so, it becomes immediately clear that the psychological and social domains are represented as predictors, effects, or both in the framework in Figure 2.4. Therefore, candidate specifications for the purpose of investigating frailty pathways will necessarily be those representing physical frailty. Among physical conditions found in this framework, physical inactivity and chronic disease are components of more prominent physical frailty identifiers such as the CHS frailty phenotype (Fried et al., 2001) and FRAIL tool (Abellan van Kan et al., 2010) respectively. Two less prominent physical frailty identifiers manage to avoid this situation by not having either of these two conditions as their components. The first is the Buchman modification of the CHS frailty phenotype, which in omits the physical inactivity as a component (Buchman et al., 2009). The second is Study of Osteoporotic Fractures (SOF) frailty index, which has three components, namely weight loss, chair rise inability, and reduced energy (Ensrud et al., 2007). Of significance is the finding that the SOF had equivalent ability to predict adverse outcomes as the CHS frailty phenotype, at least in women (Ensrud et al., 2008). It

could be that these two frailty specifications are also suitable for investigation of frailty pathways hypothesized in Figure 2.4.

An extreme interpretation of the adopted approach would be to consider physical frailty identifiers that are single component instruments. Grip strength (Syddall et al., 2003), walking speed (Abellan van Kan et al., 2009), Timed Up and Go (TUG) test (Savva et al., 2013), Walking While Talking Test (WWT) (Verghese et al., 2012), and walking stride time variability under fast walking conditions (Montero-Odasso et al., 2011) are some examples. Of these, only the first two have been more widely measured in research studies, thereby limiting the application of the last three instruments. Interestingly, walking speed was the strongest predictor of hospitalization among the five subcomponents of the CHS frailty phenotype while grip strength was not a significant predictor after adjusting for age, sex and other subcomponents in the Whitehall II study cohort (Bouillon et al., 2013c). However, it is quite likely that the combination of more than one subcomponent predicts adverse outcomes better than just a single subcomponent. Indeed, three to five components together predicted hospitalization much better than one or two components did, thereby confirming the existence of a dose-response relationship where their number is concerned in the same study (Bouillon et al., 2013c). This supports the idea that frailty identifiers with multiple components are likely to have stronger predictive validity than those with a single component. Moreover, those with multiple components have better face validity with respect to representing the frailty construct.

Beyond their purpose and performance, it is important that frailty identifiers have strong theoretical justification. Notably, the concept of physical frailty is underpinned by the process of sarcopenia which is characterized by age-associated loss in skeletal muscle mass and function (Fielding et al., 2011). In fact, sarcopenia has been described as the biological substrate of physical frailty (Landi et al., 2015), thereby providing the latter with a strong conceptual basis.

Given all these points, I argue that physical frailty is the most logical point at which to begin in specifying frailty for investigation of frailty pathways. The CHS frailty phenotype remains the preeminent prototype for physical frailty. For the reasons already stated, the component of low physical activity is best omitted. As mentioned, the Buchman modification of the frailty phenotype meets this requirement. Next, exhaustion may also be a symptom of depression. In fact, two out of eight items of the Center for Epidemiologic Studies Depression (CES-D) scale for depression were used to operationalize exhaustion for the development of frailty phenotype in the original study (Fried et al., 2001). Depression belongs to the psychological domain and may itself be a target for interventions to reduce frailty and its effects. If we also omit this component, then there are three remaining indicators for physical frailty, which are slow walking speed, reduced grip strength, and weight loss. On the other hand, if weight loss is omitted rather than exhaustion, then we obtain another physical frailty specification with three indicators. Thus far, there are no published reports on the validity of such specifications of frailty. In addition, the three-item SOF frailty index may also be a suitable alternative but a potential drawback is information needed on performance of chair rise, which may not be

available in secondary data sources. Ultimately, availability of data to create variables representing these components may be an important consideration in selection of candidate specifications of physical frailty.

From this review, important gaps in the understanding of frailty specifications and pathways are uncovered. Firstly, the validity of frailty pathways in a comprehensive framework has not yet been investigated. As such, they remain at best plausible, and at worst, merely hypothetical. Moreover, simultaneous effects of conditions on these pathways have received less attention. In other words, the question arises as to whether these individual conditions would still exert significant effects when controlled for other conditions which exert parallel effects. In addition, inter-relationships between these conditions including moderated and mediated effects need to be identified and quantified to identify additional yet unrecognized effects, which may be as important as known main effects. Where possible, the direction of effect of associations with frailty from cross-sectional studies requires clarification. Finally, the feasibility and validity of candidate physical frailty specifications discussed are uncertain. Further study to address these knowledge gaps in the pursuit of understanding frailty pathways is clearly merited.

The strengths of this review lie in its broad literature search and focus on synthesis of concepts, as well as its critical analysis. On the other hand, its main limitation is the lack of emphasis on the quality of available evidence, though this is justified given that providing critical review is the main objective here. Moreover, in view of the numerous relevant papers identified, detailed discussion of each predictor or instrument is not attempted.

2.6 Conclusion

Evidence from this literature review confirms that physical, psychological, and social conditions including those in the domains are represented on frailty pathways. They largely concern predictors of frailty, while there is less information on conditions that influence its impact on adverse outcomes. A few suitable candidate specifications of frailty are available for investigation of frailty pathways, but they may need to be modified for purpose. Further empirical work to evaluate the validity of frailty specifications and to estimate predictive, moderated, and mediated effects of multidimensional conditions on frailty pathways is warranted to gain better understanding of the development of frailty and its outcomes.

3 Research Outline

3.1 Objectives

The proposed research will address suitable physical frailty specifications for the investigation of frailty pathways. It will also examine pathways to frailty and to its adverse outcomes.

Therefore, the specific research aims are:

1) To evaluate physical frailty specifications with respect to their validity and relationship with psychological and social frailty
2) To explore the validity of a framework of pathways to frailty and to its adverse outcomes by quantifying the relationship of physical frailty with physical, psychological, and social conditions on these pathways

There are three key research questions which I will seek to answer. They are:

1) Do physical frailty specifications based on three or four of the components of the CHS frailty phenotype have construct, concurrent, and predictive validity?
2) What conditions are physical, psychological, and social predictors of physical frailty, and what are the moderators, and mediators of their effects in older people?
3) What conditions are moderators and mediators of the effect of physical frailty on death and activity limitation in older people?

I will adopt two conceptual models for this research. The first is the working framework of the Canadian Initiative on Frailty and Aging. It provides the basis for developing a set of hypothesized frailty pathways. The second is the integral conceptual model of frailty. This offers a useful way of thinking about the three dimensions of frailty; namely, physical, psychological, and social frailty.

3.2 Methods

The study design is secondary analysis of longitudinal survey data conducted in two stages. In the first stage, I will explore candidate physical frailty specifications deemed suitable for use in investigating frailty pathways. Their validity will be evaluated and compared. The desired end will be the selection of one or two physical frailty specifications from these candidates. In the second stage, I will use the selected physical frailty specification to investigate the relationship of physical frailty with multidimensional conditions on frailty pathways. In doing so, I will advance beyond mere prediction of physical frailty and its adverse outcomes to examine moderation and mediation of these effects.

Thus, there are five sub-studies in my thesis. Their scope will be:

1) Identification of candidate physical frailty specifications and evaluation of their construct and concurrent validity

2) Evaluation of predictive validity of candidate physical frailty specifications
3) Examination of the effects of predictors of physical frailty including moderated and mediated effects using latent growth curve analysis
4) Examination of the effect of physical frailty on death with focus on moderated and mediated effects using discrete time survival analysis
5) Examination of the effect of physical frailty on activity limitation with focus on moderated and mediated effects using autoregressive cross-lagged analysis.

The subjects for the last two sub-studies are chosen because of their relevance of longevity (lifespan) and healthy living (healthspan) of older people.

I will use data from the English Longitudinal Study of Ageing (ELSA) to conduct these five sub-studies. Before that, a description of the main features of ELSA, and discussion of its feasibility and limitations for the research purpose will be provided in the next section.

3.3 Contribution

This research will build on the existing knowledge base on predictors and effects of frailty in older people, and will expand on it in two key areas. In the first, suitable specifications of frailty for study of frailty pathways will be identified, and their feasibility and validity carefully examined. For the second, potentially modifiable conditions on hypothesized frailty pathways will be identified and the magnitude of their effects estimated. I expect that the findings will contribute to informing health and social policies on target conditions to focus on for population-level strategies that address the prevention and management of frailty in older people. At the very least, they can serve as a springboard from which future research on frailty pathways may be conducted.

3.4 Originality

The research will critically review and further develop theoretical concepts related to frailty specification and pathways. The novelty of this work lies in its:

1) specification of frailty in a form that permits its relationship with potentially remediable physical, psychological, and social conditions to be examined as distinct and separate elements on frailty pathways
2) investigation of frailty in a single frailty framework, based on the working framework of the Canadian Initiative on Frailty and Aging, which integrates health and social conditions seamlessly, while considering their simultaneous effects

4 Data Feasibility

4.1 Description of the English Longitudinal Study of Ageing

The English Longitudinal Study of Ageing (ELSA) is sponsored by various government departments of the United Kingdom, and the National Institutes on Aging (NIA) of the United States of America. Data collection and processing is coordinated by University College London (UCL) Research Department of Epidemiology and Public Health, Institute for Fiscal Studies (IFS), National Centre for Social Research (NATCEN), and The University of Manchester, School of Social Sciences.

ELSA was started in 2002 and is still ongoing. It is a panel study with successive biennial waves. The primary objective is to collect longitudinal data from a representative sample of the English population aged 50 years and older to observe change in their health, economic and social circumstances over time. Its primary aim is to provide high-quality multidisciplinary data that can inform on the causes and consequences of outcomes relevant to older people. A secondary aim is to assist in planning for an ageing population, while ensuring that the healthcare and pension systems will meet emerging needs.

ELSA surveys residents of England aged 50 years and older who live in private residential addresses, thereby excluding those living in institutions and the homeless. Its sampling frame comprised adults aged 50 years and older who responded in 3 years of the Health Survey for England (HSE): 1998, 1999 and 2001. This sampling design had two phases.

Phase One: The Health Survey for England (HSE) is a survey of people living in private households who are nationally representative in terms of their age, gender, geographic area and socio-demographic characteristics. Each year, a new random sample is selected using the Postcode Address File (PAF) as the sampling frame, and a two-stage stratified random sampling process (Taylor et al., 2007).

> 1st stage: Random sample of primary sampling units (PSUs) based on postcode sectors, with probability proportional to total number of addresses within the PSU was carried out. Stratification was achieved through ordering of the PSUs as per local authority and percentage of households with a household head in a non-manual occupation, to facilitate representativeness by local health authority and socio-economic group. Systematic sampling of the list at fixed intervals from a random starting point was performed.
>
> 2nd stage: Simple random sampling of a fixed number of addresses from the PAF was drawn from each selected postcode. Eligible individuals from each household were invited to participate in HSE. The total number of households for HSE in these three survey years was 31,051.

Phase Two: The ELSA wave 1 (2002) sample was selected from the 31,051 households of the HSE sample based on the following eligibility criteria:

1) households that responded to HSE
2) households that included at least one individual born on or before 29 February 1952, who remained alive according to administrative records, and gave permission to be contacted in the future.

The final number of households for ELSA was 11,578. These yielded 18,813 individuals, who also included cohabitating spouses or partners who were living within the household at the time of the HSE interview and born after 29 February 1952.

The sample was refreshed at wave 3 (2006) with individuals aged 50 to 52 years on 1 March 2006, and at wave 4 (2008) with those aged 50 to 74 years on 1 March 2008, using the same eligibility criteria as those for wave 1.

There were two modes of data collection. The first mode is face-to-face Computer-Assisted Personal Interviewing (CAPI) plus a self-completion paper questionnaire for waves 1 to 7 (2002, 2004, 2006, 2008, 2010, 2012, and 2014). The second mode is additional nurse visit and assessment only for waves 2 (2004), 4 (2008), and 6 (2012). Overall, the response rate at wave 2 for eligible core members (successfully interviewed in wave 1) was 82% (Scholes et al., 2008).

4.2 Data availability

The key data elements required and available for this research can be categorized as follows:

1) Demographic information: age, gender
2) Physical frailty indicators: walking speed, hand grip strength, weight, report of exhaustion, and physical activity level
3) Multidimensional conditions on frailty pathways:
    a. Physical: chronic disease (hypertension, angina, myocardial infarction, heart failure, arrhythmia, diabetes mellitus, stroke, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, psychiatric condition, and dementia), allostatic load (systolic blood pressure, diastolic blood pressure, blood total cholesterol-HDL-cholesterol ratio, blood triglyceride level, blood C-reactive protein level, blood glycosylated hemoglobin level, blood fibrinogen level, waist-hip ratio, and peak flow rate), body mass index (BMI), smoking habit, alcohol consumption, and physical activity level
    b. Psychological: depressive symptoms (CES-D: Center for Epidemiologic Studies Depression Scale) (Radloff, 1977), and cognitive performance (memory and executive function tests)
    c. Social: educational attainment (qualifications), wealth (total non-pension wealth), social support indicators (children, other family member, and friends:

"criticizes the respondent", "lets the respondent down", "gets on the nerves of respondent", “understand the way you feel”, “can rely on if you had a serious problem”, “can open up to them if you need to talk”), and social integration indicators (living without spouse or partner, contact with children, other family members, and friends, membership of any organization, club, or society)

4) Outcomes of physical frailty: death (year), activities of daily living, self-reported health, and quality of life (CASP: Control, Autonomy, Self-realization, and Pleasure measure) (Howel, 2012)

Most of these data elements are available across waves 1, 2, 4, and 6. Notable exceptions are cognitive performance and waist-hip ratio (a component of allostatic load) at wave 6. In addition, death data is only available till February 2012, and so is incomplete for wave 6. Data on childhood event history is available in the Life History Interview conducted at wave 3, but are not considered, given that this information would not be available for wave 2 respondents who died or dropped out by then. Although available, genetic information is not the focus of the intended research.

As expected with longitudinal data, missing values are encountered for all variables except for age, gender, and death. With successive waves, missing values due to loss to follow up and death increase. For the subset of respondents aged 65 to 89 years, these occur in up 10% for most variables, but up to approximately 50% for certain variables such those constituting allostatic load at wave 6. Methods for handling these missing values in a principled and explicit manner with appropriate assumptions will be employed.

4.3 Summary

Overall, data availability is adequate for the research. The major challenge is missing values for most variables sought, and this will necessitate appropriate handling. In addition, missing information on specific parameters, such as cognitive performance and waist-hip ratio at wave 6, would need to be borne in mind when constructing variables for the statistical analyses.

Part Two

Frailty Pathways: Developing Suitable Frailty Specifications for Their Investigation

5 First Paper

5.1 Introduction

The need to develop a physical frailty specification for investigation of frailty pathways has already been alluded to. This section comprises two papers that address this task.

To recap, the preceding literature review assembled evidence on a wide range of frailty instruments that have been developed to identify frailty in older people. It takes the view that different instruments are best suited for different purposes. Thus far, the issue of the suitable instruments for investigating frailty pathways has not received much attention in the literature. An argument is made to adopt a narrower concept of physical frailty when considering instruments for this purpose. This contrasts with prevailing efforts to conceptualize frailty as a broader concept that extends across physical, psychological, and social domains. The main reason is that some key components of the multidimensional concept of frailty would themselves be included on pathways to frailty and its adverse outcomes. This renders the investigation of the relationships of frailty with its potential predictors and effects even more challenging. Moreover, physical frailty is a concept that is underpinned by the biological process of sarcopenia, which is age-associated loss of skeletal muscle mass and function. When physical frailty is the adopted concept for frailty instruments for investigating frailty pathways, then the Cardiovascular Health Study (CHS) frailty phenotype (Fried et al., 2001) is an excellent choice among others to consider. Its conceptual framework is represented by the cycle of frailty (Xue et al., 2008a). Here, sarcopenia holds a key position in the sense that pathways emanating from it lead to slowness, weakness, and exhaustion which are positioned immediately downstream. In turn, these conditions eventually result in important health-related outcomes, such as falls, disability, and dependency. Indeed, sarcopenia has been summarily described as the biological substrate of physical frailty (Landi et al., 2015).

For the CHS frailty phenotype, the component of physical inactivity is problematic as it is a key predictor of frailty that needs to be included on frailty pathways. The Buchman modification of the CHS frailty phenotype omits this component while retaining the other four. In addition, the component of exhaustion could also prove to be problematic. Besides having physical causes, it may also be a manifestation of depression, which lies in the psychological domain. Depression is a key condition on frailty pathways and has clear association with frailty, although the direction of the relationship is unclear (Collard & Oude Voshaar, 2012). Therefore, the decision to retain or omit this component from candidate physical frailty specifications needs to be carefully made.

At this point, it is worthwhile reviewing other frailty instruments that focus on physical frailty alone, and which may also be reasonable alternatives to the CHS frailty phenotype. Besides the Buchman modification of the CHS frailty phenotype mentioned, three other instruments merit consideration. The first is the FRAIL tool, which consists of five self-reported items,

namely **f**atigue, **r**esistance, **a**mbulation, **i**llnesses, and **l**oss of weight. While physical inactivity is not included as an item, the presence of more than five chronic illnesses defines the item on "illnesses". This presents a similar problem in that chronic illness is another key condition on frailty pathways, and its relationship with frailty needs to be evaluated. Indeed, the prevailing notion is that frailty is an entity that is distinct from chronic illness or comorbidity, although they overlap in concept (Fried et al., 2004). The second is the Study of Osteoporotic Fractures (SOF) frailty index, which has three components, namely weight loss, chair rise inability, and reduced energy (Bilotta et al., 2012b). The SOF frailty index predicts adverse outcomes such as falls, disability, hospitalization, and death with accuracy similar to that of the CHS frailty phenotype (Bouillon et al., 2013b). Of concern, inability to rise from the chair may not be a common assessment item in longitudinal studies of ageing. The third is walking speed alone, which a good predictor of adverse outcomes (Abellan van Kan et al., 2009). It also performed best among the five components of the CHS frailty phenotype in predicting future hospitalizations (Bouillon et al., 2013c). However, it suffers from being a single item and arguably does not capture the wider concept of even just physical frailty. Thus, its face validity with respect to reflecting the concept of physical frailty is compromised. Given these issues, the three alternative frailty instruments are probably not as suitable as three or four items of the original CHS frailty phenotype for investigating frailty pathways.

Returning to the CHS frailty phenotype, a candidate physical frailty specification comprising four indicators, which are slowness, weakness, exhaustion, and weight loss is obtained when only physical inactivity is omitted. As mentioned, this specification parallels the Buchman modification of the CHS frailty phenotype. If weight loss is additionally dropped, then a specification with three items comprising slowness, weakness, and exhaustion is obtained. On the other hand, if exhaustion is dropped instead due to concerns on its relationship with depression, then an alternative specification with three items comprising slowness, weakness, and weight loss is obtained. At this point, these three physical frailty specifications appear to be equally promising, and will be have their validity evaluated. For the validation process, I will adopt a previously proposed approach to defining frailty (Rockwood, 2005).

Before that, I will consider the face validity of these candidate specifications. The picture of an older person walking slowly, having decreased strength, being easily fatigued, and having unintentional loss of weight reflects what is commonly understood of as frailty among health care professionals and researchers. Secondly, content validity is arguably almost assured since the four indicators of candidate specifications are drawn from the five components of the CHS frailty phenotype. Moreover, these indicators parallel some of the components of other physical frailty instruments, namely FRAIL tool and SOF frailty index. Indeed, weakness, exhaustion, and weight loss are included as indictors across these three frailty instruments, whereas slowness is included by two of them.

A version of the following paper is published in the journal, *AGE* (Ding, 2016). Here, I evaluate construct validity, which comprises convergent and discriminant validity, as well as concurrent

validity, which is an important aspect of criterion validity. Some of the foregoing key points are unavoidably repeated as this is a self-contained journal article. References are in a separate list just before the Supplementary Materials (page 71).

5.2 Developing Physical Frailty Specifications for Investigation of Frailty Pathways in Older People

Abstract

Different frailty definitions are suitable for different purposes. When investigating its key multidimensional predictors and effects, narrower definitions of frailty that exclude these elements may be more desirable. For this purpose, candidate physical frailty specifications are developed, and then evaluated on their construct and concurrent validity. For 4638 participants aged 65 to 89 years from wave 2 (2004) of the English Longitudinal Study of Ageing, confirmatory factor analysis is performed to create physical frailty specifications with four indicators (slowness, weakness, exhaustion, and weight loss) and with three indicators (slowness, weakness, and either exhaustion or weight loss). Using derived factor scores, their convergent, discriminant, and concurrent validity are compared. For specifications with four indicators and with three indicators including exhaustion, slowness contributes dominantly to the physical frailty factor. However, with three indicators including weight loss, weakness contributes most. Where represented, weight loss only contributes minimally. Higher factor scores are significantly associated with chronic diseases, functional impairment, and poor self-rated health, although less so for the third specification. Factor scores for the first two specifications have low correlation with psychological and social frailty while those for the third have negligible correlation. Factor scores increase with higher Frailty Index, although again less so for the third specification. Minor differences are seen across gender. On account of their convergent, discriminatory, and concurrent validity, physical frailty specifications with four indicators and with three indicators including exhaustion hold promise for use in investigation of frailty pathways involving multidimensional predictors and effects.

Keywords

Frailty, specification, aged, frailty pathways, validity

Introduction

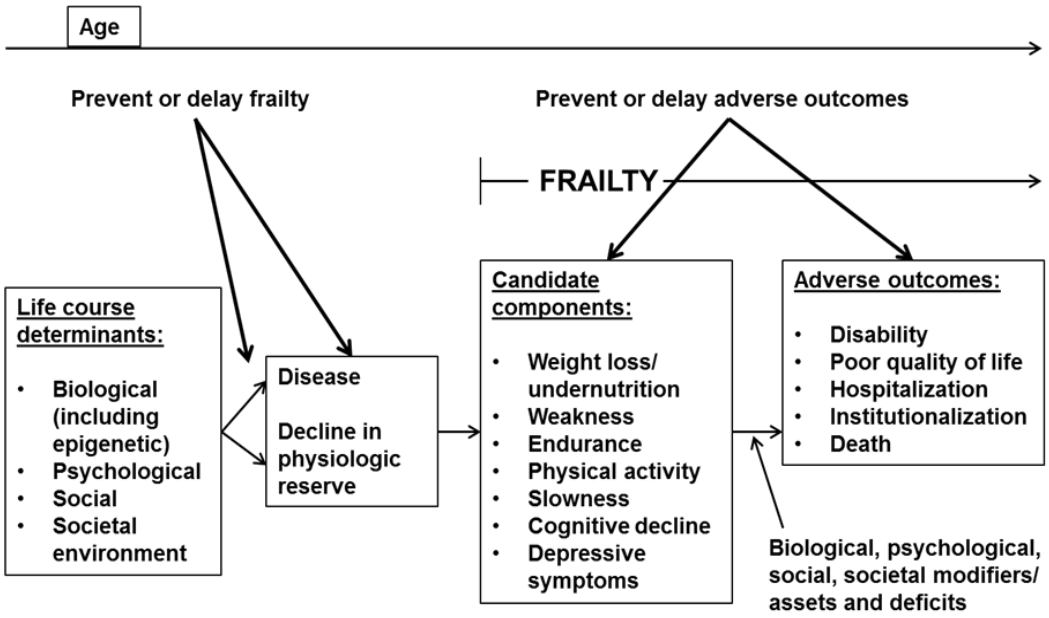
Frailty is widely regarded as the multidimensional loss of an individual's reserves that results in vulnerability to developing adverse health-related outcomes (Espinoza & Walston, 2005; Lally & Crome, 2007; Pel-Littel et al., 2009). It is conceptualized as the transitional state between robustness and functional decline (Lang et al., 2009). The estimated prevalence of frailty is about 10% among people aged 65 years living in the community (Collard et al., 2012). Beyond mere numbers of affected people in any population, frailty is unfortunately associated with increased risk of death, disability, falls, hospitalization, and institutionalization (Daniels et al., 2008; Ensrud et al., 2009; Ensrud et al., 2008; Jones et al., 2005; Kiely et al., 2009; Pilotto et al., 2012; Woo et al., 2012). Consequently, frailty plays a central role in determining the well-being of older people, and has major public health importance (Woo et al., 2006).

Over the past decade, the wide array of frailty instruments available (Pialoux et al., 2012) attests to the absence of a universally accepted concept. Nevertheless, recent efforts to forge consensus among international experts have achieved some degree of agreement on suitable instruments for the recognition of frailty in older persons (Morley et al., 2013). These instruments reflect different albeit overlapping concepts. Among them, two have gained greater prominence. The Cardiovascular Health Study (CHS) frailty phenotype is probably the most widely adopted. It conceptualizes frailty as a geriatric syndrome resulting from decline in multiple physiologic systems, and is operationalized by requiring presence of at least three of its five components: shrinking (unintentional weight loss), weakness (low hand grip strength), poor endurance and energy (self-reported exhaustion), slowness (slow walking speed), and low physical activity level (based on self-report) (Fried et al., 2001). The Frailty Index (FI) is possibly the second most widely applied instrument, and is based on a deficit accumulation approach (Rockwood & Mitnitski, 2007; Rockwood et al., 2004). A count is taken of deficits, which are a collection of symptoms, signs, diseases, disabilities, or test abnormalities. Selected deficits should be associated with poorer health status, should increase with age, but not saturate too early, must as a group cover a range of systems, and must be the same for a group of people followed serially (Searle et al., 2008). An increasing number of deficits raise the likelihood of being frail. It is expressed as the ratio of actual number of deficits to total possible number of deficits, and is therefore a scalar measure ranging from 0 to 1. Besides these two instruments, the FRAIL tool was developed to identify older persons who are at risk for frailty. It consists of five self-reported items, which are **f**atigue, **r**esistance, **a**mbulation, **i**llnesses, and **l**oss of weight. Presence of three or more items defines frailty (Abellan van Kan et al., 2008; Morley et al., 2013). In addition, the Tilburg Frailty Indicator (TFI) is based on an integral conceptual model of frailty, which explicitly recognizes its multidimensional nature by defining losses in one of more of physical, psychological, and social functioning domains through its 15 items (Gobbens et al., 2010a). It is scored from 0 to 15, with higher scores representing higher levels of frailty (Gobbens et al., 2010b). While CHS frailty phenotype and FRAIL focus on the physical domain, FI and TFI attempt to measure frailty across more than a single domain.

Not surprisingly, all these four instruments predict future adverse outcomes in older people reasonably well (Abellan van Kan et al., 2008; Fried et al., 2001; Gobbens et al., 2012; Rockwood et al., 2007). Moreover, where head-to-head comparisons are available, their predictive performance were shown to be approximately equivalent (Ravindrarajah et al., 2013; Woo et al., 2012). Past debate on which instrument is best among them appears to have run out its course over recent years and may now be less relevant in moving frailty research and public policy agendas forward. Rather, there is a growing sense that different instruments are best suited for different purposes (Cesari et al., 2014; Martin & Brighton, 2008).

Mapping of different frailty instruments to specific roles such as clinical screening, population studies, and biomedical research has been proposed (Bouillon et al., 2013; Cesari et al., 2014; Morley et al., 2013). However, less work has been done in developing suitable specifications for investigating frailty pathways, which represent relationships between frailty and its multidimensional predictors and effects. The working framework proposed by the Canadian Initiative on Frailty and Aging Frailty provides an excellent reference for this endeavor, and is illustrated in Figure 1.

Figure 1. Working framework proposed by the Canadian Initiative on Frailty and Aging Frailty (adapted from Bergman, 2004 with modifications)

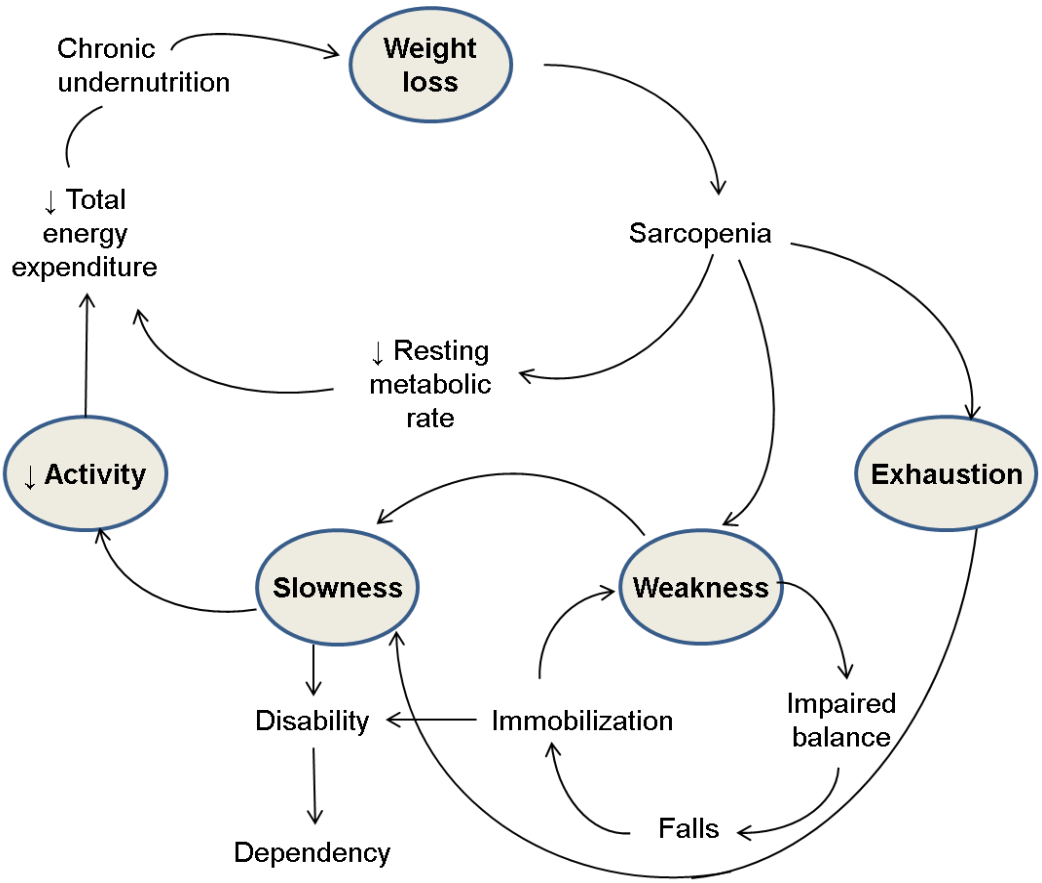


It conceptualizes frailty as having seven components including five items of the Frailty Phenotype and two additional items, namely depression and impaired cognition (Bergman et al., 2004). However, both depression and impaired cognition are psychological factors that could very well be represented as predictors and effects of frailty on its pathways. Having these as components of the frailty specification and at the same time as predictors or effects renders

the task of teasing out their relationship with frailty very challenging. More recently, the integral concept of frailty proposed by Gobbens was built on the Canadian framework. Here, frailty is explicitly specified as having separate physical, psychological, and social domains (Gobbens et al., 2010a). Doing so allows physical frailty to be disaggregated from the other two frailty domains, and in turn facilitates less constrained exploration of the relationship of frailty with its multidimensional predictors and effects. The adoption of this latter approach holds promise for developing frailty specifications that can be usefully applied when investigating relationships on these frailty pathways.

In developing candidate physical frailty specifications for investigating frailty pathways, the CHS frailty phenotype provides a good starting point particularly as it is widely considered the prototype for physical frailty. Its conceptual framework is represented by the cycle of frailty in which its five components are positioned in a set of pathways (Xue et al., 2008) as illustrated in Figure 2.

Figure 2. Modified representation of the cycle of frailty (adapted from Xue 2008)



In this framework, sarcopenia holds a key position in the cycle of frailty in the sense that it is on the main pathway loop that includes weight loss, decreased total energy expenditure, and chronic undernutrition. Moreover, pathways emanating from it eventually lead to important health-related endpoints, namely impaired balance, falls and injuries, immobilization, disability, and dependency. In these pathways to adverse outcomes, weakness and exhaustion are positioned immediately downstream to sarcopenia and slowness immediately follows weakness. Given this framework, it may be argued that among the five components of the CHS frailty phenotype, the cluster of exhaustion, weakness, and slowness appears central to the physical frailty concept and closest in proximity to its adverse outcomes. In addition, two of these five components pose interesting challenges. Firstly, low physical activity is considered a predictor of frailty while its counter, exercise is a modifier of frailty's effect (Daniels et al., 2008; Strawbridge et al., 1998). On this account, it might be best excluded from the set of physical frailty indicators. Indeed, Buchman used the remaining four items to construct a composite measure of physical frailty albeit using body mass index instead of weight loss (Buchman et al., 2009). Secondly, exhaustion may at times be a manifestation of depression in older people. In fact, two out of eight items of the Center for Epidemiologic Studies Depression (CES-D) scale were used to operationalize the component of exhaustion in the original study on the CHS frailty phenotype (Fried et al., 2001). Moreover, depression resides within the psychological dimension, and could itself be a potential target for interventions to reduce frailty and its effects. However, given that exhaustion is more typically related to physical conditions, it is unclear whether dropping it from the set of frailty indicators is necessary. With these points in mind, candidate physical frailty specifications based on the CHS frailty phenotype could omit physical inactivity and possibly exhaustion, thereby retaining three or four of the five original indicators.

Over this backdrop, the aims of this study are twofold. The first is to develop physical frailty specifications that are suitable for investigation of frailty pathways. These will be based on three or four components of the CHS frailty phenotype. The second is to evaluate and compare candidate specifications on their convergent, discriminant, and concurrent validity. The ultimate purpose is to obtain a frailty specification that can be used to quantify the relationships of frailty with its multidimensional predictors and effects. Ultimately, knowledge on these elements can inform broad strategies employing population-level interventions that seek to reduce frailty and its adverse effects in older people.

Methods

Data

Panel data from wave 2 (2004) of the English Longitudinal Study of Ageing (ELSA) (Marmot et al., 2015) provides the requisite information. This is longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013a). ELSA respondents aged 65 to 89 years at wave 2 are included. Those aged 90 years and older have their age merely coded as “90”, and are thus excluded. All participants gave informed consent. Ethical approval for ELSA was granted by the Multicenter Research and Ethics Committee. Ethical oversight for this study is provided by procedures of the London School of Economics Ethics Policy.

Measures

Indicators for physical frailty are based on four components of the CHS frailty phenotype (Fried et al., 2001). *Slowness* is the average gait speed (in m/s) of two attempts at walking a distance of 2.4 m multiplied by -1. *Weakness* is the dominant hand grip strength in kg, which is multiplied by 1.5 for women. The difference in expectation of grip strength mirrors population-independent cut-off values proposed for the CHS frailty phenotype criteria (Saum et al., 2012). After that, values are reversed through multiplying them by -1. *Weight loss* is a binary variable for decrease in weight of more than 5 kg from wave 0 to 2. Weight at wave 0 is used as the reference because this was not measured at wave 1. *Exhaustion* is also a binary variable based on a positive reply to either or both of two items of the CES-D scale on whether the respondent “felt everything they did during the past week was an effort” and “could not get going much of the time in the past week” (Radloff, 1977).

Using three permutations of these indicators, candidate physical frailty specifications are developed. The first specification has all four indicators namely slowness, weakness, exhaustion, and weight loss. Using latent class analysis of the CHS frailty phenotype, estimated probabilities of individual components for frail and non-frail states suggests that slowness and weakness discriminated best between them (Bandeen-Roche et al., 2006). Thus, these two indicators are retained for remaining specifications. The second specification drops weight loss leaving the other three indicators. For the third, exhaustion instead of weight loss is dropped in view of the potential concerns already alluded to.

For psychological frailty, three indicators adapted from the TFI are constructed. Firstly, *impaired cognition* is based on total cognitive index, which combines test scores for memory, and executive function, which are recoded (0 to 49) so that higher scores indicate poorer function. Secondly, *depressive symptoms* are measured by number of positive items in the CES-D scale. Given that the physical frailty indicator of exhaustion is based on two of its eight items, only the remaining six are used. Thirdly, *low resilience* is measured in relation to three facets of

adversity previously proposed (Demakakos et al., 2008). Objective financial adversity is defined as being in the lowest quintile of total non-pension wealth. Self-perceived financial adversity is the report of sometimes or more often having too little money to spend on needs. Widowhood is the change of marital status from being married or single in wave 1 to being widowed in wave 2. The criterion for establishing resilience under these three facets of adversity is a CES-D score of three or less. Each facet is scored in an ordinal manner with “-1” if both adversity and resilience criteria are satisfied, “1” if only the criterion for adversity is satisfied, and “0” if only the criterion for resilience is satisfied or if neither criterion is satisfied. Summing up those for the three facets, a total score ranging from -3 to 3 is obtained where higher scores indicate lower resilience.

For social frailty, three indicators adapted from the TFI and based on previous work on social isolation (Steptoe et al., 2013b) are constructed. Firstly, *loneliness* is measures by the Revised UCLA Loneliness Score, which comprises three items and scored from 3 to 9 (Hughes et al., 2004). Secondly, *poor social integration* is a combination of 5 items (scored 0 to 14) on whether participants have no spouse and partner living with them, had little contact with children, had little contact with other family members, had little contact with friends, and were not a member of any organization, club or society. Little contact was defined as less than monthly contact by meeting, phoning, or writing or email. Thirdly, *poor social support* is the combined scores on three items (score 0 to 54) on whether there is lack positive support, and occurrence of negative support. Lack of positive support is measured by negative answers to questions on “understand the way you feel”, “can rely on if you had a serious problem”, and “can open up to them if you need to talk” with respect to children, other family members, and friends. Negative support is measured by positive answers to questions on whether children, other family members, and friends "criticizes the respondent", "lets the respondent down", and "gets on the nerves of respondent".

The FI (Rockwood & Mitnitski, 2007; Rockwood et al., 2004) is computed as the number of positive items out of 30 illnesses and functional impairments divided by 30, thereby deriving a scalar value of 0 to 1 (Searle et al., 2008). In line with previously proposed cut-off values, people with FI of 0.08 or less are categorized as not frail, those with FI of 0.25 or more are frail, while the remaining are pre-frail (Song et al., 2010).

Statistical Analyses

Confirmatory factor analysis (CFA) is performed in turn for the three candidate physical frailty specifications. Unique factor scores for each participant are obtained for each specification. CFA is then repeated for subgroups defined by gender. Construct validity is assessed by considering convergent and discriminant validity. For convergent validity, functional impairment (number of basic activities of daily living (BADL) and instrumental activities of daily living (IADL) performed with difficulty), comorbidity (number of chronic illnesses), and poor self-rated health are regressed in turn on physical frailty factor scores (Rockwood, 2005). Coefficients of the

latter adjusting for age are obtained. For discriminant validity, Pearson's coefficient is used to quantify the correlation of physical frailty factor scores with those of psychological and social frailty factors. Factor scores for the latter two were also derived from CFA using their respective indicators. Pearson's coefficient higher than 0.90 indicates very high correlation, 0.71 to 0.90 indicates high correlation, 0.51 to 0.70 indicates moderate correlation, 0.31 to 0.50 indicates low correlation, and 0.30 indicates negligible correlation (Hinkle, 2003). To assess concurrent validity, FI is regressed on physical frailty factor scores and their coefficients adjusting for age are examined. For all validity checks, analyses are performed for the whole group and then in subgroups defined by gender.

CFA is performed with Mplus version 7.4 (Muthén & Muthén, 1998-2012) using maximum likelihood estimation with robust standard errors (MLR), which handles missing values by implementing full information maximum likelihood (FIML). MLR is selected over WLSMV (weighted least squares with mean- and variance-adjustment) because of better handling of missing values. For other regression analyses, missing values are handled by multiple imputation using chained equations to generate 20 sets. In using FIML and multiple imputation, the assumption of missing at random (MAR) is held. All other data analyses are performed with Stata version 13.1. Statistical significance is taken at p-value of less than 0.05.

Results

Data of 4,638 people (2,070 male and 2,568 female) aged from 65 to 89 years are analyzed. Their characteristics are summarized in Table 1. They have on average two chronic illnesses. More than one a quarter of them has some degree of functional impairment measured by basic activities of daily living. As expected, physical performance measured by walking speed and hand grip strength is worse among female participants. Frailty measured by both modified CHS frailty phenotype and Frailty Index is more common among them too. Thus, a significant proportion of participants have health issues and functional limitations. Among psychological measures, female participants display less resilience. Somewhat surprisingly, there were only minimal differences in social measures across gender.

Table 1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included for analyses

Variables	All	By gender	
		Male	Female
General:			
Mean age, years (SD)	74.0 (6.3)	73.5 (6.2)	74.3 (6.4)
Female, n/N (%)	2,568/4,638 (55.4)	-	-
Mean chronic disease count (SD)	1.9 (1.4)[1]	1.8 (1.4)[2]	2.0 (1.4)[3]
Number of basic activities of daily living (BADL) items with difficulty, n (%)			
- 0	3,389/4,635 (73.1)	1,560/2,070 (75.4)	1,829/2,565 (71.3)
- 1 or 2	948/4,635 (20.5)	389/2070 (18.8)	559/2,565 (21.8)
- 3 or 4	220/4,635 (4.8)	95/2,070 (4.6)	125/2,565 (4.9)
- 5 or 6	78/4,635 (1.7)	26/2,070 (1.3)	52/2,565 (2.0)
Number of instrumental activities of daily living (IADL) items with difficulty, n/N (%)			
- 0	3,308/4,635 (71.4)	1,593/2,070 (77.0)	1,715/2,565 (66.9)
- 1 or 2	991/4,635 (21.4)	358/2,070 (17.3)	633/2,565 (24.7)
- 3 or 4	236/4,635 (5.1)	77/2,070 (3.7)	159/2,565 (6.2)
- 5 or 6 or 7	100/4,635 (2.2)	42/2,070 (2.0)	58/2,565 (2.3)
Self-rated health, n/N (%)			
- excellent or very good	1,554/4565 (34.0)	674/2,029 (33.2)	880/2,536 (34.7)
- good	1,528/4,565 (33.5)	686/2,029 (33.8)	842/2,536 (33.2)
- fair or poor	1,483/4,565 (32.5)	669/2,029 (33.0)	814/2,536 (32.1)

Physical:			
Mean average walking speed, m/sec (SD)	0.82 (0.28)[4]	0.86 (0.27)[5]	0.78 (0.28)[6]
Hand grip strength (dominant hand), kg (SD)	25.9 (10.2)[7]	33.4 (8.9)[8]	19.6 (6.1)[9]
Exhaustion, n/N (%)	1,490/4,510 (33.0)	568/1,997 (33.0)	992/2,5103(33.0)
Weight loss >5 kg from waves 0 to 2, n/N (%)	587/3,590 (16.4)	255/1,608 (15.9)	332/1,982 (16.8)
Frailty status by modified CHS frailty phenotype, n/N (%)			
- Not frail	866/3,242 (26.7)	485/1,462 (33.2)	381/1,780 (21.4)
- Pre-frail	1,758/3,242 (54.2)	775/1,462 (53.0)	983/1,780 (55.2)
- Frail	618/3,242 (19.1)	202/1,462 (13.8)	416/1,780 (33.4)
Frailty status by Frailty Index [a], n/N (%)			
- Not frail	1,444/3,647 (39.6)	774/1,639 (47.2)	670/2,008 (33.4)
- Pre-frail	1,486/3,647 (40.8)	629/1,639 (38.4)	857/2,008 (42.7)
- Frail	717/3,647 (20.7)	236/1,639 (24.4)	481/2,008 (33.9)
Psychological:			
Mean cognitive impairment score (SD)	18.9 (6.5)[10]	19.3 (6.4)[11]	18.5 (6.5)[12]
Mean CESD-8 [c] score (SD)	1.7 (2.0)[13]	1.3 (1.7)[14]	1.9 (2.1)[15]
Mean low resilience score [d] (SD)	0.20 (0.83)[16]	0.13 (0.80)[17]	0.26 (0.84)[18]
Social:			
Loneliness score [e] (SD)	4.2 (1.5)[19]	4.0 (1.4)[20]	4.3 (1.6)[21]
Mean poor social support score [f] (SD)	13.7 (7.0)[22]	14.7 (7.0)[23]	12.9 (6.8)[24]
Mean poor social integration score [g] (SD)	6.6 (2.5)[25]	6.7 (2.6)[26]	6.5 (2.5)[27]
Outcome:			
Two-year mortality, n/N (%)	278/4,638 (6.0)	147/2,070 (7.1)	131/2,568 (5.1)

[a] Frailty Index: 30 items (score 0 to 1)

[b] Cognitive impairment score: score 0 to 49

[c] CESD-8: Center for Epidemiologic Studies Depression Scale - 8 items (score 0 to8)

[d] Low resilience score: 3 items (score 3 to 12)

[e] Loneliness score: Revised UCLA Loneliness Score - 3 items (score 3 to 9)

[f] Low social support score: 18 items (score 0 to 54)

[g] Poor social integration score: 6 items (score 0 to 15)

Unless indicated otherwise, N = 4,638 for all, 2,070 for male, and 2,568 for female.

N = [1]4,608 [2]2,052 [3]2,556 [4]4,092 [5]1,826 [6]2,266 [7]3,869 [8]1,760 [9]2,109 [10]4,348 [11]1,945 [12]2,403 [13]4,479 [14]1,987 [15]2,492 [16]3,854 [17]1,946 [18]2,460 [19]3,854 [20]1,746 [21]2,106 [22]3,339 [23]1,529 [24]1,810 [25]3,267 [26]1,506 [27]1,761

Table 2 summarizes the results of CFA for the three physical frailty specifications. For four indicators, slowness contributes most to the physical frailty factor whereas weakness and

exhaustion do so to a lesser extent. Weight loss contributes much less. Similarly, for three indicators including exhaustion, slowness contributes more than weakness and exhaustion do. On the other hand, for three indicators including weight loss, weakness contributes most with slowness doing so less. Here again, weight loss contributes minimally. These patterns are generally consistent across gender with only minor differences seen.

Table 2. Measurement model for three specifications of physical frailty using confirmatory factor analysis (CFA) with full information maximum likelihood (FIML)

Physical frailty specification	Standardized coefficient (standard error)		
	All	**By gender**	
		Male	**Female**
Four indicators:			
Slowness [a]	0.76 (0.03)	0.73 (0.05)	0.77 (0.03)
Weakness [b]	0.54 (0.02)	0.47 (0.04)	0.56 (0.03)
Exhaustion [c]	0.55 (0.02)	0.56 (0.04)	0.54 (0.03)
Weight loss [d]	0.28 (0.03)	0.24 (0.06)	0.31 (0.04)
Three indicators including exhaustion:			
Slowness [a]	0.78 (0.03)	0.79 (0.05)	0.78 (0.04)
Weakness [b]	0.52 (0.02)	0.43 (0.04)	0.55 (0.03)
Exhaustion [c]	0.54 (0.03)	0.53 (0.04)	0.54 (0.03)
Three indicators including weight loss:			
Slowness [a]	0.60 (0.05)	0.45 (0.08)	0.68 (0.06)
Weakness [b]	0.68 (0.05)	0.76 (0.13)	0.63 (0.06)
Weight loss [d]	0.30 (0.03)	0.26 (0.06)	0.33 (0.04)

p-values are <0.05 for all coefficients

[a] Slowness: mean gait speed multiplied by a factor of -1

[b] Weakness: dominant hand grip strength multiplied by a factor of -1 (males) or -1.5 (females)

[c] Exhaustion: positive response to either or both of two items of CES-D scale on “could not get going much of the time in the past week” and “felt everything they did during the past week was an effort”

[d] Weight loss: decrease in weight of more than 5 kg from wave 0 to wave 2

N = 4,547 (all) 2,019 (male) 2,528 (female) for first two specifications; N=4,440 (all) 1,985 (male) 2,455 (female) for the third specification

Factor loading patterns reflect stronger correlation among slowness, weakness, and exhaustion, compared with their correlation with weight loss. These differences are supported by tetrachoric correlation coefficients of weight loss with the other three indicators (0.16 to 0.19) being much lower than those between the other three (0.29 to 0.43) for the whole group as shown in Table 6 of the Supplementary Materials. Histograms showing approximately normal

distribution of derived factor scores for the three physical frailty specifications are provided in Figure 3 of the Supplementary Materials.

In terms of convergent validity, Table 3 shows that for one standard deviation (SD) increase in the physical frailty factor score, the number of chronic diseases increases by 0.28 to 0.35 across specifications and gender after adjusting for age. Similarly, for one SD increase in physical frailty factor score, the combined number of items of BADL and IADL performed with difficulty increases by 0.36 to 0.51. Finally, for one SD increase in physical frailty factor score, the number of categories of poor self-rated health increase by 0.38 to 0.54.

Table 3. Linear regression of chronic disease, functional status, and self-rated health on factor scores for three physical frailty specifications adjusted for age: standardized coefficients (95% confidence interval)

	All	By gender	
		Male	Female
Number of chronic diseases:			
4 indicators	0.35 (0.32 to 0.38) [a]	0.34 (0.29 to 0.38)	0.34 (0.30 to 0.39)
3 indicators (including exhaustion)	0.34 (0.31 to 0.37) [b]	0.33 (0.29 to 0.38)	0.34 (0.30 to 0.38)
3 indicators (including weight loss)	0.30 (0.27 to 0.33) [c]	0.28 (0.23 to 0.33)	0.29 (0.25 to 0.34)
Number of basic and instrumental activities of daily living items performed with difficulty:			
4 indicators	0.49 (0.46 to 0.52) [d]	0.46 (0.42 to 0.50)	0.51 (0.47 to 0.55)
3 indicators (including exhaustion)	0.48 (0.46 to 0.51) [e]	0.45 (0.41 to 0.50)	0.50 (0.46 to 0.54)
3 indicators (including weight loss)	0.39 (0.36 to 0.43) [f]	0.36 (0.31 to 0.41)	0.41 (0.37 to 0.45)
Categories of poor self-rated health:			
4 indicators	0.51 (0.48 to 0.53) [g]	0.48 (0.43 to 0.52)	0.54 (0.51 to 0.58)
3 indicators (including exhaustion)	0.50 (0.47 to 0.53) [h]	0.47 (0.43 to 0.51)	0.53 (0.50 to 0.57)
3 indicators (including weight loss)	0.40 (0.37 to 0.43) [i]	0.38 (0.33 to 0.43)	0.44 (0.40 to 0.48)

P-values are <0.05 for all coefficients.

[a] AIC/BIC = 15,902/15,922 r^2 = 0.12; [b] AIC/BIC = 15,917/15,935 r^2 = 0.12; [c] AIC/BIC = 16,071/16,090 r^2 = 0.09; [d] AIC/BIC = 18,572/18,591 r^2 = 0.25; [e] AIC/BIC = 18,600/18,620 r^2 = 0.25; [f] AIC/BIC = 19,048/19,067 r^2 = 0.17; [g] AIC/BIC = 13,018/13,038 r^2 = 0.23; [h] AIC/BIC = 13,047/13,066 r^2 = 0.22;

[i] AIC/BIC = 13,483/13,503; r^2 = 0.14;

N = 4,638 for all, 2,070 for male, and 2,568 for female

Regression coefficients are of similar magnitude across gender except for the specification with three indicators including weight loss where they are clearly higher for female participants. Overall, regression coefficients for physical frailty factor scores with four indicators and with three indicators including exhaustion are very similar. However, their coefficients are higher

than those with three indicators including weight loss, particularly for prediction of BADL and ADL difficulties, as well as poor self-rated health where there is minimal or no overlap of confidence intervals. The likely explanation is that as individual indicators, slowness, weakness, and exhaustion predict these outcomes better than weight loss does. This is supported by the results of linear regression analyses shown in Table 7 of the Supplementary Materials, which show that slowness and exhaustion predict these three outcomes best, followed distantly by weakness, and finally, weight loss. Notably, Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) values for models with the first two specifications are similar, while those with the third specification are higher (see footnote of Table 3). This means that the goodness-of-fit of models with the first two specifications are similar but better than those with the third specification. In addition, r-squared values and therefore, the variance explained for models with the first two specifications are also very similar but higher than those with the third specification (see footnote of Table 3). Overall, these findings indicate that the first two physical frailty specifications have higher convergent validity than the third.

For discriminant validity, Table 4 shows that physical frailty factor scores for the first two specifications have low correlation with psychological frailty and negligible correlation with social frailty. In contrast, physical frailty factor score for the third specification has negligible correlation with the other frailty domains, suggesting higher discriminant validity. Nevertheless, all Pearson's coefficients are well below the arbitrary 0.85 cut-off level where greater values are regarded as indicating low discriminant validity. Equally important, the correlation coefficients between the three different physical frailty specifications (“multi-method”) are in the region of 0.88 to 1.00 and therefore much larger than those between physical frailty and psychological frailty or social frailty (“multi-trait”), which are from 0.12 to 0.41. This further supports discriminant validity. The corresponding Modified Multi-trait Multi-Method (MTMM) Matrix is provided in Table 8 of the Supplementary Materials.

Where concurrent validity is concerned, multiple linear regression analyses obtained statistically significant coefficients for all three physical frailty specifications as shown in Table 5. For one SD increase physical frailty factor scores, the FI increases by 0.61 to 0.76 SD. There are minor variations of regression coefficients across gender. Overall, regression coefficients are higher for specifications with four indicators and with three indicators including exhaustion, than those for the third specification. Yet again, AIC and BIC values for models with the first two specifications are similar while those with the third specification are higher. R-squared values are almost equivalent for the first two specifications and higher than those of the third (see footnote of Table 5). This means that the goodness-of-fit of models and variance explained by models with the first two specifications are similar but better or higher than those with the third specification. Together, these findings indicate that concurrent validity for the first two specifications is higher than that for the third.

Table 4. Correlation of factor scores for three physical frailty specifications with those for psychological and social frailty, and between factor scores for three physical frailty specifications (modified multi-trait multi-method analysis): Pearson's coefficient (95% confidence interval)

	Pearson's correlation coefficient (Standard error)		
	All	By gender	
		Male	Female
Between physical and psychological frailty:			
4 indicators	0.41 (0.38 to 0.43)	0.38 (0.34 to 0.42)	0.40 (0.36 to 0.43)
3 indicators (including exhaustion)	0.40 (0.37 to 0.43)	0.38 (0.34 to 0.42)	0.39 (0.35 to 0.43)
3 indicators (including weight loss)	0.29 (0.26 to 0.32)	0.26 (0.22 to 0.30)	0.28 (0.24 to 0.32)
Between physical and social frailty:			
4 indicators	0.16 (0.13 to 0.20)	0.18 (0.14 to 0.23)	0.17 (0.12 to 0.22)
3 indicators (including exhaustion)	0.16 (0.13 to 0.19)	0.18 (0.13 to 0.23)	0.17 (0.12 to 0.21)
3 indicators (including weight loss)	0.12 (0.08 to 0.15)	0.13 (0.08 to 0.18)	0.14 (0.09 to 0.18)
Between specifications of physical frailty:			
3 indicators (including exhaustion) and 3 indicators (including weight loss)	0.89 (0.87 to 0.90)	0.88 (0.86 to 0.90)	0.89 (0.87 to 0.90)
4 indicators and 3 indicators (including exhaustion)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
3 indicators (including weight loss) and 4 indicators	0.90 (0.89 to 0.91)	0.90 (0.88 to 0.91)	0.90 (0.89 to 0.92)

P-values are <0.05 for all correlation coefficients.

N = 4,638 for all, 2,070 for male, and 2,568 for female

Table 5. Linear regression of Frailty Index on factor scores for three physical frailty specifications adjusted for age with multiple imputation: standardized coefficients

	All	By gender	
		Male	Female
4 indicators	0.76 (0.73 to 0.79) [a]	0.76 (0.71 to 0.80)	0.76 (0.72 to 0.79)
3 indicators (including exhaustion)	0.75 (0.72 to 0.78) [b]	0.74 (0.70 to 0.79)	0.74 (0.71 to 0.78)
3 indicators (including weight loss)	0.62 (0.59 to 0.65) [c]	0.61 (0.55 to 0.66)	0.61 (0.57 to 0.65)

P-values are <0.05 for all physical frailty factor score coefficients.

[a] AIC/BIC = -6,998/-6,978 r^2 = 0.44; [b] AIC/BIC = -6,918/-6,899 r^2 = 0.43; [c] AIC/BIC = -5,977/-5,957 r^2 = 0.30;

N = 4,638 for all, 2,070 for male, and 2,568 for female

As sensitivity analysis, the CFA for physical frailty and regressions for evaluating convergent and concurrent validity are repeated using the WLSMV estimator. Comparison of coefficients obtained using MLR and WLSMV estimators are provided in Table 9 to 11 in the Supplementary Materials. Overall, only trivial differences are observed in the coefficients, which do not change the interpretation of the results.

Discussion

This study reports the development of frailty specifications for investigating multidimensional predictors and effects of frailty such as those proposed by the working framework of the Canadian Initiative on Frailty and Aging. Rather than adopting a broad definition, narrower focus on physical frailty is employed to enhance prospective application when investigating its relationship with multidimensional elements on frailty pathways. In addition, physical frailty is viewed as a construct and is thus developed as a factor. Unlike the case with established frailty instruments including the CHS frailty phenotype where contribution of separate components is arbitrarily assumed and then fixed, latent variable analysis through CFA is performed to empirically derive the relationship of each indicator with the physical frailty factor. Furthermore, CFA allows measurement error to be accounted for, which is particularly relevant as performance measures are used as indicators This combined approach represents an advance on the frailty specification proposed in the working framework of the Canadian Initiative on Frailty and Aging and further builds on the that put forth in the integral concept of frailty (Bergman et al., 2004; Gobbens et al., 2010a).

To begin with, content validity is retained given that the selected indicators used are drawn from the original components of the CHS frailty phenotype, which is still widely regarded as the prototype of physical frailty. Higher weightage is accorded to slowness, weakness, and exhaustion given the relative importance of their positions in the cycle of frailty. Thus, the physical frailty specification with three indicators including exhaustion could be considered as having the essential set of indicators. Furthermore, for candidate specifications examined, slowness is central to the physical frailty factor except for the case with three indicators including weight loss. Weight loss clearly contributes little and an argument may be made for its exclusion as an indicator at least based on the findings from this study. It is notable that our results are generally consistent across gender. More crucially, higher convergent and concurrent validity with four indicators and with three indicators including exhaustion are demonstrated over the third specification. Although the latter performs better on discriminant validity, the first two specifications have sufficiently low correlation with psychological and social frailty to suggest that overlap of their constructs is probably not large enough to be of practical concern. This is important when examining the relationship of physical frailty with multidimensional elements including those which are closely related to or are themselves deployed as indicators of psychological and social frailty.

Given these findings, physical frailty specifications with four indicators and that with three indicators including exhaustion appear to be suitable candidates for use in investigation of frailty pathways. Minimal contribution of weight loss as the fourth indicator suggests that three indicators, namely slowness, weakness, and fatigue may be sufficient to represent physical frailty. However, the performance of these physical frailty specifications in predicting adverse health-related outcomes needs to be separately evaluated. This is an issue that is addressed in further research.

Although encouraging, these findings should to be viewed in the context of the study limitations. Firstly, data from only one population is used and therefore there is uncertainty on the extent to which these findings may be generalized to other populations. To address this issue, the measurement model from this study needs to be applied to data from other populations in future work. Next, secondary data is used. The consequence is that choice of variables representing physical frailty is inevitably restricted. Nevertheless, selected variables arguably have face validity. The major challenge is the quantification of weight loss, which is by necessity across the span of four years due to weight measurements not being available in wave 1. It remains to be seen whether weight loss may perform better as an indicator when change is measured across a shorter period such as two years. Thirdly, missing data may introduce bias in our analyses. Multiple imputation is used to handle this issue here and requires the missing at random (MAR) assumption. Notwithstanding the inevitable uncertainty on the extent of bias introduced, this is not likely to be large enough to change the conclusions on the validity of physical frailty specifications evaluated here.

On the other hand, the strengths of this study include the use of ELSA, which offers representative, reliable and high quality data that has produced a wealth of information on how older people age in England. Moreover, the relatively large sample size allows greater precision in estimation. Lastly, availability of physical performance measures for two physical frailty indicators provides more detailed information than questionnaire data alone would.

In conclusion, narrowing of the frailty specification to that of physical frailty is argued on the grounds that multidimensional elements on frailty pathways are best excluded from the set of its indicators. Suitable indicators are drawn from components of the CHS frailty phenotype and include slowness, weakness, and exhaustion with or without weight loss. In addition to retaining face and content validity, these two physical frailty specifications have demonstrated reasonable convergent, discriminatory, and concurrent validity using the data of older people living in England. Together, they hold promise as physical frailty specifications to be applied in the investigation of frailty pathways.

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Supplementary Materials

Table 6. Tetrachoric correlations between indicators for physical frailty specified as binary variables: coefficients (N)

	Slowness	Weakness	Exhaustion	Weight loss
All				
Slowness	1.00 (4,092)			
Weakness	0.43 (3,530)	1.00 (3,869)		
Exhaustion	0.43 (4,067)	0.29 (3,844)	1.00 (4,510)	
Weight loss	0.18 (3,325)	0.19 (3,509)	0.16 (3,572)	1.00 (3,590)
Male				
Slowness	1.00 (1,826)			
Weakness	0.43 (1,604)	1.00 (1,760)		
Exhaustion	0.41 (1,812)	0.24 (1,742)	1.00 (1,997)	
Weight loss	0.13 (1,484)	0.22 (1,591)	0.17 (1,595)	1.00 (1,608)
Female				
Slowness	1.00 (2,266)			
Weakness	0.41 (1,926)	1.00 (2,109)		
Exhaustion	0.43 (2,255)	0.31 (2,102)	1.00 (2,513)	
Weight loss	0.22 (1,841)	0.17 (1,918)	0.15 (1,977)	1.00 (1,982)

P-values are <0.05 for all coefficients

Binary variables for slowness and weakness are created by adopting a proposed modification of the Fried frailty criteria that uses population-independent cutpoints (Saum et al., 2012).

Table 7. Linear regression of chronic disease, functional status, and self-rated health on four binary components of the CHS frailty phenotype adjusted for age with multiple imputation: standardized coefficients (95% confidence interval)

	All	By gender	
		Male	Female
Number of chronic diseases:			
Slowness	0.71 (0.62 to 0.79)	0.68 (0.55 to 0.82)	0.70 (0.58 to 0.82)
Weakness	0.37 (0.28 to 0.46)	0.31 (0.16 to 0.46)	0.38 (0.25 to 0.50)
Exhaustion	0.74 (0.66 to 0.83)	0.83 (0.69 to 0.96)	0.66 (0.55 to 0.77)
Weight loss	0.29 (0.16 to 0.42)	0.32 (0.12 to 0.51)	0.26 (0.55 to 0.77)
Number of basic and instrumental activities of daily living items performed with difficulty:			
Slowness	1.40 (1.27 to 1.52)	1.34 (1.16 to 1.52)	1.42 (1.24 to 1.59)
Weakness	0.78 (0.63 to 0.93)	0.72 (0.52 to 0.93)	0.79 (0.59 to 0.98)
Exhaustion	1.65 (1.53 to 1.77)	1.60 (1.43 to 1.78)	1.66 (1.51 to 1.82)
Weight loss	0.54 (0.29 to 0.79)	0.48 (0.08 to 0.88)	0.57 (0.30 to 0.84)
Categories of poor self-rated health:			
Slowness	0.79 (0.72 to 0.86)	0.81 (0.71 to 0.91)	0.79 (0.70 to 0.88)
Weakness	0.44 (0.37 to 0.52)	0.42 (0.30 to 0.53)	0.50 (0.40 to 0.60)
Exhaustion	0.92 (0.86 to 0.99)	0.94 (0.85 to 1.05)	0.92 (0.84 to 1.00)
Weight loss	0.34 (0.24 to 0.44)	0.35 (0.19 to 0.50)	0.33 (0.20 to 0.47)

P-values are <0.05 for all coefficients.

N = 4,638 for all, 2,070 for male, and 2,568 for female

Table 8. Modified Multi-trait Multimethod Matrix for physical, psychological, and social frailty: Pearson's coefficients for the whole group

		Physical frailty			Psychological frailty	Social frailty
		4 indicators	3 indicators including exhaustion	3 indicators including weight loss		
Physical frailty	4 indicators	**1.00**	**1.00**	**0.90**	0.41	0.16
	3 indicators including exhaustion	**1.00**	**1.00**	**0.89**	0.40	0.16
	3 indicators including weight loss	**0.90**	**0.89**	**1.00**	0.29	0.12
Psychological frailty		0.41	0.40	0.29	1.00	-
Social frailty		0.16	0.16	0.12	-	1.00

N = 4,638

Table 9. Measurement model for three specifications of physical frailty with confirmatory factor analysis (CFA) using maximum likelihood with robust standard errors (MLR) compared with weighted least squares with mean- and variance-adjustment (WLSMV)

Physical frailty specification	Standardized coefficient (standard error)	
	MLR	WLSMV
Four indicators:		
Slowness [a]	0.76 (0.03)	0.74 (0.02)
Weakness [b]	0.54 (0.02)	0.54 (0.02)
Exhaustion [c]	0.55 (0.02)	0.58 (0.02)
Weight loss [d]	0.28 (0.03)	0.28 (0.03)
Three indicators including exhaustion:		
Slowness [a]	0.78 (0.03)	0.76 (0.02)
Weakness [b]	0.52 (0.02)	0.53 (0.02)
Exhaustion [c]	0.54 (0.03)	0.57 (0.02)
Three indicators including weight loss:		
Slowness [a]	0.60 (0.05)	0.58 (0.05)
Weakness [b]	0.68 (0.05)	0.70 (0.05)
Weight loss [d]	0.30 (0.03)	0.29 (0.03)

P-values are <0.05 for all coefficients.

[a] Slowness: mean gait speed multiplied by a factor of -1

[b] Weakness: dominant hand grip strength multiplied by a factor of -1 (males) or -1.5 (females)

[c] Exhaustion: positive response to either or both of two items of CES-D scale on “could not get going much of the time in the past week” and “felt everything they did during the past week was an effort”

[d] Weight loss: decrease in weight of more than 5 kg from wave 0 to wave 2

N = 4,547 for first two specifications; N = 4,440 for the third specification

Table 10. Linear regression of chronic disease, functional status, self-rated health on factor scores, and Frailty Index for three physical frailty specifications adjusted for age using maximum likelihood with robust standard errors (MLR) compared with weighted least squares with mean- and variance-adjustment (WLSMV): standardized coefficients (95% confidence interval)

Physical frailty specifications	Number of chronic diseases		Number of basic and instrumental activities of daily living items performed with difficulty		Categories of poor self-rated health		Frailty Index	
	MLR	WLSMV	MLR	WLSMV	MLR	WLSMV	MLR	WLSMV
4 indicators	0.35 (0.32 to 0.38)	0.35 (0.32 to 0.38)	0.49 (0.46 to 0.52)	0.49 (0.46 to 0.52)	0.51 (0.48 to 0.53)	0.50 (0.48 to 0.53)	0.76 (0.73 to 0.79)	0.76 (0.73 to 0.79)
3 indicators (including exhaustion)	0.34 (0.31 to 0.37)	0.34 (0.31 to 0.37)	0.48 (o.46 to 0.51)	0.48 (0.45 to 0.51)	0.50 (0.47 to 0.53)	0.50 (0.47 to 0.53)	0.75 (0.72 to 0.78)	0.75 (0.72 to 0.78)
3 indicators (including weight loss)	0.30 (0.27 to 0.33)	0.29 (0.26 to 0.32)	0.39 (0.36 to 0.43)	0.38 (0.35 to 0.41)	0.40 (0.37 to 0.43)	0.39 (0.36 to 0.42)	0.62 (0.59 to 0.65)	0.61 (0.57 to 0.64)

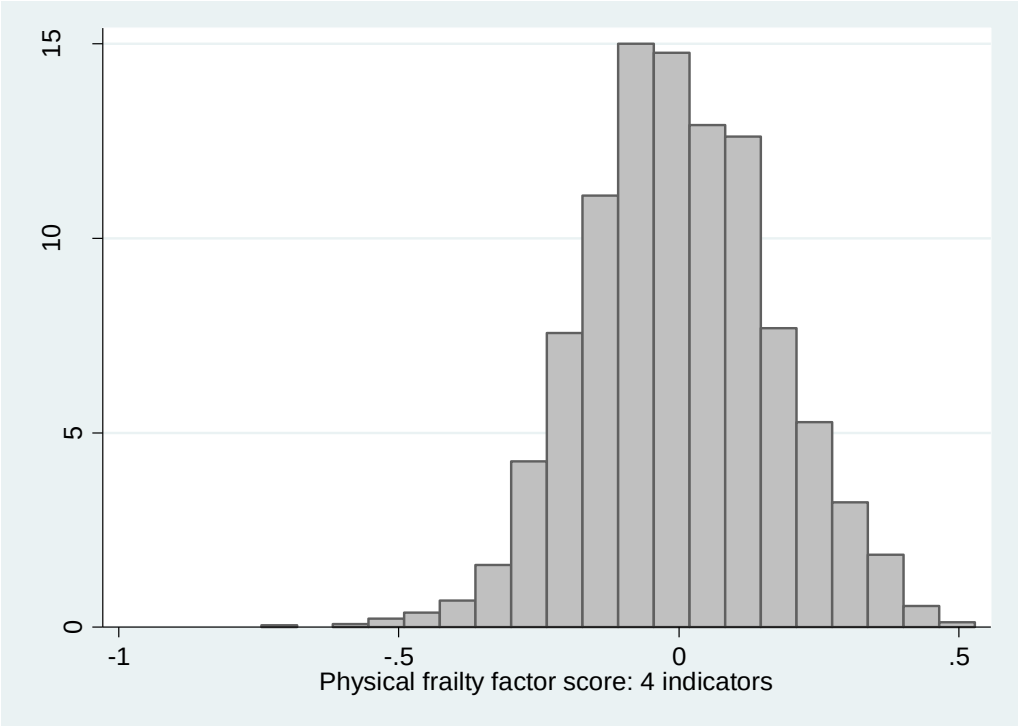
N = 4,638 for all, 2,070 for male, and 2,568 for female

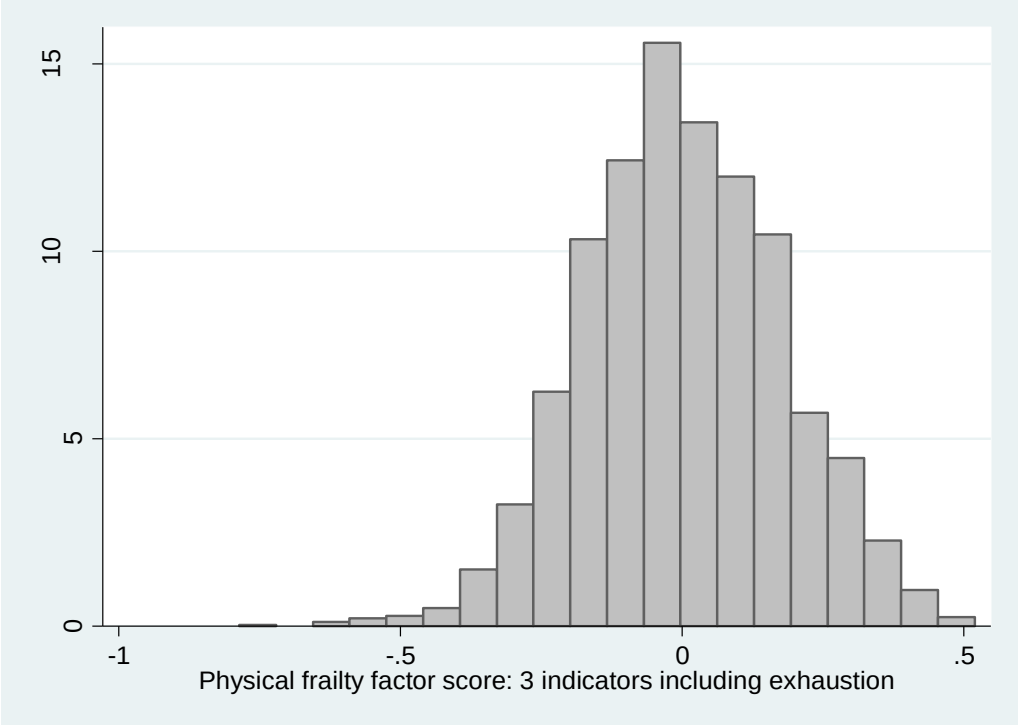
Table 11. Correlation of factor scores for three physical frailty specifications with those for psychological and social frailty using maximum likelihood with robust standard errors (MLR) compared with weighted least squares with mean- and variance-adjustment (WLSMV): Pearson's coefficient (95% confidence interval)

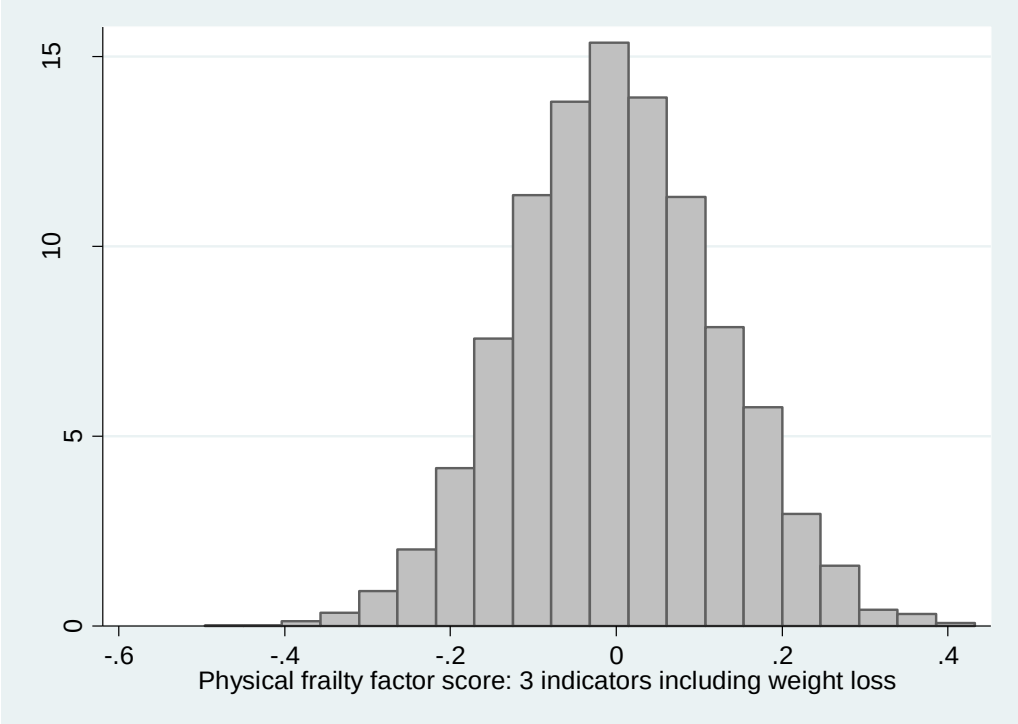
Physical frailty specifications	Psychological frailty		Social frailty	
	MLR	WLSMV	MLR	WLSMV
4 indicators	0.41 (0.38 to 0.43)	0.41 (0.38 to 0.43)	0.16 (0.13 to 0.20)	0.16 (0.13 to 0.20)
3 indicators (including exhaustion)	0.40 (0.37 to 0.43)	0.40 (0.37 to 0.43)	0.16 (0.13 to 0.19)	0.16 (0.13 to 0.19)
3 indicators (including weight loss)	0.29 (0.26 to 0.32)	0.29 (0.26 to 0.31)	0.12 (0.08 to 0.15)	0.12 (0.08 to 0.15)

N = 4,638 for all, 2,070 for male, and 2,568 for female

Figure 3. Distribution of factor scores for the three physical frailty specifications







N = 4,547 for first two specifications; N = 4,440 for the third specification

5.3 Further thoughts

I have argued in favor of a narrower physical frailty specification for investigation of frailty pathways to avoid overlap of its construct with psychological and social conditions on these pathways. I have also discussed the face and content validity of two physical frailty specifications based on the original CHS frailty phenotype, which has five components. The first specification has three indicators namely, slowness, weakness, and exhaustion, while the second has four indicators with the addition of weight loss.

Following that, I demonstrate construct validity of these two physical frailty specifications through the findings on convergent and discriminant validity. Convergent validity is shown by higher physical frailty factor scores being significantly associated with chronic diseases, functional impairment, and poor self-rated health. These conditions are expected to present or be more severe with increasing physical frailty. On the other hand, discriminant validity is shown by their factor scores having low correlation with psychological and social frailty. This lends support to physical frailty as specified, being a distinct construct in relation to the other two domains of frailty. Furthermore, concurrent validity is shown in that their factor scores increase with higher Frailty Index (FI) values. The latter is another established instrument for measuring frailty, but based on the different concept of deficit accumulation.

With these conclusions, I will now proceed with evaluating predictive validity of the two candidate specifications for physical frailty.

6 Second Paper

6.1 Introduction

Having demonstrated construct and concurrent validity of the two candidate physical frailty specifications, one with four indicators and the other with three indicators including exhaustion, I now turn the attention to the question of their predictive validity. While prediction by no means implies causation, it is nevertheless an important attribute that should be possessed by any candidate physical frailty specification. The preceding literature review revealed that the majority of frailty instruments available are strong predictors of future adverse outcomes such as death and disability, and that the most prominent instruments have approximately equivalent ability to do so. This sets the stage for the task at hand.

Beyond merely demonstrating that the two candidate physical frailty specifications can predict these adverse outcomes, I will focus on two additional issues. Firstly, these candidate specifications with three or four indicators should ideally have equivalent or almost equivalent predictive ability as the specification with five indicators, which fully represents the CHS frailty phenotype (Fried et al., 2001). If so, this lends further support for the use of these subsets of the five indicators. Secondly, the candidate specifications should have predictive ability similar to that of another established frailty instrument, namely the Frailty Index (FI) (Rockwood & Mitnitski, 2007) . Having predictive ability that approximates that of FI certainly makes a stronger case for the suitability of candidate specifications.

To assess their predictive ability, data from consecutive waves of the English Longitudinal Study of Ageing (ELSA) will again be used. Predicted adverse outcomes that are important to older people, their families, and wider society are selected. They are death, functional impairment, poor self-rated health, and poor quality of life. A special challenge faced concerns death being a joint outcome or competing risk with the other three outcomes. Predicting the last three outcomes without considering the possibility of death occurring may introduce bias. Although there are sophisticated methods of handling this situation, I will for now opt for the simpler approach of restricting analyses to survivors when evaluating prediction of these three outcomes. This facilitates ease of interpreting the results. Moreover, this is a reasonable approximation of the truth if the mortality rate for respondents of ELSA is relatively low, as anticipated.

In the following paper, some of the foregoing key points are unavoidably repeated as this is a self-contained journal article. References specifically for this paper are in a separate list just before the Supplementary Materials (pages 102 and 103). Relevant Mplus input files are provided in the Appendix. At the time of writing, a version of this paper is being considered for publication in a gerontology journal.

6.2 Predictive Validity of Two Physical Frailty Specifications Developed for Investigation of Frailty Pathways in Older People

Abstract

This study evaluates the predictive validity of two physical frailty specifications with three indicators, namely slowness, weakness, and exhaustion, and four indicators with addition of weight loss, which were developed for investigating frailty pathways. For 4,368 respondents aged 65 to 89 years from wave 2 of the English Longitudinal Study of Ageing, prediction of death, basic and instrumental activities of daily living (BADL and IADL) difficulty, and poor quality of life (reverse of Control, Autonomy, Self-realization, and Pleasure or CASP-19) at wave 3 by factor scores for these two candidate specifications is compared with those of alternative specifications with three and five indicators, and Frailty Index (FI), using c-statistics, standardized coefficients, and r-squared values. The candidate specifications predict these outcomes as well or better than the alternative with three indicators, but marginally worse than that with five indicators. Compared with FI, they predict death and poor quality of life similarly, but perform worse for functional impairment. Minor differences are observed across gender. Predictive validity of the two candidate physical frailty specifications with three and four indicators is demonstrated for death, functional impairment, and poor quality of life two years later. These findings offer evidence to support their suitability for investigating frailty pathways.

Keywords

Death, functional impairment, quality of life, frailty phenotype, frailty index

Introduction

Frailty is defined as a state where there is increased vulnerability to developing increased dependency and mortality with exposure to stressors (Morley et al., 2013). It is estimated that one out of every 10 community-dwelling older people is frail. While a plethora of instruments developed to identify frailty in older people are available (Sternberg et al., 2011), different instruments are thought to be best suited for different purposes (Martin & Brighton, 2008). The choice of instruments for investigation of frailty pathways that incorporate predictors and effects has received some degree of attention in recent years. In developing a working framework for understanding frailty, the Canadian Initiative on Frailty and Aging incorporated biological, psychological, social, and environmental factors across the life course as predictors of frailty, and as modifiers along pathways from frailty to its adverse outcomes. In this framework, seven core components of frailty were proposed. They are weakness, poor endurance, reduced physical activity, slow gait, unintentional weight loss, cognitive decline, and depressive symptoms (Bergman et al., 2004). Of these components, five represent the physical while two represent the psychological dimensions of frailty. Furthermore, conditions represented by these components may be on frailty pathways, and thereby exacerbating the challenges of examining the relationship of frailty with these very elements. On the basis of the Canadian framework, the integral conceptual model of frailty was subsequently proposed with the main difference being that frailty is explicitly specified as having distinct physical, psychological, and social domains (Gobbens et al., 2010a). This allows physical frailty to be disaggregated from the other two frailty domains. This in turn permits less constrained exploration of the relationship of frailty with its multidimensional predictors and effects. The Tilburg Frailty Indicator (TFI) operationalizes this frailty concept (Gobbens et al., 2010b). The adoption of this approach holds promise for developing frailty specifications that can be applied when investigating relationships along these frailty pathways.

In developing frailty specifications restricted to the physical domain, the Cardiovascular Health Study (CHS) frailty phenotype (Fried et al., 2001) is an excellent point of reference. The frailty phenotype is arguably the most widely adopted among existing frailty concepts (Buta et al., 2016). It conceptualizes frailty as being a geriatric syndrome resulting from decline in multiple physiologic systems, and operationalized by requiring the presence of at least three of its five components: shrinking (unintentional weight loss of at least 5% in the prior year), weakness (hand grip strength in the lowest quintile adjusting for gender and body mass index), poor endurance and energy (self-reported exhaustion), slowness (slowest quintile of the population on the basis of 15-feet walk adjusting for gender and standing height), and low physical activity level (lowest gender-specific quintile of weighted score of kilocalories expended per week based on self-report). Sarcopenia, which is the loss of muscle mass and function that occurs with increasing age (Rolland et al., 2008), is closely related to the frailty phenotype (Mijnarends et al., 2015), and considered the biological substrate of physical frailty (Landi et al., 2015). It is the condition underpinning the frailty phenotype concept, and holds a key position on the cycle of frailty (Xue et al., 2008). In the latter, pathways emanating from sarcopenia lead to

manifestations of the frailty phenotype, namely slowness, weakness, and exhaustion, which may in turn lead to adverse health-related outcomes including functional dependency. This frailty specification predicted mortality at three years with an adjusted hazard ratio (HR) of 2.24. Worsening activities of daily living disability over three years could also predicted with adjusted HR of 1.98 (Fried et al., 2001). A modification of the frailty phenotype developed by Buchman comprises four out of the five components of the frailty phenotype. Physical activity is omitted and weight loss is replaced by body mass index. The ability to predict death, and future disability was retained (Buchman et al., 2011; Buchman et al., 2009).

Thus, physical frailty specifications with their indicators based on different permutations of the five components of the frailty phenotype are developed. In selecting the appropriate combinations of these indicators for candidate physical frailty specifications, physical inactivity is excluded as it represents a predictor of physical frailty that is amenable to interventions, and that could also potentially reduce its adverse effects, prevent or delay its onset, and slow its progression (Landi et al., 2010). Using the remaining components, specifications with *e*ither three indicators, namely slowness, weakness, and exhaustion, or four indicators with the addition of weight loss had their construct and concurrent validity demonstrated (Ding, 2016). Of note, the second specification is analogous to the modification of the frailty phenotype using four measures (Buchman et al., 2011).

As the next step, the predictive validity of these two candidate physical frailty specifications is assessed to further evaluate their suitability for application in the investigation of relationships on frailty pathways. It is important for candidate physical frailty specifications to be able to predict important adverse outcomes reasonably well, and if possible, to the extent that established frailty instruments do. Only then can we be confident that these specifications represent suitable concepts of physical frailty for investigating frailty pathways.

Therefore, the primary aim of this study is to evaluate the predictive validity of these two candidate physical frailty specifications with respect to four selected outcomes. More specifically, the first research question asks: how well do the two candidate physical frailty specifications with three indicators including exhaustion, and with four indicators with the addition of weight loss predict death, functional impairment measured by basic and instrumental activities of daily living (BADL and IADL) difficulties, and quality of life two years later? The secondary aims are twofold. To begin with, the predictive ability of these two specifications is quantified to evaluate how well they compare with alternative specifications with five indicators mirroring the CHS frailty phenotype, and three indicators where weight loss substitutes exhaustion, as well as Frailty Index (FI), which is another established frailty instrument (Rockwood & Mitnitski, 2007). Thus, the second research question asks: how well do these two candidate physical frailty specifications predict these four adverse outcomes, compared with the specification with five indicators, the alternative with three indicators including weight loss, and FI? Next, predictive ability is evaluated across gender to determine if there are any important differences. Thus, the third research question asks: do the two

candidate physical frailty specifications predict these four adverse outcomes differently across gender? To achieve these aims and answer these questions, panel data from the English Longitudinal Study of Ageing (ELSA) is used. ELSA is a longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013), and is still ongoing.

Methods

Data

Panel data from waves 2 and 3 (2004 and 2006) of the English ELSA (Marmot et al., 2015) is used. All participants gave informed consent. Ethical approval for ELSA was granted from the Multicentre Research and Ethics Committee. Ethical oversight for this analysis is provided by procedures of the London School of Economics Ethics Policy.

Measures

Physical frailty is measured at wave 2 (2004). Its indicators are based on the five components of the CHS frailty phenotype (Fried et al., 2001). *Slowness* is the average gait speed (in m/s) of two attempts at walking a distance of 2.4 m multiplied by -1. *Weakness* is measured by the dominant hand grip strength in kg, which is multiplied by 1.5 for women. The differential handling of raw grip strength values in men and women mirrors the relative differences in gender-specific and population-independent values for grip strength proposed for the CHS frailty phenotype criteria (Saum et al., 2012). After that, values are reversed through multiplying them by -1. *Weight loss* is a binary variable for decrease in weight of 5 kg or more from waves 0 to 2. *Exhaustion* is also a binary variable based on a positive reply to either or both of two items of the CES-D scale on whether the respondent "felt everything they did during the past week was an effort" and "could not get going much of the time in the past week" (Radloff, 1977). *Low physical activity* is a binary variable for whether the respondent had the lowest of four categories of physical activity (sedentary).

The two candidate physical frailty specifications have indicators that are based on four (slowness, weakness, exhaustion, and weight loss) and three (slowness, weakness, and exhaustion) out of the five components of the CHS frailty phenotype. The two alternative specifications are based on further permutations of these components with five (slowness, weakness, exhaustion, weight loss, and low physical activity) and three (slowness, weakness, and weight loss) indicators. Confirmatory factor analysis (CFA) is performed for each of these four specifications to obtain their respective factor scores for each participant. For this, full information maximum likelihood (FIML), which is analogous to multiple imputation, but without actual creation of imputed datasets, is implemented to handle missing values under the missing at random (MAR) assumption. FI (Rockwood & Mitnitski, 2007) is computed as the number of positive items out of 30 illnesses and functional impairments, which is then divided by 30 to obtain a score of 0 to 1 (Searle et al., 2008). For descriptive purposes, and in line with proposed cut-off values, the respondent is not frail if FI is 0.08 or less, frail if FI is 0.25 or more if frail, and pre-frail if FI is in between these values (Song et al., 2010).

Four outcome variables are measured at wave 3 (2006), namely: death, number of six items of basic activity of daily living (BADL: eating, transferring, walking, toileting, dressing, and bathing) performed with difficulty, number of seven items of instrumental activity of daily living (IADL: using a map to get around, preparing meals, shopping for groceries, making telephone calls, taking medications, doing housework, managing money) performed with difficulty, and reverse of CASP-19 (Control, autonomy, self-realization, and pleasure) quality of life score (Howel, 2012).

Statistical Analyses

For regression analyses, multiple imputation with chained equations is implemented to handle missing values while holding the MAR assumption. The *mi* set of commands of Stata statistical package is used to generate 20 sets of imputed values for estimation procedures that follow.

Predictive validity of the four physical frailty specifications is assessed in two ways depending on whether the outcome measure is binary or continuous. For death at two years, which is a binary measure, logistic regression is performed with the factor scores for the four specifications and FI in turn as predictors while holding age constant. This is repeated for two separate groups according to gender. Estimates of odds ratio and c-statistics, which is a measure of model discrimination, are compared across specifications. For BADL difficulty, IADL difficulty, and poor quality of life (reverse of CASP-19 score) as outcomes among survivors at two years, linear regression is performed with the factor scores for the four specifications and FI as predictors in turn, while holding their corresponding values at wave 2 (2004) and age constant. Estimates of standardized coefficients and r^2, which is a measure of variance explained, are compared across specifications. To construct these models and perform estimation, *mi estimate*, *mibeta* and *lroc* Stata commands are used.

CFA is performed using Mplus version 7.4 (Muthén & Muthén, 1998-2012). All other analyses are performed with Stata version 14.1. Statistical significance is assessed at the 5% level.

Results

Table 1 summarizes the characteristics of 4,638 respondents aged 65 to 89 years or older included for analyses at wave 2 (2004). Respondents assessed to be pre-frail and frail according to their Frailty Index (FI) scores accounted for 41 and 20 percent respectively. These proportions are higher for women. Physical performance on walking and hand grip strength is worse, and exhaustion is more common among women. Significant weight loss of more than 5 kg over the previous 4 years is experienced by one out of every seven participants, and is marginally more common in women. More than 25 percent of respondents have functional impairment defined as having difficulty in performing any item of basic activities of daily living (BADL), with this impairment being more common among women. A similar pattern is seen for instrumental activities of daily living (IADL). On the other hand, quality of life levels assessed by mean CASP-19 scores are almost identical across gender.

Table 1. Description of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included for analyses

Variables		All	By gender	
			Male	Female
Baseline characteristics (wave 2):				
Mean age, years (SD)		74.0 (6.3)	73.5 (6.2)	74.3 (6.4)
Female, n/N (%)		2,568/4,638 (55.4)	-	-
Mean average walking speed, m/sec (SD)		0.82 (0.28)[1]	0.86 (0.27)[2]	0.78 (0.28)[3]
Grip strength (dominant hand), kg (SD)		25.9 (10.2)[4]	33.4 (8.9)[5]	19.6 (6.1)[6]
Weight loss > 5kg (waves 0 to 2), n/N (%)		587/3,590 (16.4)	255/1,608 (15.9)	332/1,982 (16.8)
Exhaustion, n/N (%)		1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)
Frailty status by Frailty Index [a], n/N (%)				
- Not frail		1,444/3,647 (39.6)	774/1,639 (47.2)	670/2,008 (33.4)
- Pre-frail		1486/3,647 (40.8)	629/1,639 (38.4)	857/2,008 (42.7)
- Frail		717/3,647 (19.7)	236/1,639 (14.4)	481/2,008 (24.0)
Number of basic activities of daily living (BADL) items performed with difficulty, n/N (%):	0	3,389/4,635 (73.1)	1,560/2,070 (75.4)	1,829/2,565 (71.3)
	1 or 2	948/4,635 (20.5)	389/2,070 (18.8)	559/2,565 (21.8)
	3 or 4	220/4,635 (4.8)	95/2,070 (4.6)	125/2,565 (4.9)
	5 or 6	78/4,635 (1.6)	26/2,070 (1.3)	52/2,565 (2.0)
	mean, (SD)	0.51 (1.08)[7]	0.47 (1.03)[8]	0.54 (1.11)[9]

Number of instrumental activities of daily living (IADL) items performed with difficulty, n/N (%):	0	3,308/4,635 (71.4)	1,593/2,070 (77.0)	1,715/2,565 (66.9)
	1 or 2	991/4,635 (21.4)	358/2,070 (17.3)	633/2,565 (24.7)
	3 or 4	236/4,635 (5.1)	77/2,070 (3.7)	159/2,565 (6.2)
	5 to 7	100/4,635 (2.2)	42/2,070 (2.0)	58/2,565 (2.3)
	mean, (SD)	0.58 (1.20)[7]	0.47 (1.13)[8]	0.68 (1.25)[9]
Quality of life: CASP score [b], (SD)		42.3 (8.7)[10]	42.4 (8.5)[11]	42.2 (8.9)[12]
Outcomes (at wave 3):				
Death, n/N (%)		278/4,638) (6.0)	147/2,070 (7.1)	131/2,568 (5.1)
Number of basic activities of daily living (BADL) items performed with difficulty, n (%):	0	2,694/3,671 (73.4)	1,222/1,625 (75.2)	1,472/2,046 (72.0)
	1 or 2	721/3,671 (19.6)	297/1,625 (18.3)	424/2,046 (20.7)
	3 or 4	195/3,671 (5.3)	83/1,625 (5.1)	112/2,046 (5.5)
	5 or 6	61/3,671 (1.7)	23/1,625 (1.4)	38/2,046 (1.9)
	mean, (SD)	0.52 (1.09)[13]	0.48 (1.04)[14]	0.55 (1.13)[15]
Number of instrumental activities of daily living (IADL) items performed with difficulty, n (%):	0	2,643/3,671 (72.0)	1,260/1,625 (77.5)	1,383/2,046 (67.6)
	1 or 2	738/3,671 (20.1)	267/1,625 (16.4)	471/2,046 (23.0)
	3 or 4	190/3,671 (5.2)	54/1,625 (3.3)	136/2,046 (6.7)
	5 to 7	100/3,671 (2.7)	44/1,625 (2.7)	56/2,046 (2.7)
	mean, (SD)	0.61 (1.27)[13]	0.49 (1.21)[14]	0.70 (1.32)[15]
Quality of life: CASP score [b], (SD)		40.3 (8.4)[16]	40.5 (8.2)[17]	40.2 (8.5)[18]

[a] Frailty Index: 30 items (0 to 1); Not frail $\leq$0.08, Pre-frail >0.08 but <0.25, Frail $\geq$0.25;

[b] CASP-19: Control, autonomy, self-realization, and pleasure (CASP) measure of quality of life (19 items)

Unless indicated otherwise, N = 4,638 for all, 2,070 for male, and 2,568 for female.

N = [1]4,092 [2]1,826 [3]2,266 [4]3,869 [5]1,760 [6]2,109 [7]4,635 [8]2,070 [9]2,565 [10]3,305 [11]1,534 [12]1,771 [13]3,671 [14]1,625 [15]2,046[16]2,834 [17]1,300 [18]1,534

By two years, 6 percent of participants have died with this proportion being higher for men. Among survivors, there is a minimal increase in functional impairment judging from the proportions of those who have difficulty with three or more items of BADL and IADL at wave 3 (7.0% and 7.9%) compared with wave 2 (6.4% and 7.3%). Mean BADL and IADL scores increase marginally by 0.01 and 0.03 respectively among survivors, with no differences across gender. Minor reduction in quality of life is observed in decrease in CASP-19 scores over the same period, again with no clear differences across gender.

The results of CFA for the four physical frailty specifications are provided in Table 6 of the Appendix. Slowness contributes most to the physical frailty factor as judged by its factor loading values being largest among indicators, except in the case of the alternative specification with three indicators including weight loss. For the latter, weakness contributes the most. Where

included as an indicator, weight loss contributes by far the least with low standardized factor loading values of 0.3 or less.

Prediction of death at two years by physical frailty specification factor scores and FI is summarized in Table 2. For the whole group, one unit of increase in physical frailty factor scores for the two candidate physical specifications increased the odds of death at two years by 50 to 57 percent holding age constant. Their corresponding c-statistics for prediction of death at two years range from 0.72 to 0.73, which indicates an intermediate level of model discrimination. This means that the probability that predicted risk is higher among those who experience the outcome than those who do not in 72 to 73% (Cook, 2007).

Table 2. Prediction of death at two years by physical frailty factor scores of four specifications and by Frailty Index (FI) using logistic regression holding age constant: odds ratios and c-statistics

	5 indicators	**4 indicators**	**3 indicators (with exhaustion)**	**3 indicators (with weight loss)**	**Frailty Index**
All:					
Factor score/FI: OR	1.83*	1.57*	1.50*	1.39*	1.54*
C-statistic	0.75	0.73	0.72	0.71	0.75
Male:					
Factor score/FI: OR	2.22*	1.98*	1.92*	1.68*	1.73*
C-statistic	0.77	0.75	0.75	0.73	0.77
Female:					
Factor score/FI: OR	1.88*	1.66*	1.53*	1.62*	1.45*
C-statistic	0.76	0.75	0.74	0.74	0.74

OR: odds ratio

* p-value <0.05

N = 4,638 for all, 2,070 for male, and 2,568 for female (missing values handled by multiple imputation)

Factor scores and Frailty Index are standardized.

The alternative specification with three indicators has lower c-statistic (0.71). In contrast, the c-statistic for the specification with five indicators and FI is marginally higher (0.75). Overall, c-statistic is marginally higher for men than women or the same, except in the case of the alternative specification with three indicators where the converse is true. More importantly, the two candidate specifications have higher c-statistics for men than the alternative specification with three indicators does. However, the c-statistics for specification with five indicators and FI are higher than those for the two candidate specifications, albeit only in men in the case of FI. Thus, overall, the two candidate specifications predict death at two years slightly better than the

alternative specification with three indicators, but slightly worse than the specification with five indicators and FI.

Prediction of functional impairment in terms of difficulty performing BADL at wave 3 among survivors is shown in Table 3. Since the analyses are adjusted for baseline BADL performance, the results are interpreted as reflecting *change* in BADL difficulty. One standard deviation of increase in physical frailty factor score for both specifications with three indicators including exhaustion, and with four indicators at wave 2 predicts 0.15 standard deviation increase of BADL items performed with difficulty, holding constant their corresponding performance at wave 2 and age. For the whole group and across gender, standardized coefficients for the two candidate physical frailty specifications are higher than those of the alternative specification with three indicators, but lower than those of the specification with five indicators. However, standardized coefficients for FI are higher. Variance of BADL difficulty at wave 3 explained by physical frailty, BADL difficulty at wave 2, and age, which is reflected by the r-squared values follows the same pattern as standardized coefficients across specifications, with the exception that those for the two candidate specifications and alternative specification with three indicators are equivalent for the whole group and among women. Overall, the two candidate physical frailty specifications predict *change* in BADL difficulty similarly. However, their predictive ability is better than the alternative specification with three indicators, but worse than those of the specification with five indicators and FI.

Table 3. Prediction of basic activities of daily living (BADL) difficulty among survivors at wave 3 by physical frailty factor scores of four specifications and by Frailty Index (FI) holding constant BADL difficulty at wave 2 and age: standardized coefficients and r^2

Number BADL items performed with difficulty	**5 indicators**	**4 indicators**	**3 indicators (with exhaustion)**	**3 indicators (with weight loss)**	**Frailty Index**
<u>All:</u>					
Factor score/FI	0.18*	0.15*	0.15*	0.10*	0.34*
r^2	0.42	0.41	0.41	0.41	0.45
<u>Male:</u>					
Factor score/FI	0.20*	0.17*	0.18*	0.11*	0.39*
r^2	0.41	0.40	0.41	0.39	0.44
<u>Female:</u>					
Factor score/FI	0.19*	0.15*	0.15*	0.12*	0.33*
r^2	0.43	0.42	0.42	0.42	0.45

* p-value <0.05

N = 4,360 for all, 1,923 for male, and 2,437 for female (missing values handled by multiple imputation)

Prediction of functional impairment in terms of difficulty performing IADL at wave 3 among survivors is shown in Table 4. Here again, as the analyses are adjusted for baseline IADL performance, the results are interpreted as reflecting *change* in IADL difficulty. One standard deviation of increase in physical frailty factor score for both specifications with three indicators including exhaustion and with four indicators predicts 0.12 standard deviation increase in IADL items performed with difficulty, holding constant their performance at wave 2 and age. As with prediction of BADL difficulty, standardized coefficients for the two candidate physical frailty specifications are again higher than those of the alternative specification with three indicators, but lower than those of the specification with five indicators for the whole group and across gender. Again, standardized coefficients for FI are much higher. However, there are only marginal differences across specifications and FI in terms of variance of IADL difficulty explained by frailty reflected by r-squared values for the whole group and across gender. Overall, prediction of *change* in IADL difficulty by the two candidate physical frailty specifications is similar. Differences with other specifications and FI mirror those for prediction of BADL.

Table 4. Prediction of instrumental activities of daily living (IADL) difficulty among survivors at wave 3 by physical frailty factor scores of four specifications and by Frailty Index (FI) holding constant IADL difficulty at wave 2 and age: standardized coefficients and r^2

Number IADL items performed with difficulty	5 indicators	4 indicators	3 indicators (with exhaustion)	3 indicators (with weight loss)	Frailty Index
All:					
Factor score/FI	0.14*	0.12*	0.12*	0.09*	0.20*
r^2	0.49	0.49	0.49	0.49	0.50
Male:					
Factor score/FI	0.12*	0.11*	0.11*	0.09*	0.16*
r^2	0.50	0.50	0.50	0.50	0.51
Female:					
Factor score/FI	0.16*	0.13*	0.13*	0.11*	0.22*
r^2	0.49	0.48	0.48	0.48	0.49

* p-value <0.05

N = 4,360 for all, 1,923 for male, and 2,437 for female (missing values handled by multiple imputation)

Finally, prediction of poor quality of life measured by reverse of CASP-19 scores at wave 3 among survivors is shown in Table 5. Yet again, as the analyses are adjusted for baseline poor quality of life, the results are interpreted as reflecting *change* in poor quality of life score. One standard deviation of increase in physical frailty factor score for the specification with three

indicators including exhaustion and with four indicators at wave 2 predicts 0.10 standard deviation increase in reverse of CASP-19 score, holding constant reverse of CASP-19 score at wave 2 and age. For the whole group and across gender, standardized coefficients for the two candidate physical frailty specifications are higher than those of the alternative specification with three indicators, but approximate those of the specification with five indicators. However, as for BADL and IADL, standardized coefficients for FI are higher. Nevertheless, variance of poor quality of life reflected by model r-squared values are almost equivalent across all frailty specifications and even FI, with minimal gender-specific differences. Thus, prediction of *change* in poor quality of life by the different physical frailty specifications is approximately equivalent, though possibly slightly worse than by FI.

Table 5. Prediction of poor quality of life score (reverse of CASP-19[a]) among survivors at wave 3 by physical frailty specifications and by Frailty Index (FI) holding constant reverse of CASP-19 score at wave 2 and age: standardized coefficients and r^2

Reverse of CASP-19 score	**5 indicators**	**4 indicators**	**3 indicators (with exhaustion)**	**3 indicators (with weight loss)**	**Frailty Index**
All:					
Factor score/FI	0.10*	0.10*	0.10*	0.06*	0.13*
r^2	0.59	0.59	0.59	0.59	0.60
Male:					
Factor score/FI	0.12*	0.11*	0.11*	0.07*	0.15*
r^2	0.58	0.58	0.58	0.58	0.59
Female:					
Factor score/FI	0.09*	0.10*	0.10*	0.07*	0.13*
r^2	0.60	0.60	0.60	0.60	0.60

* p-value <0.05

[a] CASP-19: Control, autonomy, self-realization, and pleasure (CASP) measure of quality of life (19 items)
N = 4,360 for all, 1,923 for male, and 2,437 for female (missing values handled by multiple imputation)

Discussion

It is worth reiterating that this study represents an important segment of the process of developing suitable physical frailty specifications for investigating the relationship of frailty with multidimensional conditions within a framework of frailty pathways. The first research question is unequivocally answered by the finding that the two candidate physical frailty specifications significantly predict death, functional impairment, and quality of life two years later. Obtaining answers to the second and third research questions requires further evidence on the predictive performance of candidate frailty specifications. To this end, three sets of findings are relevant.

The first set of findings relates to comparative performance of the four physical frailty specifications in their prediction of selected adverse outcomes, and answers in part the second research question. The two candidate specifications with three indicators (slowness, weakness and exhaustion) or four indicators (addition of weight loss) have approximately equivalent predictive ability for death, functional impairment, and poor quality of life two years on. They perform similarly or better than the alternative specification with three indicators including weight loss. On the other hand, their predictive ability is marginally worse that of the specification with five indicators including low physical activity, which mirrors the well-known CHS frailty phenotype. Together, these results demonstrate that the two candidate specifications have reasonable performance with respect to predicting these adverse outcomes, albeit not to the level that might be achieved when the fifth component of the CHS frailty phenotype, namely low physical activity, is included as an additional indicator. In a sense, this is expected given that low physical activity itself predicts death and functional impairment (McPhee et al., 2016; Nazroo et al., 2008; Stessman et al., 2009). That said, the difference between the predictive performance of the two candidate specifications and that with five indicators is marginal. Moreover, the argument against including low physical activity as a component of a physical frailty specification when investigating frailty pathways that has already been put forth.

The next set of findings concern the predictive performance of the two candidate physical frailty specifications across the four adverse outcomes benchmarked against another established frailty instrument, and answers the remaining part the second research question. Their comparative performance is mixed in that prediction ability of the two candidate specifications with respect to death and poor quality of life is similar to that of FI, but worse for functional impairment. The latter finding is not surprising given that FI includes items including chronic illnesses, as well as psychological and social conditions. More crucially, FI also includes items on physical function, which would certainly boost its correlation with future functional impairment. Nevertheless, it may be argued that at least for prediction of IADL difficulty and poor quality of life, there is marginal or no improvement in variance explained by FI when already accounting for prior levels of these outcomes and age. Thus, the performance of the two candidate specifications is approximately equivalent to or worse than FI, depending on which adverse outcomes are being predicted.

The final set of findings provides insight on the predictive performance of the two candidate physical frailty specifications across gender and answers the third research question. In general, the predictive performance of the two candidate physical frailty specifications is broadly similar across gender, although minor differences in standardized coefficients and proportion of variance explained are observed.

Given these findings, predictive validity of the two candidate physical frailty specifications with three indicators including slowness, weakness, and fatigue, and with four indicators with the addition of weight loss is arguably demonstrated. Their prediction of adverse outcomes that matter to older people such as death, functional impairment, and poor quality of life is only marginally inferior to the alternative specification that is equivalent of the CHS frailty phenotype, and mixed in comparison with another established frailty instrument, the FI. Notably, their predictive validity applies across gender. However, it is uncertain how they would compare with other frailty instruments that explicitly include multiple frailty domains such as the Tilburg Frailty Indicator (TFI). In the case of TFI, physical rather than psychological or social frailty contributes most to its predictive validity (Gobbens et al., 2012). This lends further support to the notion that despite lacking indicators drawn from other frailty domains, physical frailty specifications such as those evaluated in this study are unlikely to be significantly disadvantaged where predicting key adverse outcomes is concerned. While prediction of death and future disability with a physical frailty specification comprising four indicators was previously reported (Buchman et al., 2011; Buchman et al., 2009), this is, as far as the author is aware, the first report demonstrating the predictive validity of a physical frailty specification with only three out of five components of the CHS frailty phenotype as its indicators.

The main strength of this study lies in the use of ELSA, which offers representative, reliable, and high quality data, that has produced a wealth of information on the experiences and consequences of ageing. In addition, the four selected outcomes are those that are important to most older people and their families, and comprise both objective and subjective measures. On the other hand, a number of study limitations are acknowledged. Firstly, secondary data is used, and the usual drawbacks of relying solely on retrospective information apply. Secondly, missing data are assumed to be missing at random (MAR) which may or may not be the case depending on the variable concerned. Data being missing not at random (MNAR) is not explored as doing so would unnecessarily complicate the predictive models. In any case, all frailty specifications being compared are subject to the same potential bias arising from the missing data on the outcomes examined. Thirdly, the large proportion of zero values for BADL and IADL difficulty raises the issue of whether use of zero-inflated negative binomial regression (ZINB) or negative binomial regression (NB) models would be more appropriate when predicting these two outcomes. While doing so would be ideal, the *mibeta* command used for these predictions does not accommodate ZINB and NB models. In any case, different specifications being compared would suffer from similar inefficiency and bias resulting from use of linear regression models to compare their predictive performance. Finally, data from a single

population is used. Consequently, the extent to which these findings may be generalized to other populations is at best uncertain.

In conclusion, the evidence on predictive validity of the two candidate physical frailty specification gathered from this study builds on previous evidence of their construct and concurrent validity (Ding, 2016). This is achieved while employing a narrower definition of frailty that represents its physical domain. Taken together, they suggest that physical frailty specifications with three indicators (slowness, weakness and exhaustion) and four indicators (addition of weight loss) are suitable for employment in the investigation of frailty pathways.

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Supplementary Materials

Table 6. Measurement models for four specifications of physical frailty using confirmatory factor analysis (CFA)

Physical frailty specification	Standardized coefficient (Standard error)		
	All	By gender	
		Male	Female
Five indicators:			
Slowness [a]	0.80 (0.02)	0.73 (0.03)	0.76 (0.02)
Weakness [b]	0.52 (0.02)	0.53 (0.02)	0.54 (0.02)
Exhaustion [c]	0.56 (0.02)	0.57 (0.04)	0.56 (0.03)
Weight loss [d]	0.28 (0.03)	0.22 (0.05)	0.31 (0.04)
Low physical activity [e]	0.76 (0.02)	0.84 (0.03)	0.73 (0.03)
Four indicators:			
Slowness [a]	0.76 (0.03)	0.67 (0.03)	0.71 (0.02)
Weakness [b]	0.54 (0.02)	0.57 (0.03)	0.58 (0.03)
Exhaustion [c]	0.55 (0.02)	0.53 (0.04)	0.55 (0.03)
Weight loss [d]	0.28 (0.03)	0.23 (0.06)	0.30 (0.04)
Three indicators including exhaustion:			
Slowness [a]	0.78 (0.03)	0.68 (0.03)	0.72 (0.02)
Weakness [b]	0.52 (0.02)	0.56 (0.03)	0.57 (0.03)
Exhaustion [c]	0.54 (0.03)	0.53 (0.04)	0.55 (0.03)
Three indicators including weight loss:			
Slowness [a]	0.59 (0.05)	0.48 (0.03)	0.55 (0.03)
Weakness [b]	0.68 (0.05)	0.73 (0.04)	0.75 (0.04)
Weight loss [d]	0.29 (0.03)	0.22 (0.05)	0.28 (0.04)

P-values are <0.05 for all coefficients.

[a] Slowness: mean gait speed multiplied by a factor of -1

[b] Weakness: dominant hand grip strength reversed and for female gender, multiplied by a factor of 1.5

[c] Exhaustion: positive response to either or both of two items of CES-D scale on “could not get going much of the time in the past week” and “felt everything they did during the past week was an effort”

[d] Weight loss: decrease in weight of more than 5 kg from wave 0 to wave 2

[e] Low physical activity: lowest (sedentary) of four categories of physical activity

Full information maximum likelihood (FIML) is used to handle missing values.

N for physical frailty specifications (whole group, men, women): 4,569, 2,033, 2,536 (5 indicators); 4,547, 2019, 2,528 (4 indicators); 4,547, 2019, 2,528 (3 indicators including exhaustion); 4,440, 1985, 2455 (3 indicators including weight loss);

6.3 Further thoughts

In this paper, I demonstrate predictive validity of the two candidate specifications of physical frailty. Beyond confirming that their factor scores predict death, functional impairment, and poor quality of life, I show that they perform at levels that are almost equivalent to those of an alternative physical frailty specification based on five indicators. The latter reflects physical frailty based on the full complement of CHS frailty phenotype components. In addition, these two specifications are comparable with FI in prediction of death and poor quality of life.

Together, the evidence gathered in the first two papers suggests that these two candidate physical frailty specifications are suitable for employment in the investigation of frailty pathways. Furthermore, the specification with three indicators namely, slowness, weakness, and exhaustion is probably more advantageous than the one with four indicators including weight loss, given that it is more parsimonious and requires less data. This is particularly relevant where serial weight data are not available to measure change when constructing the indicator on weight loss. Thus, I will use the specification with three indicators (slowness, weakness, and exhaustion) in the next three papers to investigate pathways to physical frailty and its adverse outcomes.

Part Three

Frailty Pathways: Exploring Predictors, Moderators, and Mediators

7 Preamble

7.1 Substantive considerations

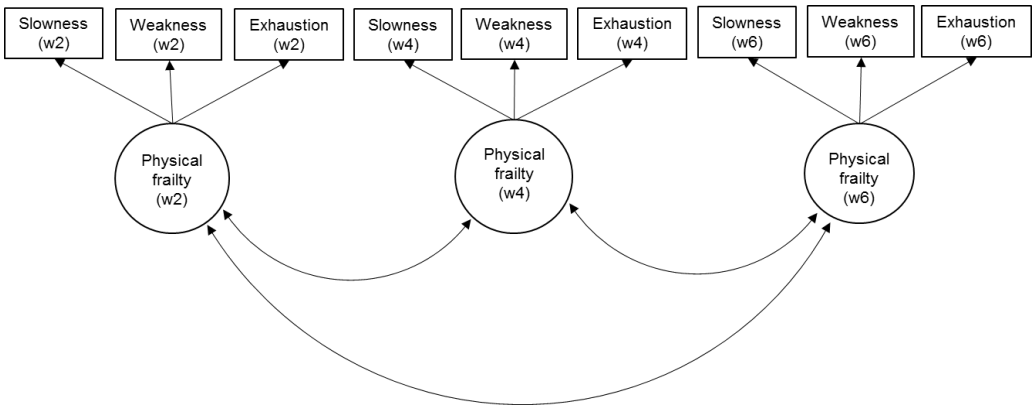
I have described the development of suitable physical frailty specifications for investigation of frailty pathways in the first two papers. From here, I will now use the specification with three indicators, namely slowness, weakness, and exhaustion in favor of that with four indicators which has weight loss as the additional indicator. The reason for that there is little added value using four indicators in terms of construct, concurrent, and predictive validity, based on the results obtained in the first and second papers. Furthermore, the specification with three indicators is a more parsimonious option where data requirements and analyses are concerned. With the decision made on which physical frailty specification to use, the focus now shifts to the research questions I have set out to answer.

To recap, the overarching research aim is to achieve a good understanding of conditions predicting frailty and those influencing the development of its adverse outcomes in older people. In the third paper, I will examine physical, psychological, and social conditions that predict physical frailty and explore their moderators and mediators. Following that in the fourth paper, I will investigate the effect of physical frailty on death, with particularly focus on moderation and mediation of this effect by selected conditions. Finally, in the fifth paper, I will investigate the effect of physical frailty on a key facet of functional impairment, namely activity limitation, while again focusing on conditions that moderate and mediate its effect. Throughout these papers, the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) will be the conceptual model for frailty pathways. An adapted and simplified version of this working framework is provided in Figure 2.3 (page 34).

7.2 Methodological considerations

Given the availability of longitudinal data from ELSA, the opportunity arises to examine the progression of physical frailty across time for the individual older person (intra-individual change) as well as differences in progression over time across older persons (inter-individual differences). To take advantage of this opportunity, the measurement model for physical frailty first needs to be established. As mentioned, physical frailty is measured by its three indicators, namely slowness, weakness, and exhaustion. Given that slowness and weakness are measured by walking speed and hand grip strength respectively, and that data for these measures are only available at waves 2, 4, and 6 of ELSA, physical frailty will only be specified at these three time points. Figure 7.1 illustrates the measurement model for physical frailty across the three time points.

Figure 7.1. Measurement model for physical frailty over waves 2, 4, and 6 of the English Longitudinal Study of Ageing



w2: wave 2 w4: wave 4 w6: wave 6
Circle: latent variable
Rectangle: observed variable
Single-headed straight arrow: effect of one variable on another
Double-headed curved arrow: covariance between two variables

The next issue is that of measurement invariance across time points, or longitudinal invariance. This concerns whether the physical frailty construct is the same across time. A detailed discussion of measurement invariance is beyond the scope of this thesis. Nevertheless, it suffices to mention that for simplicity, I will assume and thus, adopt strong (or scalar) invariance for the physical frailty construct across waves 2, 4, and 6. Strong invariance imposes equality of loadings and intercepts across time. This is to avoid the situation where the operationalization of physical frailty changes across these three time points, which would not only be conceptually problematic, but would also complicate the interpretation of models that use a changing physical frailty measurement. Moreover, there is no substantive expectation of non-invariance across time points, each having a mixture of different ages of respondents, with only average age increasing.

With the measurement model established, the structural model relating conditions and physical frailty is constructed. I will employ three different models for the next three papers, with the choice depending on the research question and whether the outcome variable is binary or continuous. For the third paper, I use latent growth curve models to estimate the effects of physical, psychological, and social conditions on physical frailty. Latent growth curve models are a flexible approach to investigating change in a variable over time. Here, linear latent growth curve models are constructed where change in physical frailty is assumed to be and thus, specified as constant over time. Given this, the measurement model is a linear latent growth model has physical frailty with multiple indicators as its “curve” portion. It also includes

an intercept factor, which represents initial physical frailty (at wave 2) and a slope factor, which represents physical frailty change over time (waves 2, 4, and 6). The structural part of the model incorporates time-invariant and time-varying predictors of physical frailty arising from physical, psychological, and social dimensions.

For the fourth paper, I use discrete time survival analysis to estimate the effect of physical frailty at wave 2 on death across waves 3 to 5. Physical frailty is measured by factor scores derived from confirmatory factor analysis for physical frailty at wave 2. Given that death is a binary variable, the effect of physical frailty can be estimated by logistic regression, where regression coefficients are transformed to obtain the hazard rate for each time point using the formula:

$$h_{ti} = 1 / (1 + e^{-\beta t})$$

The discrete time survival model requires a series of binary repeated measures, which are coded as 0 if death has not occurred yet, 1 if death occurs during that period *t*, and missing if death has already occurred or censored. Physical frailty and a broad set of physical, psychological, and social conditions, all at wave 2, are predictors of death.

Finally, for the fifth paper, I use autoregressive cross-lagged analysis to estimate the effect of lagged physical frailty factor scores on activity limitation (waves 4 and 6). Autoregressive cross-lagged models are characterized by the outcome variable being regressed by its own lagged measure (auto-regression) as well as that of the lagged predictor (cross-lagged effect). The underlying concept is based on two rationales. Firstly, the inclusion of the lagged outcome controls for pre-existing differences in the outcome. This addresses the possibility that the existing relationship between the lagged predictor and lagged outcome explains the relationship between the lagged predictor and (non-lagged) outcome, where the latter relationship is the one of interest. Secondly, the stable aspects of the outcome variable are removed, so that the estimated cross-lagged effect represents the effect of the predictor on the *change* of the outcome (Newsom, 2015). The estimated effects are also controlled for those of a broad set of physical, psychological, and social conditions at wave 2.

As mentioned, beyond estimating the effects of multidimensional predictors on physical frailty, and that of physical frailty on its outcomes, attention is paid to their moderated effects using stratified analyses, thereby answering questions concerning *for whom* the effects of predictors are stronger. In addition, their indirect effects are estimated through exploring mediated effects to answer questions on *how* predictors exert their effects. Furthermore, moderated mediation or moderation of these indirect effects (also known as conditional indirect effects) is also explored.

Another methodological issue is the handling of missing values due to unit and item non-response. Throughout the analyses, full information maximum likelihood (FIML) will be implemented for both types of missing values with the assumption that missing values are missing at random (MAR). FIML is analogous to multiple imputation although actual no imputation data are created. Rather, the missing data is handled within the analysis model

using maximum likelihood estimation, which identifies population parameters having the highest probability of producing the sample data. It uses all available data to generate their estimates and assumes multivariate normality (Enders, 2011). FIML handles item non-response for physical frailty indicators in the measurement model by using all observed values of indicators for the estimation, even for respondents with observed values in fewer than three indicators. Missing values for dependent variables are handled similarly. On the other hand, FIML handles item non-response in predictor variables by treating them as dependent variables through the procedure of estimating their sample means or variances, thereby using them for estimation of model parameters.

I will not be applying sample weights for unit non-response given that description is not the focus of the three papers. Moreover, maximum likelihood is a reasonable option for handling attrition in longitudinal studies (Davis-Kean & Jager, 2012), including attrition due to mortality (Feng et al., 2006). In addition, to address the possibility that missing values for the outcome variable may be missing not at random (MNAR), I will also conduct sensitivity analyses including the use of a method of handling MNAR in the growth curve context, to observe whether the results have important differences from those obtained in the main analyses.

Lastly, additional sensitivity analyses are conducted to explore whether the findings are robust to violations of specific key assumptions. These assumptions are:

1) No unobserved confounding: To relax this assumption, the analyses are repeated while including a “phantom variable”, which is a latent variable that represents unmeasured confounders. The strength of its relationship with exposures and mediators is varied, while observing any important changes in the estimation of exposure-outcome relationship of interest.
2) No exposure-mediator interaction: To relax this assumption, this interaction is included in the model, while observing for any important changes in the estimated mediated effect.
3) Normal distribution of the outcome variable: Where right skewed distribution or count data with excess zero values are encountered, results of alternative analyses with negative binomial regression models are compared with those using standard linear regression. Zero-inflated models are not used given that interpretation of their results is less straightforward.

8 Third Paper

8.1 Introduction

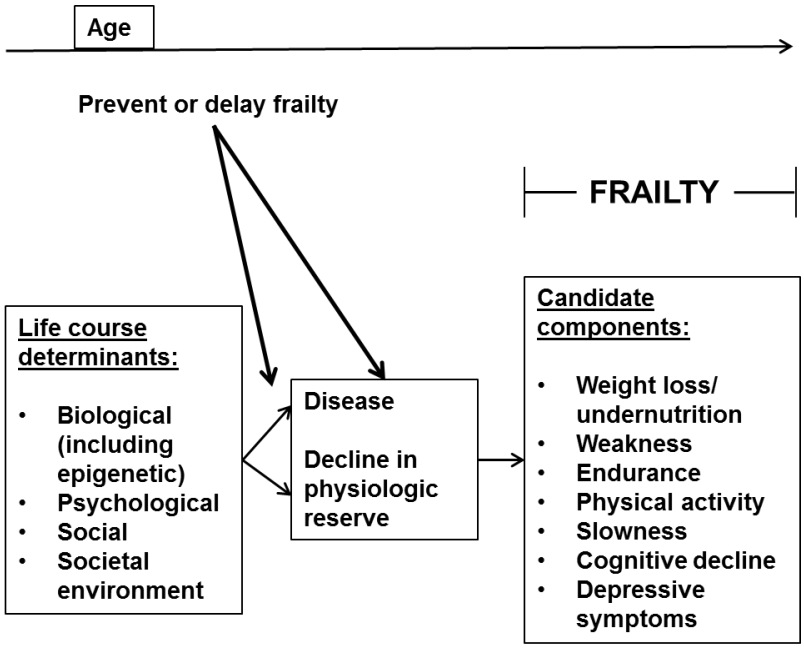
For the third paper, the research aim is to explore the validity of a framework of pathways to frailty by quantifying the relationship of physical frailty with multidimensional conditions on these pathways. Specifically, I will seek to answer the research question: “What physical, psychological, and social conditions are predictors of physical frailty, and which are moderators and mediators of their effects in older people?”. Before that, I will outline the substantive and methodological considerations for the task.

The foregoing literature review has identified that older age, female gender, chronic disease, allostatic load, low physical activity, being underweight, obesity, smoking, heavy drinking, poorer cognition, depression, having less education, lower income, being social isolated, financial strain, genetic influences, and poor social conditions in childhood all predict higher risk of developing frailty. In most instances, these conditions have been studied with only a limited set of control predictors. Given that these conditions are likely to be correlated to varying degrees with each other, it is not entirely clear which of them truly predict the development of frailty in older people after controlling for the effects of other predictors. Moreover, their inter-relationships may be more complex. Specifically, it is possible that some of these conditions may moderate others, while some others may mediate the effects of others. A more precise understanding of the pathways from predictors to frailty is needed. To this end, a more detailed examination of these frailty pathways is a worthwhile endeavor.

As mentioned, I will use the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) as the conceptual model for investigating pathways to physical frailty. The left side of this working framework is the focus of this paper and is reproduced in Figure 8.1 (page 113). To reflect life course determinants (box on the left in Figure 8.1), physical, psychological, and social predictors will be included in the analyses. Genetic information and social conditions in early life may be relevant to the development of physical frailty in late life. However, given that data on social conditions in childhood are only available for a subset of respondents at wave 3 of the English Longitudinal Study of Ageing (ELSA) and that genetic influences are not the focus of this paper, they will not be included as predictors. Disease and decline in physiologic reserves (box in the center of Figure 8.1) are designated as mediators of the effects of predictors in this framework. As such, indirect effects of predictors through these two conditions will be included in the analyses in addition to their direct effects on physical frailty. In doing so, I seek to answer the question on *how* these predictors cause physical frailty by unpacking the “black box” of mechanisms through which they exert their effects on development of physical frailty. In addition, moderation of these predictors by selected conditions will also be explored to answer the question on *for whom* they exert their effects. As mentioned previously, physical frailty is specified with three indicators

(Ding, 2016) rather than with the seven components proposed in this framework (box on the right in Figure 8.1).

Figure 8.1. Pathways to frailty adapted from the working framework of the proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004)



Although a rich set of multidimensional predictors are included in the analyses, particular attention will be paid to the effects of those which are potentially modifiable such as lifestyle-related, psychological, and social conditions. Other conditions including gender and age serve to control their estimated effects. Ultimately, the objective is to identify target conditions at which to direct population-wide interventions to prevent or delay physical frailty.

As mentioned in the previous chapter, I will use latent growth curve analysis to examine pathways to physical frailty progression. To better handle measurement error, I will employ multiple indicators of physical frailty for the latent growth curve analysis.

The following paper examines pathways to physical frailty to gain insight on their complex nature. Some of the foregoing key points are unavoidably repeated as this is a self-contained journal article. References specifically for this paper are again in a separate list just before the Supplementary Materials (pages 136 to 139). Relevant Mplus input files are provided in the Appendix. A version of this paper has been published in the journal, *Biogerontology* (Ding et al., 2017).

8.2 Multidimensional predictors of physical frailty in older people: identifying how and for whom they exert their effects

Joint work with Associate Professor Jouni Kuha (Departments of Statistics and Methodology, London School of Economics) and Professor Michael Murphy (Department of Social Policy, London School of Economics)

Abstract

Physical frailty in older people is an escalating health and social challenge. We investigate its physical, psychological, and social predictors, including *how* and *for whom* these conditions exert their effects. For 4,638 respondents aged 65 to 89 years from the English Longitudinal Study of Ageing, we examine prediction of physical frailty change over waves 2, 4 and 6 by physical, psychological, and social conditions using latent growth curve analysis with multiple indicators, and repeat the analyses after stratification by gender, age group, and selected conditions that are possible moderators. In addition, we explore their indirect effects through disease and physiologic decline, including the aforementioned stratified analyses. We find that chronic disease, allostatic load, low physical activity, depressive symptoms, cognitive impairment, and poor social support all predict future physical frailty. Furthermore, both chronic disease and allostatic load mediate the effects of low physical activity, depressive symptoms, and cognitive impairment on future physical frailty. Finally, although poor social integration is itself not a predictor of future physical frailty, this condition moderates the indirect effect of poor social support through chronic disease by rendering it stronger. By virtue of their roles as predictor, mediator, or moderator on pathways to physical frailty, chronic disease, allostatic load, low physical activity, cognitive impairment, depressive symptoms, poor social support, and perhaps, poor social integration are potentially modifiable target conditions for population-level health and social interventions to reduce the risk of developing physical frailty or its worsening in older people.

Key words: aged, mediators, moderators, growth curve, allostatic load, social support, social integration

Introduction

Frailty denotes the multidimensional loss of an individual's reserves that occurs with greater probability with advancing age. This loss results in vulnerability to developing adverse health outcomes (Lally & Crome, 2007). In biomedical circles, frailty is widely considered to be a clinical syndrome with an underlying biological basis, and is thought to be a transitional state between robustness and functional decline (Lang et al., 2009). Its prevalence from different studies that used a range of frailty instruments for its diagnostic categorization yielded an estimate of 10.7% among adults aged 65 years and older (Collard et al., 2012). From this, we can infer that one out of every 10 community-dwelling older people is frail. There is overwhelming evidence that frailty confers increased risk of adverse health outcomes that matter to older people. These include death (Buchman et al., 2009; Cawthon et al., 2007; Gu et al., 2009; Mitnitski et al., 2004; Rockwood et al., 2011), disability (Avila-Funes et al., 2008; Romero-Ortuno et al., 2011; Woo et al., 2006), falls (Bilotta et al., 2012; Samper-Ternent et al., 2012), cognitive impairment and dementia (Auyeung et al., 2011; Boyle et al., 2010; Woo et al., 2006), lower health-related quality of life (Kanauchi et al., 2008), hospitalization (Bilotta et al., 2012), greater health services utilization (Rockwood et al., 2011), and institutionalization in long-term care facilities (Jones et al., 2005). In view of these consequences, frailty plays a central role in the well-being of older people at the individual and societal levels, and therefore has major public health importance. Moreover, with the projection of rapid growth in the number of older people living across the world, frailty presents a rapidly escalating societal challenge on a global scale (Conroy, 2009). Finally, given its impact, frailty has been described as the most problematic expression of ageing (Clegg et al., 2013).

On a more positive note, accumulating evidence suggests that frailty is an addressable issue. For example, targeted interventions such as exercise have shown promise in reducing incident frailty in selected groups of older people (Mohandas et al., 2011). Without doubt, reducing frailty at the population level is a desirable goal. To this end, a more precise understanding of predictors of frailty holds the key to delaying its onset and slowing its progression. This knowledge can in turn assist in informing the formulation of health and social policies that address frailty in older people.

Research on frailty over the past two decades has yielded important information on its predictors. To date, most of the available evidence concerns the physical domain. For example, older age (Fallah et al., 2011; Ottenbacher et al., 2009) and female gender increase the likelihood of developing frailty (Etman et al., 2012; Peek et al., 2012; Woods et al., 2005). Genetic factors play an important role with data from multi-generational families suggesting that its contribution is comparable with that of environmental factors (Garibotti et al., 2006). Chronic disease (Ottenbacher et al., 2009; Strawbridge et al., 1998; Syddall et al., 2010; Woods et al., 2005), allostatic load (Gruenewald et al., 2009), and chronic systemic inflammation (Barzilay et al., 2007) are specific medical conditions associated with developing frailty. Low physical activity (Strawbridge et al., 1998), being underweight, overweight, or obese (Woods et al.,

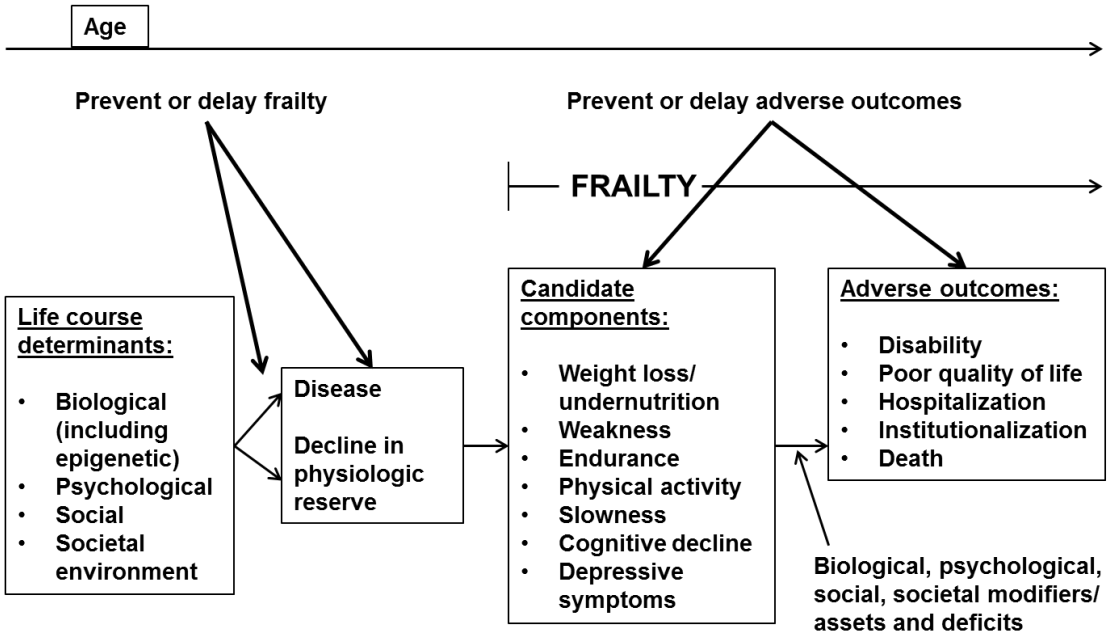
2005), smoking (Woods et al., 2005) and heavy drinking (Strawbridge et al., 1998) are lifestyle-related conditions that also increase the risk of frailty.

Beyond the physical domain, lower cognition and depression are psychological conditions that confer higher risk of incident frailty (Ottenbacher et al., 2009; Strawbridge et al., 1998; Woods et al., 2005). In the social realm, having less education and lower income, non-white collar occupation, living alone, and being social isolated are all associated with increased risk of developing frailty or worsening of frailty (Alvarado et al., 2008; Etman et al., 2012; Peek et al., 2012; Strawbridge et al., 1998; Syddall et al., 2010; Woods et al., 2005). Financial strain also increases this risk (Alvarado et al., 2008; Peek et al., 2012). These findings are likely to reflect the effect of chronic stressors. From a life course perspective, poor social conditions in childhood such as experiencing hunger and having challenging socioeconomic circumstances also increases the risk of developing frailty (Alvarado et al., 2008). Conversely, social support characterized by perceived emotional support from family or friends protects against increasing degrees of frailty (Peek et al., 2012). Participation in group activities also confers lower risk of incident frailty in older persons (Fushiki et al., 2012).

More recently, a life course epidemiological approach was proposed to offer a more comprehensive framework for investigating determinants and effects of frailty in older people. It attempts to integrate rather than segregate biological and social risk factors. In doing so, this approach can be valuable in conceptualizing multiple determinants that exert their dynamic effects across different age bands (Kuh, 2007). Typically, there is explicit temporal ordering of exposures and inter-relationships among these variables. Their effects are either direct or through intermediate conditions, also designated as mediators. A tangible output is a set of pathways for these conditions that serves as a suitable framework for the application of statistical modeling techniques such as structural equation modeling (Ben-Shlomo & Kuh, 2002).

Adopting a life course approach, Bergman developed the working framework of the Canadian Initiative for Frailty and Aging, which provides a graphical representation of multidimensional exposures across the life span in hypothesized pathways to frailty (Bergman et al., 2004). An adapted and simpler version of this framework is shown in Figure 1. Focusing on its left side, we see that life course determinants of frailty include physical, psychological, and social conditions. Their effects are mediated by disease and physiologic reserve decline. This framework offers a useful starting point for assembling a set of predictors on pathways to physical frailty in older people. To date however, empirical studies examining the concurrent and interacting effects of multidimensional predictors of frailty represented in this framework have not yet been reported.

Figure 1. Working framework of the Canadian Initiative for Frailty and Aging (adapted from Bergman, 2004 with modifications)



Building on the Canadian framework, the integral conceptual model of frailty was subsequently proposed (Gobbens et al., 2010). In this model, frailty is explicitly specified as having distinct physical, psychological, and social domains. Doing so allows physical frailty to be disaggregated from the other two frailty domains. This in turn permits less constrained exploration of the relationship of frailty with its multidimensional predictors and effects. Adopting this approach to specifying frailty, a physical frailty specification with three indicators, namely, slowness, weakness and exhaustion was developed and its construct and concurrent validity demonstrated (Ding, 2016).

Following this review, we study pathways to frailty as hypothesized in the working framework of the Canadian Initiative for Frailty and Aging with three research questions in mind. Our first question focuses on key multidimensional conditions that predict physical frailty. More specifically, what are the effect sizes of physical, psychological, and social predictors of physical frailty controlling for the effects of each other? Our second question concerns *for whom* these multidimensional predictors exert their effects. Particularly, to what extent are the effects of key predictors influenced by other predictors? Our third question examines *how* these predictors exert their effects. More precisely, are the effects of predictors mediated by disease and decline in physiological reserve as suggested by the working framework of the Canadian Initiative for Frailty and Aging? In answering these questions, we seek to advance beyond merely confirming that specific physical, psychological, and social conditions are indeed predictors of physical frailty, to further estimating their effects over and above each other. In addition, we examine the roles of key conditions in moderating the effects of other conditions

and in mediating indirect effects. To this end, we will operationalize the aforementioned physical frailty specification with three indicators and use it in the analysis of panel data of older people from the English Longitudinal Study of Ageing (ELSA). ELSA is a longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013). It offers a broad range of reliable and multidimensional data across biennial waves beginning from 2002, and is currently still ongoing.

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Methods

Data

Our study population comprises 4,638 respondents aged 65 to 89 years at wave 2 (2004) of ELSA (Marmot et al., 2015). Those aged 90 years and older are excluded because their age is uniformly coded as “90”. All respondents gave informed consent. Ethical approval for ELSA was granted by the Multicenter Research and Ethics Committee. Ethical oversight for this study is provided by procedures of the London School of Economics Ethics Policy.

Physical frailty is specified by three indicators drawn from those of the Cardiovascular Health Study (CHS) frailty phenotype (Fried et al., 2001), namely slowness, weakness, and exhaustion. *Slowness* is operationalized as the average gait speed (in m/s) of two attempts at walking 2.4 m, but with values reversed through multiplication by -1. *Weakness* is measured by the dominant hand grip strength in kg, which is multiplied by 1.5 for women. The differential handling of raw grip strength values in men and women is based on gender-specific and population-independent values for grip strength proposed for the CHS frailty phenotype criteria (Saum et al., 2012). After that, values are reversed through multiplying them by -1. *Exhaustion* is a binary variable based on a positive response to at least one of two items in the Center for Epidemiologic Studies Depression Scale (CES-D scale) (Radloff, 1977) on whether the respondent “felt everything they did during the past week was an effort” and “could not get going much of the time in the past week” (Radloff, 1977). Data for gait speed and hand grip strength are only available at waves 2, 4, and 6. From among different permutations of the five components of the CHS frailty phenotype, the combination of these three indicators has been shown and argued to be preferred in representing the physical frailty construct for investigation of frailty pathways (Ding, 2016). Confirmatory factor analysis (CFA) with these three indicators for waves 2 (2004), 4 (2008), and 6 (2012) is performed while assuming and therefore, imposing scalar (strong) invariance over time where all loadings and intercepts are held constant across time. This measurement model is then incorporated in the full structural model. In addition, unique physical frailty factor scores for each respondent are derived at the three time points and then utilized to describe the study population.

To further describe frailty status in our study population, a 30-item Frailty Index (FI) based on a deficit accumulation approach is constructed and represented as a scalar measure ranging from 0 to 1 (Rockwood & Mitnitski, 2007). In accordance with previous reports, FI values of at least 0.25 define frailty (Rockwood et al., 2007).

Physical frailty is the outcome of interest that is specified at waves 2, 4, and 6 as factors with multiple indicators on a latent growth curve. Based on the Canadian working framework and evidence assembled from the literature, physical, psychological, and social conditions are shortlisted for inclusion as predictors in our models. Beyond *age* and *gender*, physical predictors include *obesity* (binary: body mass index (BMI) of 30 kg/m^2 or more with reference to

BMI less than 30 kg/m^2 but more than 20 kg/m^2), being *underweight* (binary: BMI of 20 kg/m^2 or less with reference to BMI less than 30 kg/m^2 but more than 20 kg/m^2), *low physical activity* (four levels of decreasing intensity activity related to occupation and exercise), *chronic disease* (count of conditions from 0 to 14), *allostatic load* (score of 0 to 9), *smoking* history ((binary: whether ever smoked), and *high alcohol intake* (binary: whether had alcohol drink almost every day in the past 12 months). Allostatic load reflects physiological dysregulation in multiple body systems and is specified by nine biomarkers including blood pressure readings, anthropometric measurements, and blood tests for cholesterol levels, glucose control, and inflammatory markers (Gruenewald et al., 2009). For each biomarker, a score of one is awarded for values beyond a cut-off level reflecting high risk, with a score of zero given if otherwise.

Psychological predictors include *depressive symptoms*, which is based on a count of six out of eight items (score of 0 to 6) of the CESD Scale. The two omitted items are those already used to measure exhaustion as a physical frailty indicator. *Cognitive impairment* is measured by reversing a cognitive index based on the combined memory and executive function test performance (score of 0 to 49).

Social predictors include *low education* (binary: no qualifications compared with any qualification), and *low wealth* (binary: lowest 2 deciles compared with highest 8 deciles of non-pension wealth). Additionally, *poor social integration* reflecting social isolation is based on a combined score on five items (score of 0 to 14) concerning whether respondents have no spouse or partner living with them, had little contact with children, had little contact with other family members, had little contact with friends, and were not a member of any organization, club or society. Contact includes meeting, phoning, or writing or email. Its precise specification is adapted from that of a previous study (Banks et al., 2010). Finally, *poor social support*, in terms of deficient emotional support, and reflecting negative social interaction with family and friends is measured by the combined scores on three items each on whether there is lack positive support, and the occurrence of negative support (score of 0 to 54). Lack of positive support is measured by negative answers to questions on “understand the way you feel”, “can rely on if you had a serious problem”, and “can open up to them if you need to talk” with respect to children, other family members, and friends. Negative support is measured by positive answers to questions on whether children, other family members, and friends "criticizes the respondent", "lets the respondent down", and "gets on the nerves of respondent". This specification is again based on the aforementioned previous study (Banks et al., 2010).

Statistical analyses:

A series of structural equation models using latent growth curve analysis are developed to examine the effect of predictors on physical frailty. The growth curve is specified as linear and measured by multiple indicators for physical frailty at waves 2, 4, and 6. Random effects capture inter-individual differences in physical frailty development that are conceptualized as two growth factors. The first is the intercept growth factor, which reflects physical frailty at wave

2, and represents inter-individual differences in initial physical frailty at wave 2. The other is the slope growth factor, which reflects physical frailty change across waves 2 to 6, and represents inter-individual differences in physical frailty trajectory over time.

Model 1 concerns prediction of initial physical frailty and its change over time. It comprises two parts. The first part is the regression of the intercept and slope factors for physical frailty on predictors that are designated as time-invariant variables, such as age (at wave 2) and gender. Other predictors such as smoking history, high alcohol intake, low education level, and low wealth are not expected to change over the three time points for the vast majority of respondents. Obesity is also designated as time-invariant, given that BMI data are not always available at the three time points. The second part is the regression of physical frailty factors at waves 2, 4, and 6 on their lagged time-varying predictors, namely chronic disease, allostatic load, low physical activity, depressive symptoms, cognitive impairment, poor social support, and poor social integration measured at waves 1, 2, and 4 respectively. Wave 1 is used given that data is not available for six out of seven of these variables at wave 0. In addition, stratified analyses according to gender and age group (below 75 years and at least 75 years) are performed. Model 2 extends Model 1 by examining moderation of the effects of predictors on physical frailty by low physical activity, depressive symptoms, low social support, and low social integration using stratified analyses of two subgroups defined by whether values are below or above their mean values. Equivalent effects across time are constrained to be equal.

Model 3 extends Model 1 by including mediation of the effects of predictors on change in physical frailty. The indirect effects of time-varying predictors (waves 1, 2, and 4) on physical frailty factor (waves 2, 4, and 6) that are mediated by chronic disease and allostatic load (waves 2, 4, and 6) are estimated. These indirect effects are estimated by obtaining the product of the coefficients of the predictor-mediator and mediator-outcome effects, and then using Sobel's test to test their significance (Sobel, 1982). Gender and age group-specific effects are also estimated with stratified analyses. Absence of predictor-mediator interaction is assumed. Finally, Model 4 extends Model 3 by including stratified analyses to explore moderation of these indirect effects (moderated mediation) by the four conditions examined in Model 2,

Mathematical equations for Models 1 to 4, as well as graphical representations of Models 1 and 3 are provided in the Supplementary Materials (Figures 3 and 4 respectively for the latter). The models are estimated using maximum likelihood with robust standard errors (MLR). Missing values for dependent variables due to both attrition and item non-response are handled by full information maximum likelihood (FIML) with the assumption of missing at random (MAR). FIML is a procedure that is analogous to multiple imputation, but without actual creation of imputation datasets. Rather, missing data is handled within the analysis model using maximum likelihood estimation, which identifies population parameters having the highest probability of producing the sample data. It uses all available data to generate estimates and assumes multivariate normality. It is also implemented for predictor variables by treating them as dependent variables through estimating their sample means.

Sensitivity analysis is explored in two ways. Firstly, the MAR assumption is relaxed to consider the possibility that missing values for the outcome variable are missing not at random (MNAR). This is particularly relevant given that missing values due to death or drop out may be MNAR. To perform this, Wu and Carroll's selection model (Enders, 2011), which is a shared parameter model that is conditional on the latent factors, is incorporated in Model 1 to explore the extent to which results change when MNAR is considered. In this model, growth curve analysis is augmented with logistic regression equations that predict binary missing data indicators (at waves 4 and 6) using the two growth factors as well as time-invariant and time-varying predictors. In other words, initial physical frailty and its rate of change over time, as well as predictors of physical frailty all predict propensity for missing data. Graphical representation of Model 1 incorporating this selection model is shown in Figure 5 of the Supplementary Materials. Secondly, depressive symptoms are measured by the full set of eight items of the CESD instrument rather than just the six selected items.

Mplus version 7.4 (Muthén & Muthén, 1998-2012) is used to perform structural equation modeling while STATA version 14.1 is used for all other analyses. Statistical significance is primarily assessed at the 5% level. However, for examination of moderation using four separate regression models, Bonferroni's correction is implemented to adjust for multiple comparisons such that statistical significance is assessed at the 1.25% level.

Results

Table 1 shows the characteristics of the study population at wave 2 (2004). The mean age is 74 years, and women comprise 55% of respondents. Using the Frailty Index, almost 20% of them are classified as being frail at wave 2, with this proportion being higher among women and those aged 75 years and older. This proportion increases to almost 25% at wave 6, with corresponding increase over time observed across gender and age group. Among multidimensional conditions at baseline (wave 2), there are minor gender-specific differences in levels of chronic disease, allostatic load, low physical activity, cognitive impairment, and poor social integration. However, differences are more marked for obesity and depressive symptoms, which affect women more. As expected, women report less smoking, alcohol consumption, and poor social support, but have lower education and wealth. Those in the older age group have higher levels of chronic disease, allostatic load, depressive symptoms, cognitive impairment, and poor social integration, while having lower levels of physical activity, educational attainment, and wealth than those younger. For them, smoking is more common while obesity and heavy alcohol intake are less so. They also have better social support.

Table 1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses

Variables		All	By gender		By Age group	
			Male	Female	< 75 years	>= 75 years
General:						
Mean age, years (SD)		74.0 (6.3)	73.5 (6.2)	74.3 (6.4)	69.3 (2.8)	80.2 (3.9)
Female, n/N (%)		2,568/4,638 (55.4)	-	-	1,399/2,643 (52.9)	1,169/1,995 (58.6)
Physical frailty:						
Mean average walking speed, m/sec (SD):		0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
Hand grip strength, kg (SD)		25.9 (10.2)[6]	33.4 (8.9)[7]	19.6 (6.1)[8]	28.4 (10.2)[9]	22.2 (8.2)[10]
Exhaustion, n/N (%):		1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
Frailty by Frailty Index, n/N (%):	Wave 2	717/3,647 (19.7)	236/1,639 (14.4)	481/2,008 (24.0)	322/2,207 (14.6)	395/1,440 (27.4)
	Wave 4	507/2,371 (21.4)	158/1,051 (15.0)	349/1,320 (26.4)	279/1,571 (17.8)	228/800 (28.5)
	Wave 6	438/1,774 (24.7)	145/768 (18.9)	293/1,006 (29.1)	285/1,325 (21.5)	153/449 (34.1)

Physical:					
Obesity, n (%)	1,018/3,976 (25.6)	400/1,783 (22.4)	618/2,193 (28.2)	662/2,328 (28.4)	356/1,648 (21.6)
Mean chronic disease count [out of 14] (SD)	1.9 (1.4)[11]	1.8 (1.4)[12]	2.0 (1.4)[13]	1.8 (1.4)[14]	2.1 (1.5)[15]
Mean allostatic load score [out of 8] (SD)	2.0 (1.5)[16]	1.9 (1.5)[17]	2.1 (1.5)[18]	1.9 (1.5)[19]	2.1 (1.5)[20]
Mean low physical activity level, [0 of 3] (SD)	1.2 (0.9)[21]	1.1 (0.9)[22]	1.3 (0.9)[23]	1.0 (0.9)[24]	1.4 (0.9)[25]
Smoking history, n (%)	2,963/4,634 (63.9)	1,567/2,069 (75.7)	1,396/2,565 (54.5)	1,649/2,639 (62.5)	681/1,995 (65.9)
Heavy alcohol intake, n (%)	1,249/3,871 (32.3)	720/1,742 (41.3)	529/2,129 (24.9)	792/2,344 (33.8)	457/1,527 (29.9)
Psychological:					
Mean CESD-8 score [0 to 8] (SD)	1.7 (2.0)[26]	1.3 (1.7)[27]	1.9 (2.1)[28]	1.5 (1.9)[29]	1.9 (2.0)[30]
Mean cognitive impairment score [0 to 49] (SD)	27.5 (6.3)[31]	26.3 (6.4)[32]	25.5 (6.5)[33]	24.1 (6.0)[34]	28.4 (6.3)[35]
Social:					
Low education, n (%)	2,256/4,618 (48.9)	885/2,061 (41.5)	1,401/2,557 (54.8)	1,158/2,630 (44.0)	1,098/1,998 (55.2)
Low wealth, n (%)	980/4,557 (21.5)	365/2,022 (18.1)	615/2,535 (24.3)	454/2,584 (17.6)	526/1,973 (26.7)
Mean poor social support score [0 to 54] (SD)	13.7 (7.0)[36]	14.7 (7.0)[37]	12.9 (6.8)[38]	13.9 (7.0)[39]	13.3 (6.8)[40]
Mean poor social interaction score [0 to 14] (SD)	6.6 (2.5)[41]	6.7 (2.6)[42]	6.5 (2.5)[43]	6.4 (2.5)[44]	7.0 (2.6)[45]

Frailty: Frailty Index >=0.25

CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)

Unless indicated otherwise, N=4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old).

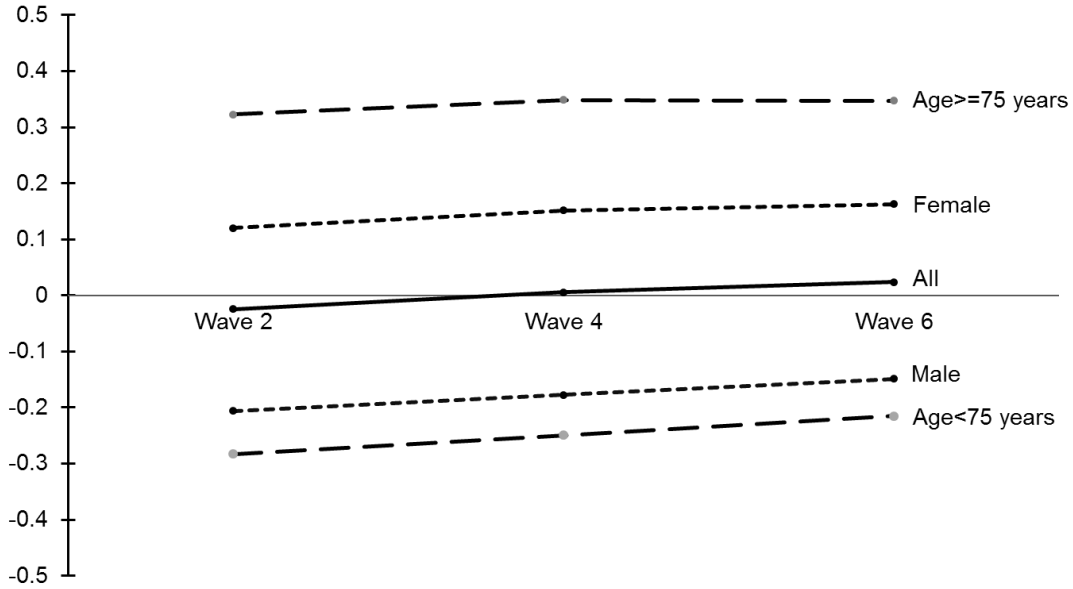
N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]3,869 [7]1,760 [8]2,109 [9]2,276 [10]1,593 [11]4,608 [12]2,052 [13]2,556 [14]2,617 [15]1,991 [16]2,319 [17]1,064 [18]1,255 [19]1,436 [20]883 [21]4,567 [22]2,032 [23]2,535 [24]2,611 [25]1,956 [26]4,479 [27]1,987 [28]2,492 [29]2,586 [30]1,893 [31]4,349 [32]1,946 [33]2,403 [34]2,546 [35]1,803 [36]3,339 [37]1,529 [38]1,810 [39]2,068 [40]1,271 [41]3,267 [42]1,506 [43]1,761 [44]2,035 [45]1,232

Among the performance measures on which the three indicators for physical frailty are based, hand grip strength (weakness) clearly decreases at successive waves across gender and age group, while walking speed (slowness) does so very minimally or not at all. The trends are mixed for exhaustion with either increase or decrease in proportion reporting this across waves (Supplementary Materials, Table 6). Notably, missing values increase to 50 to 60% by wave 6. In addition, time-varying predictors show increased mean values across waves, with most also

doing so across gender and age group (Supplementary Materials, Table 7). Here, missing values occur in 30 to 40% of cases by wave 4.

Graphical representation of derived physical frailty factor scores (unadjusted) at waves 2, 4, and 6 is provided in Figure 2. Over this period, mean physical frailty factor score increases by approximately 0.05. This is a relatively small increase considering that the standard deviation (SD) of factor scores at wave 2 is 0.81. Mean factor scores for women and those in the older group are higher.

Figure 2. Trajectories of unadjusted physical frailty factor scores across wave 2, 4, and 6 of the English Longitudinal Study of Ageing: mean values for whole group and subgroups



N = 4,560 (all), 2,025 (male), 2,535 (female), 2,616 (less than 75 years old), and 1,944 (at least 75 years old)

Table 2 shows that even after controlling for the effects of other predictors, older age, female gender, obesity, being underweight, low education, and low wealth are all associated with higher levels of initial physical frailty given their positive and significant coefficients in the first column. On the other hand, smoking is not significantly associated with initial physical frailty, while high alcohol intake has a negative and significant coefficient, and is therefore associated with lower levels of initial physical frailty. Coefficients in the second to fifth columns of Table 2 indicate that the magnitude of effect for obesity is larger among women, while that for low education is larger among men. In addition, the magnitude of effect for older age is larger among those at least 75 years of age, while that for low wealth is larger among those below 75

years of age. However, all these differences across gender and age group are not statistically significant.

Table 2. Predictors of initial physical frailty: standardized coefficients of latent growth curve models

	All	Gender		Age	
		Male	Female	< 75 years	>= 75 years
Effects of time-invariant predictors (wave 2) on physical frailty intercept factor					
Older age	0.563*	0.569*	0.584*	0.207*	0.443*
Female gender	0.419*	-	-	0.449*	0.484*
Obesity	0.101*	0.036	0.152*	0.132*	0.091*
Underweight	0.051*	0.085	0.033	0.064	0.048
Smoking history	0.038	0.032	0.043	0.059*	0.017
High alcohol intake	-0.101*	-0.078*	-0.120*	-0.129*	-0.083*
Low education	0.147*	0.189*	0.116*	0.177*	0.141*
Low wealth	0.113*	0.112*	0.122*	0.163*	0.078*

* Indicates p-value <0.05

Standardized coefficients are interpreted as change in physical frailty intercept in standard deviation (SD) units for a one SD increase in continuous predictors, or from zero to one for binary predictors (female gender, obesity, underweight, smoking history, high alcohol intake, low education, and low wealth).

N = 4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old)

Of greater interest are those associations with future physical frailty across waves 2, 4, and 6, which better reflect their true predictive effects. Firstly, the correlation between the intercept (initial physical frailty) and slope (physical frailty change) factors is -0.206 (p-value>0.05), which indicates a non-significant trend towards higher levels of initial physical frailty being associated with less steep increase in physical frailty over time. This could be related in part to a ceiling effect. Next, none of the time-invariant predictors predict greater increase in physical frailty levels over time controlling for the effects of other predictors as shown by the non-significant coefficients in the first column in the upper section of Table 3. However, the predictive effect of older age is stronger and significant in men and those less than 75 years of age, although these differences across gender and age group are not statistically significant. Among time-varying predictors, chronic disease, allostatic load, low physical activity, depressive symptoms, cognitive impairment, and poor social support all predict higher future physical frailty levels controlling for the effects of other time-varying predictors as well as those of time-invariant predictors on the physical frailty slope factor. The statistically significant coefficients in the first column in the lower section of Table 3 indicate that one SD increase in levels of these conditions predicts increase of 0.07 to 0.24 SD in physical frailty levels two years later. These

are non-trivial effects given that the mean physical frailty level of the study population only increases by 0.06 SD over two years. Judging by the coefficients in the second to fifth columns, the magnitude of effect is generally consistent across gender and age group except for those for depressive symptoms and poor social support, which are higher in the older age group, although these differences are also not significant. Notably, poor social integration did not predict higher physical frailty levels.

Table 3. Predictors of future physical frailty (waves 2, 4, and 6): standardized coefficients from latent growth curve models

	All	Gender		Age	
		Male	Female	< 75 years	>= 75 years
Effects of time-invariant predictors (wave 2) on physical frailty slope factor					
Older age	0.288	0.481*	0.132	0.226*	-0.071
Female gender	0.062	-	-	0.294	-0.560
Obesity	0.156	0.210	0.114	0.104	0.214
Underweight	-0.040	<0.001	-0.063	-0.058	0.029
Smoking history	-0.058	-0.028	-0.089	-0.074	-0.003
High alcohol intake	0.019	-0.010	0.047	0.073	-0.101
Low education	-0.058	0.077	-0.139	-0.055	-0.030
Low wealth	0.100	-0.039	0.174	0.090	-0.051
Effects of lagged time-varying predictors (waves 1, 2, and 4) on physical frailty factor (waves 2, 4, and 6)					
Chronic disease	0.236*	0.264*	0.220*	0.259*	0.271*
Allostatic load	0.108*	0.132*	0.088*	0,118*	0.130*
Low physical activity	0.189*	0.191*	0.193*	0.205*	0.192*
Depressive symptoms	0.115*	0.130*	0.108*	0.108*	0.167*
Cognitive impairment	0.182*	0.222*	0.160*	0.181*	0.195*
Poor social support	0.067*	0.065*	0.074*	0.063*	0.109*
Poor social integration	0.007	0.029	-0.015	0.016	-0.024

* Indicates p-value <0.05

For time-invariant predictors, standardized coefficients are interpreted as change in physical frailty slope in standard deviation (SD) units for one SD increase in continuous predictors, or from zero to one for binary predictors (female gender, obesity, underweight, smoking history, high alcohol intake, low education, and low wealth). For time-varying predictors, standardized coefficients are interpreted as increase in physical frailty factor in SD units for their one SD increase.

N = 4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old)

Beyond gender- and age group-specific effects observed, effects of predictors in specific subgroups are of interest. For these, moderated effects are relevant and are shown in Table 4.

Table 4. Moderation of predictors of future physical frailty: standardized coefficients from latent growth curve models

	Low physical activity		Depressive symptoms		Poor social support		Poor social integration	
	Below mean [a]	Above mean [b]	Below mean [c]	Above mean [d]	Below mean [e]	Above mean [f]	Below mean [g]	Above mean [h]
Effects of time-invariant predictors (wave 2) on physical frailty slope factor								
Older age	0.324**	0.117	0.246*	0.157	0.342*	0.198	0.514**	0.285
Female gender	0.171	-0.174	0.106	0.012	-0.139	0.262	0.002	0.179
Obesity	0.079	0.199*	0.112	0.112	0.026	0.220	0.069	0.407*
Underweight	-0.131	0.197	-0.081	0.041	-0.112	0.021	-0.110	0.047
Smoking history	-0.001	-0.087	-0.046	0.042	-0.091	-0.021	-0.204	0.046
High alcohol intake	-0.045	0.138	-0.014	0.093	0.002	0.020	0.009	0.054
Low education	-0.063	0.029	-0.018	-0.038	-0.047	-0.024	-0.014	-0.156
Low wealth	0.171*	-0.029	0.094	0.048	0.162	0.024	0.233	0.101
Effects of lagged time-varying predictors (waves 1, 2, and 4) on physical frailty factor (waves 2, 4, and 6)								
Chronic disease	0.233**	0.243**	0.240**	0.229**	0.261**	0.216**	0.247**	0.222**
Allostatic load	0.078**	0.099**	0.108**	0.135**	0.109**	0.109**	0.095**	0.121**
Low physical activity	0.132**	0.140**	0.185**	0.189**	0.164**	0.208**	0.176**	0.191**
Depressive symptoms	0.098**	0.120**	0.054**	0.038*	0.127**	0.101**	0.111**	0.122**
Cognitive impairment	0.177**	0.207**	0.203**	0.164**	0.187**	0.181**	0.181**	0.180**
Poor social support	0.091**	0.058*	0.071**	0.009	0.068**	0.012	0.059**	0.072**
Poor social integration	-0.015	0.032	0.005	0.008	0.003	0.010	0.019	-0.011

* Indicates p-value <0.05 but >=0.0125

** Indicates p-value <0.0125 (to take into account Bonferroni's correction for 4 comparison models)

N = [a]2,819 [b]1,819 [c]3,324 [d]1,314 [e]2,275 [f]2,363 [g]2,244 [h]2,394

For time-invariant predictors, standardized coefficients are interpreted as change in physical frailty slope in standard deviation (SD) units for one SD increase in continuous predictors, or from zero to one for binary predictors (female gender, obesity, underweight, smoking history, high alcohol intake, low education, and low wealth). For time-varying predictors, standardized coefficients are interpreted as increase in physical frailty factor in SD units for their one SD increase.

Among time-invariant predictors, female gender has a stronger effect on physical frailty change among those with poorer social support and poorer social integration, while obesity has a stronger effect on physical change among those with lower physical activity, poorer social support, and poorer social integration. However, all these differences do not reach statistical significant levels. Among time-varying predictors, allostatic load has a stronger effect on future physical frailty among those with more depressive symptoms and poorer social integration, while low physical activity has a stronger effect on those with poorer social support. Yet again, these differences are relatively small and not statistically significant.

Indirect or mediated effects of time-varying predictors on physical frailty slope factor are shown in Table 5. Among these, the indirect effects of low physical activity, depressive symptoms, and cognitive impairment on physical frailty through chronic disease and allostatic load are significant given their respective coefficients in the first column. Indirect effects through chronic disease are stronger than those through allostatic load. Together, they account for at most one-fifth of the total effects of these predictors (results not shown). The indirect effects through chronic disease are generally consistent across gender and age group. The exceptions are that of cognitive impairment, which is stronger among those in the younger age group, and poor social support, which are stronger among women and those in the older age group. The indirect effect of depressive symptoms through allostatic load is stronger in men. However, all these differences are not statistically significant.

The results for moderation of indirect effects are provided in the Supplementary Materials (Table 8). Overall, there are minor and non-significant differences in indirect effects across categories of low physical activity, depressive symptoms, poor social support, and poor social integration. The exception is the stronger indirect effect of poor social support through chronic disease among those with poorer social integration, with the difference being statistically significant at the 5% level, but not at the 1.25% level.

Sensitivity analyses that explore MNAR by incorporating the Wu and Carroll selection model in Model 1 indicate that there are only minor differences in predictor coefficients, with those predicting future physical frailty being smaller, when compared with those assuming MAR using FIML. Their comparative results are shown in the Supplementary Materials (Table 9) . Notably, age significantly predicts greater increase in physical frailty levels over time, while smoking predicts initial physical frailty levels, but being underweight does not in the selection model. Other than these differences, the list of significant predictors is identical to that for the original model assuming MAR. In other words, assuming the worst-case scenario that missing values due to dropout by death or other reasons are MNAR does not change the interpretation of the key results. Furthermore, specifying depressive symptoms with the full set of eight items of the CESD instrument rather than just six of them as we did only results in marginal changes in the coefficient for depressive symptoms (results not shown). It is also worth mentioning that most of the key findings on moderation are significant when accounting for multiple comparisons with Bonferroni's correction.

Table 5. Effects of predictors (waves 1, 2, and 4) on future physical frailty (waves 2, 4, and 6) mediated by chronic disease and allostatic load (waves 2, 4, and 6): standardized coefficients from latent growth curve models

	All	Gender		Age	
		Male	Female	<75 years	>=75 years
Indirect effect on physical frailty through chronic disease:					
Low physical activity	0.052*	0.047*	0.054*	0.048*	0.065*
Depressive symptoms	0.036*	0.041*	0.029*	0.038*	0.041*
Cognitive impairment	0.015*	0.020*	0.014*	0.017*	0.004
Poor social support	0.007	0.004	0.013*	0.013*	0.001
Poor social integration	-0.004	-0.001	-0.008	-0.003	-0.012
Indirect effect on physical frailty through allostatic load:					
Low physical activity	0.007*	0.009*	0.004	0.009*	0.004*
Depressive symptoms	0.002*	0.008*	<0.001	0.002*	0.004*
Cognitive impairment	0.004*	0.002*	0.003	0.003*	0.006
Poor social support	0.001	0.003	0.001	0.003	-0.003
Poor social integration	0.001	0.002	<0.001	<0.001	0.002

* Indicates p-value <0.05

Standardized coefficients are interpreted as increase in physical frailty factor in SD units for one SD increase in the predictors.

N = 4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old)

Discussion

While much work has already done on predictors of physical frailty in older people, less is known on *for whom* and *how* they exert their effects. Thus, this study not only concerns the effects of multidimensional predictors, but also their moderators and indirect effects. We adopt a life course approach to the extent that we include candidate predictors of physical frailty that reflect conditions in earlier life such as allostatic load, smoking history, low education, and perhaps low wealth. However, genetic influences and childhood social conditions are not included although it will be ideal to do so. Although ELSA includes a life history interview conducted at wave 3, information on adverse circumstances in childhood is not available for about half of our study population, including those who died or dropped out by then. Furthermore, genetic influences are not the focus of this study.

Observing associations between baseline physical frailty and conditions measured concurrently does not necessarily permit understanding of the direction of effect. Rather, these associations describe how physical frailty levels vary with a broad set of physical, psychological, and social conditions in older people. Nevertheless, obesity, low education, and low wealth may to an extent reflect prior health and social conditions in early to mid-life, and therefore, can arguably be considered predictors of initial physical frailty. In the case of smoking, its association with initial physical frailty may be attenuated and therefore, not significant due to selection effects in that smokers with more adverse health may have died and are not available for inclusion in the study at wave 2. However, the direction of effect is less certain for high alcohol intake. Indeed, the negative association between high alcohol intake and initial physical frailty may be explained by reverse causality where people with higher frailty levels are likely to consume less alcohol by reason of their ill health.

On the other hand, we can be more confident of the predictive effects of those conditions associated with future physical frailty given their explicit temporal relationship. Here, we find that chronic disease, allostatic load, low physical activity, depressive symptoms, cognitive impairment, and poor social support all predict increase in future physical frailty levels after accounting for the effects of other measured predictors. In other words, these predictors adversely influence the trajectory of physical frailty over time. These findings provide some measure of evidence for their possible causal effects on physical frailty if we assume that the physical, psychological, and social predictors controlled for in our analyses are sufficient to account for important confounding due to omitted variables. In general, our findings are consistent those of previous studies that demonstrate the effects of specific predictors while addressing potential confounding to varying degrees. These include evidence that low physical activity increases the risk of developing frailty, with sedentary behavior being a distinct risk factor (Song et al., 2015). However, we did not observe that female gender, obesity, underweight, smoking, high alcohol intake, low education level, low wealth, and poor social interaction influence physical frailty progression as suggested by previous studies (Etman et al., 2012; Gruenewald et al., 2009; Peek et al., 2012; Strawbridge et al., 1998; Syddall et al., 2010;

Woods et al., 2005). It is possible that female gender, low education, and low wealth may have already exerted a major part of their effects on initial physical frailty, and thus may not have any additional and significant impact during the follow-up years of our study. Furthermore, the effects of other predictors such as obesity, underweight, and poor social integration may overlap with those of stronger predictors and be subsumed under the effects of the latter. Finally, our choice for operationalization of predictors may not be optimal with respect to representing the intended constructs, thereby resulting in attenuation of any true effects.

We could not demonstrate any significant gender- or age-specific effects of predictors of physical frailty. In addition, we did not find evidence of moderation by low physical activity, depressive symptoms, poor social support, and poor social integration, because observed differences in effects of predictors are not statistically significant across categories of these four conditions.

However, we identify chronic disease and allostatic load as mediators of indirect effects on physical frailty, albeit only for selected predictors. Specifically, these two conditions mediate the effects of low physical activity, cognitive impairment, and depressive symptoms. To date, similar findings have not been reported. These findings answer in part the question on *how* predictors exert their effects. Another point worth highlighting is that we have restricted the choice of candidate mediators to those identified by the Canadian working framework (Bergman et al., 2004). It is quite possible that other lifestyle-related and psychological conditions may also have roles as mediators. This is a subject for further investigation. Finally, we demonstrate the moderating effect of poor social integration on the indirect effect of poor social support through chronic disease, which reflects the role of social conditions on pathways to physical frailty. To a limited extent, this finding answers the question of *for whom* the indirect effect of predictors of physical frailty is stronger.

From a methodological perspective, our study has a few important limitations. Firstly, it is an observational investigation using secondary data. This imposes limits to which we are able to specify predictors especially those in the psychological and social domains. However, using the available data, we are able to operationalize established measurement instruments such as CESD for depressive symptoms, and implement composite measures devised by others to represent more complex constructs like poor social support and poor social integration (Banks et al., 2010). Beyond measurement, there is the possibility that unobserved confounding due to omitted variables exists, thereby introducing bias in our results. In the attempt to address this, we have carefully included a broad set of important physical, psychological, and social predictors based on the existing literature and have controlled for them in our analyses. As mentioned, genetic influences and early childhood social conditions are not included as predictors. Of interest, childhood socioeconomic position was found to be associated with relatively small reductions in gait speed and grip strength (Birnie et al., 2011). Nevertheless, unless the effects of omitted variables such as these are large and highly correlated with those of other predictors, it is not very likely that any residual confounding will be severe enough to

alter our study conclusions. Secondly, missing values which are inevitable in a longitudinal study such as ours pose challenges to validity. These are handled by FIML, which assumes that missing values are MAR. However, missing values due to dropout or death may be MNAR, given that their occurrence may be conditional on prior values of physical frailty. Thus, by way of sensitivity analyses, we incorporate more advanced modeling that takes into account that missing values may be MNAR. Indeed, these additional analyses using the shared parameter model which regresses binary missing data indicators on the two growth factors did not change the main results more than trivially, thus providing greater reassurance that our study conclusions are robust to missing values. Finally, our use of separate models for estimating moderating effects increases the risk of discovering significant effects purely by chance. To reduce this risk, we restrict our analyses to those investigating a limited set of pathways that are defined a priori, and use Bonferroni's correction to account for multiple comparisons. Applying the latter procedure, most of our key results remain statistically significant.

Our findings are relevant to health and social policy formulation. Particularly, knowledge of predictors of physical frailty progression as well as their mediators and moderators provides guidance on thinking about how physical frailty may be potentially modified by interventions. Based on the findings of our study, chronic disease, allostatic load, low physical activity, depressive symptoms, cognitive impairment, poor social support, and poor social integration represent potential target conditions for programs and policies directed at reducing physical frailty in older people. Moreover, obesity, low education, and low wealth probably represent prior conditions that could be better addressed in young and middle-aged people in the hope of reducing the risk of developing physical frailty as they transit to later life. While it might be argued that health and social care initiatives to address some of these issues may already exist in certain jurisdictions, focus on addressing specific components of allostatic load that have to date received less attention. For example, reducing chronic systemic inflammation from early life through lifestyle changes in diet, weight loss, and exercise is a specific area for attention (Nicklas et al., 2005). Equally important, population-level initiatives to identify depression and facilitate or encourage physical activity may need to be drawn up or may bear strengthening even if already in place. Poor social support is a more challenging issue to address at it occurs at the personal relationship level. Public education that highlights the importance of increasing social support, and particularly, that of providing emotional support should be explored. Poor social integration may be addressed by provision of interventions designed to reduce social isolation including social facilitation interventions involving group-based activities such as friendship clubs, day care centers, and social networking, Other useful interventions are health and social care in the form of community gatekeepers, geriatric rehabilitation, and visitation programs, as well as leisure and skill development activities such as gardening programs, computer use, and voluntary work (Gardiner et al., 2016).

Although our findings are informative, they nevertheless point to specific gaps in our understanding of physical frailty in older people. To begin with, further research to identify specific subgroups for whom the predictive effects on physical frailty are stronger is needed.

Psychological deficits and adverse social conditions may define these subgroups. Finally, and as alluded to earlier, the possibility of alternative mediators including psychological conditions such as depression should be explored.

In conclusion, our study validates at least in part the pathways to frailty put forth by the Canadian working framework (Bergman et al., 2004). Potentially modifiable predictors of future physical frailty in late life extend across more than one domain, and include low physical activity, cognitive impairment, depressive symptoms, and poor social support. In addition, obesity, low education, and low wealth may be addressable predictors in early or mid-life. Moreover, chronic disease and allostatic load are mediators, while poor social integration is a moderator on pathways to physical frailty. These findings provide supporting evidence for multi-pronged population-level health and social interventions that target these conditions in broad strategies for minimizing the development or worsening of physical frailty in older people.

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Supplementary Materials

Mathematical equations for the statistical models

Let y_{ti} denote physical frailty for individuals i = 1..., n at times t = 0, 1, and 2 corresponding to waves 2, 4, and 6 respectively, and let x_i be a vector of time-invariant predictors and w_{t-1i} be a vector of lagged time-varying predictors for y_{ti}.

The latent growth curve model for y_{ti} (Model 1) is

$$y_{ti} = \eta_{0i} + \eta_{1i}t + \gamma w_{t-1i} + \varepsilon_{ti}$$

for subject i at times t = 0, 1, and 2, where ε_{ti} is a normally distributed residual with mean 0 and variance σ_ε, and where

$$\eta_{0i} = \alpha_0 + \beta_0 x_i + \zeta_{0i} \quad \text{(a)}$$

$$\eta_{1i} = \alpha_1 + \beta_1 x_i + \zeta_{1i} \quad \text{(b)}$$

are referred to as the intercept growth factor and the slope growth factor (i.e. the coefficient of time t) respectively, and where ζ_{0i} and ζ_{1i} are normally distributed random effects with means 0 and variances $\sigma_{\zeta 0}$ and $\sigma_{\zeta 1}$ and covariance $\sigma_{\zeta 01}$.

Here, the coefficients β_0 describe the associations between the time-invariant predictors and physical frailty at wave t = 0, the coefficients β_1 the effect of time-invariant predictors on the coefficient of t on physical frailty (the time slope), and the coefficients γ the association between time-varying predictors and within-person change in physical frailty, The estimated coefficients β_0, β_1, and γ for different predictors are shown in Table 2, and the upper and lower parts of Table 3 respectively.

To estimate gender- and age-specific effects, we use the same latent growth curve model for y_{ti}, but stratified into two subgroups according to gender and age group.

Moderation: Here, we use the latent growth curve model for y_{ti} (Model 1) again, but stratified into two subgroups according to four moderating variables, namely low physical activity, depressive symptoms, poor social support, and poor social integration (Model 2).

Mediation: Here we use the results of standard linear path analysis, applied to model (b) for the slope factor. For simplicity of notation in introducing the idea, consider the case of two lagged time-varying predictors $w_{t-1i} = (v_{t-1i}, m_{t-1i})$ (the extension to cases with more variables is also analogous), the latent growth curve model for y_{ti} is then

$$y_{ti} = \eta_{0i} + \eta_{1i}t + \gamma_1 v_{t-1i} + \gamma_2 m_{t-1i} + \varepsilon_{ti}$$

Again, suppose further that

$$m_{t-1i} = \lambda_0 + \lambda_1 v_{t-1i} + \delta_{t-1i}.$$

Then the model given v_{t-1i} only, averaging over the distribution of m_{t-1i}, is

$$y_{ti} = \eta_{0i} + \eta_{1i}t + \gamma^*_1 v_{t-1i} + \varepsilon^*_{ti}$$

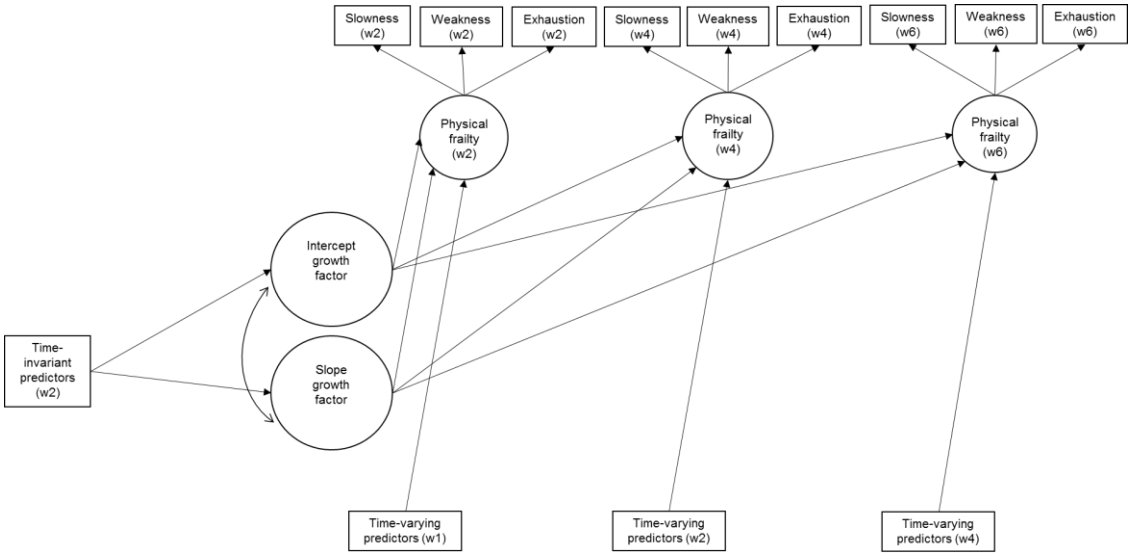
where $\varepsilon^*_{ti} = (\varepsilon_{ti} + \gamma_2 \delta_{t-1i})$ and $\gamma^*_1 = \gamma_1 + \gamma_2 \lambda_1$. Here γ^*_1 is the total effect of the variable v_{t-1i} on y_{ti}, γ_1 is the direct effect of v_{t-1i}, and $\gamma_2 \lambda_1$ the indirect effect of v_{t-1i} mediated via m_i (Model 3).

Here, to estimate gender- and age-specific effects, we use the same mediation model, but stratified into two subgroups according to gender and age group.

Moderated mediation: Here, we use the latent growth curve model for y_{ti} including mediated effects (Model 3) but stratified into two subgroups according for gender, age group, and four moderating variables, namely low physical activity, depressive symptoms, negative social interactions, and weak social network.

Here, we use the same mediation model (Model 3) again, but stratified into two subgroups according to four moderating variables, namely low physical activity, depressive symptoms, poor social support, and poor social integration (Model 4).

Figure 3. Path diagram of Model 1: conditional latent growth curve model with time-invariant and time-varying predictors



w1: wave 1 w2: wave 2 w4: wave 4 w6: wave 6

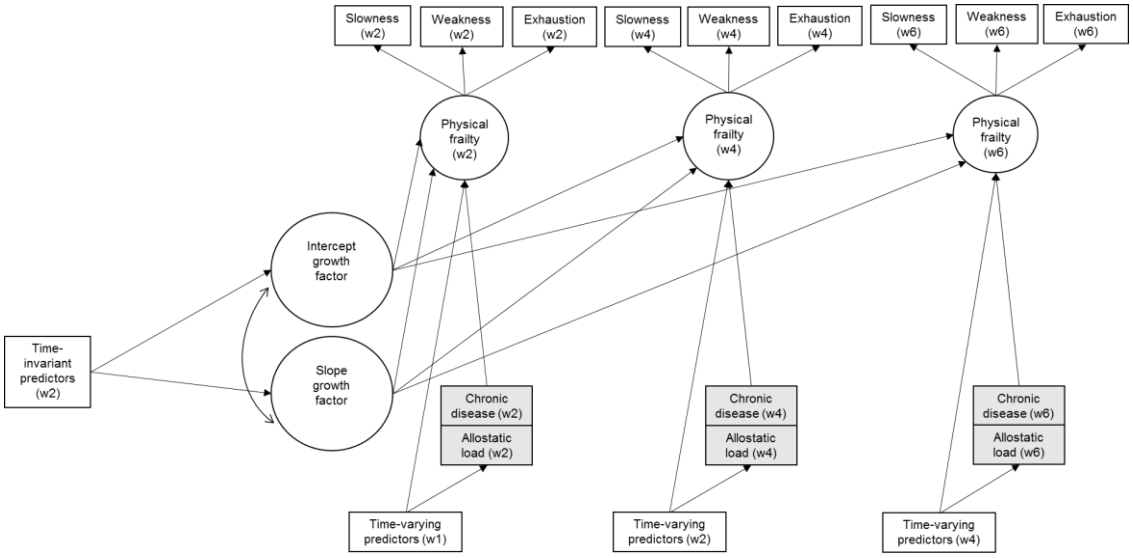
Circle: latent variable

Rectangle: observed variable

Single-headed straight arrow: effect of one variable on another

Double-headed curved arrow: covariance between two variables

Figure 4. Path diagram of Model 3: conditional latent growth curve model with time-invariant and time-varying predictors, and time-varying mediators



w1: wave 1 w2: wave 2 w4: wave 4 w6: wave 6

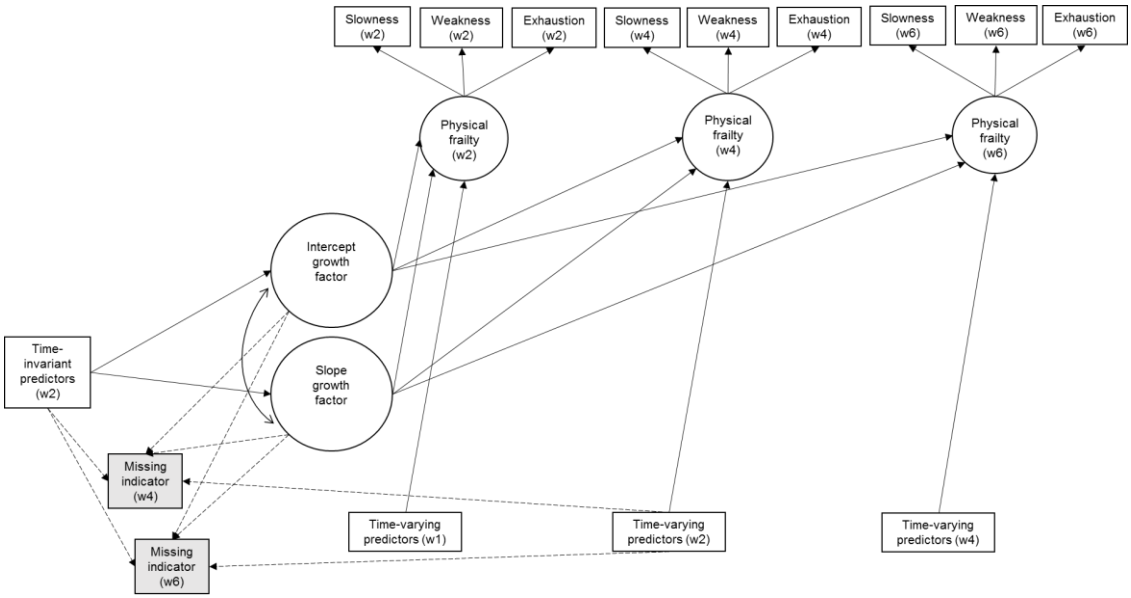
Circle: latent variable

Rectangle: observed variable

Single-headed straight arrow: effect of one variable on another

Double-headed curved arrow: covariance between two variables

Figure 5. Path diagram of Model 1: conditional latent growth curve model with time-invariant and time-varying predictors, and incorporating Wu and Carroll selection model (Enders, 2011) to handle missing not at random (MNAR) data



w1: wave 1 w2: wave 2 w4: wave 4 w6: wave 6

Circle: latent variable

Rectangle: observed variable

Single-headed straight arrow: effect of one variable on another

Double-headed curved arrow: covariance between two variables

Single-headed straight arrow (dashed): effect of one variable on another (for Wu and Carroll selection model)

Table 6. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses: physical frailty-related variables (waves 2, 4, and 6)

Variables		All	By gender		By Age group	
			Male	Female	< 75 years	>= 75 years
Physical frailty:						
Mean average walking speed, m/sec (SD):						
	Wave 2	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
	Wave 4	0.8 (0.3)[6]	0.8 (0.3)[7]	0.7 (0.3)[8]	0.8 (0.3)[9]	0.7 (0.2)[10]
	Wave 6	0.8 (0.3)[11]	0.8 (0.3)[12]	0.7 (0.3)[13]	0.8 (0.3)[14]	0.6 (0.2)[15]
Hand grip strength, kg (SD):	Wave 2	25.9 (10.2)[16]	33.4 (8.9)[17]	19.6 (6.1)[18]	28.4 (10.2)[19]	22.2 (9.0)[20]
	Wave 4	24.3 (10.2)[21]	32.0 (9.0)[22]	18.2 (6.2)[23]	26.6 (10.3)[24]	20.4 (8.6)[25]
	Wave 6	22.8 (9.5)[26]	29.6 (8.8)[27]	17.5 (5.9)[28]	24.4 (9.6)[29]	18.9 (7.9)[30]
Exhaustion, n/N (%):						
	Wave 2	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
	Wave 4	955/2,977 (32.1)	327/1,290 (25.4)	628/1,687 (37.2)	518/1,868 (27.7)	437/1,109 (39.4)
	Wave 6	632/1,962 (32.2)	218/848 (25.7)	414/1,114 (37.2)	401/1,402 (28.6)	231/560 (41.3)
Frailty by Frailty Index n/N (%):	Wave 2	717/3,647 (19.7)	236/1,639 (14.4)	481/2,008 (24.0)	322/2,207 (14.6)	395/1,440 (27.4)
	Wave 4	507/2,371 (21.4)	158/1,051 (15.0)	349/1,320 (26.4)	279/1,571 (17.8)	228/800 (28.5)
	Wave 6	438/1,774 (24.7)	145/768 (18.9)	293/1,006 (29.1)	285/1,325 (21.5)	153/449 (34.1)

Frailty: Frailty Index >=0.25

N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]2,649 [7]1,182 [8]1,467 [9]1,705 [10]944 [11]1,688 [12]754 [13]934 [14]1,254 [15]434 [16]3,869 [17]1,760 [18]2,109 [19]2,276 [20]1,593 [21]2,531 [22]1,115 [23]1,416 [24]1,621 [25]910 [26]1,868 [27]820 [28]1,048 [29]1,339 [30]529

Table 7. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses: time varying predictors and mediators across waves

Variables		All	By gender		By Age group	
			Male	Female	< 75 years	>= 75 years
Physical:						
Mean chronic disease count [out of 14] (SD):						
	Wave 2	1.9 (1.4)[1]	1.8 (1.4)[2]	2.0 (1.4)[3]	1.8 (1.4)[4]	2.1 (1.5)[5]
	Wave 4	2.2 (1.5)[6]	2.1 (1.5)[7]	2.4 (1.5)[8]	2.1 (1.5)[9]	2.5 (1.6)[10]
	Wave 6	2.1 (1.5)[11]	1.9 (1.4)[12]	2.2 (1.5)[13]	2.0 (1.5)[14]	2.3 (1.5)[15]
Mean allostatic load score [out of 8] (SD):						
	Wave 2	2.0 (1.5)[16]	1.9 (1.5)[17]	2.1 (1.5)[18]	1.9 (1.5)[19]	2.1 (1.5)[20]
	Wave 4	2.2 (1.5)[21]	2.0 (1.4)[22]	2.3 (1.5)[23]	2.1 (1.5)[24]	2.4 (1.4)[25]
	Wave 6	2.6 (1.2)[26]	2.5 (1.2)[27]	2.6 (1.2)[28]	2.6 (1.2)[29]	2.5 (1.1)[30]
Mean low physical activity level, n (%):						
	Wave 1	1.1 (0.9)[31]	1.0 (0.9)[32]	1.2 (0.9)[33]	1.0 (0.9)[34]	1.3 (0.9)[35]
	Wave 2	1.2 (0.9)[36]	1.1 (0.9)[37]	1.3 (0.9)[38]	1.0 (0.9)[39]	1.4 (0.9)[40]
	Wave 4	1.3 (1.0)[41]	1.2 (1.0)[42]	1.4 (0.9)[43]	1.1 (0.9)[44]	1.7 (1.0)[45]
Psychological:						
Mean CESD-8 score [0 to 8] (SD):	Wave 1	1.5 (1.9)[46]	1.2 (1.7)[47]	1.8 (2.0)[48]	1.4 (1.9)[49]	1.7 (2.0)[50]
	Wave 2	1.7 (2.0)[51]	1.3 (1.7)[52]	1.9 (2.1)[53]	1.5 (1.9)[54]	1.9 (2.0)[55]
	Wave 4	1.5 (1.9)[56]	1.1 (1.7)[57]	1.8 (2.0)[58]	1.3 (1.8)[59]	1.8 (2.0)[60]
Mean cognitive impairment score [0 to 49] (SD):	Wave 1	25.0 (6.6)[61]	25.2 (6.7)[62]	24.7 (6.5)[63]	23.1 (6.2)[64]	27.5 (6.3)[65]
	Wave 2	27.5 (6.3)[66]	26.3 (6.4)[67]	25.5 (6.5)[68]	24.1 (6.0)[69]	28.4 (6.3)[70]
	Wave 4	25.6 (6.8)[71]	25.8 (6.6)[72]	25.5 (6.9)[73]	24.0 (6.2)[74]	28.6 (6.7)[75]
Social:						
Mean poor social support score [0 to 54] (SD):	Wave 1	13.6 (7.1)[76]	14.9 (7.1)[77]	12.6 (6.8)[78]	13.8 (7.1)[79]	13.3 (7.0)[80]
	Wave 2	13.7 (7.0)[81]	14.7 (7.0)[82]	12.9 (6.8)[83]	13.9 (7.0)[84]	13.3 (6.8)[85]
	Wave 4	13.6 (6.9)[86]	14.5 (7.1)[87]	12.8 (6.6)[88]	13.7 (7.0)[89]	13.2 (6.6)[90]
Mean low poor social integration score [0 to 14] (SD):	Wave 1	6.6 (2.5)[91]	6.7 (2.6)[92]	6.5 (2.5)[93]	6.3 (2.5)[94]	6.9 (2.6)[95]
	Wave 2	6.6 (2.5)[96]	6.7 (2.6)[97]	6.5 (2.5)[98]	6.4 (2.5)[99]	7.0 (2.6)[100]
	Wave 4	6.8 (2.5)[101]	6.8 (2.6)[102]	6.7 (2.4)[103]	6.6 (2.4)[104]	7.2 (2.6)[105]

CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)

N = [1]4,608 [2]2,052 [3]2,556 [4]2,617 [5]1,991 [6]3,115 [7]1,350 [8]1,765 [9]1,909 [10]1,206 [11]2,400 [12]1,022 [13]1,378 [14]1,642 [15]758 [16]2,319 [17]1,064 [18]1,255 [19]1,436 [20]883 [21]1,504 [22]668 [23]836 [24]1,034 [25]470 [26]996 [27]440 [28]556 [29]763 [30]233 [31]4,572 [32]2,036 [33]2,536 [34]2,597 [35]1,975 [36]4,567 [37]2,032 [38]2,535 [39]2,611 [40]1,956 [41]3,125 [42]1,355 [43]1,770 [44]1,915 [45]1,210 [46]4,484 [47]1,999 [48]2,485 [49]2,4557 [50]1,927 [51]4,479 [52]1,987 [53]2,492 [54]2,586 [55]1,893 [56]2,960 [57]1,285 [58]1,675 [59]1,859 [60]1,101 [61]4,371 [62]1,954 [63]2,417 [64]2,503 [65]1,868 [66]4,349 [67]1,946 [68]2,403 [69]2,546 [70]1,803 [71]2,605 [72]1,145 [73]1,460 [74]1,680 [75]925 [76]3,530 [77]1,605 [78]1,925 [79]2,105 [80]1,425 [81]3,339 [82]1,529 [83]1,810 [84]2,068 [85]1,271 [86]2,236 [87]1,000 [88]1,236 [89]1,473 [90]763 [91]3,597 [92]1,641 [93]1,956 [94]2,144 [95]1,453 [96]3,267 [97]1,506 [98]1,761 [99]2,035 [100]1,232 [101]2,184 [102]984 [103]1,200 [104]1,445 [105]739

Table 8. Moderation of mediated effects on future physical frailty: standardized coefficients from latent growth curve models implementing multiple groups

	Low physical activity		Depressive symptoms		Poor social support		Poor social integration	
	Below mean [a]	Above mean [b]	Below mean [c]	Above mean [d]	Below mean [e]	Above mean [f]	Below mean [g]	Above mean [h]
Indirect effect on physical frailty through chronic disease:								
Low physical activity	0.027**	0.053**	0.051**	0.052**	0.054**	0.052**	0.051**	0.054**
Depressive symptoms	0.039**	0.030**	0.037**	0.024**	0.042**	0.033**	0.042**	0.032**
Cognitive impairment	0.013**	0.012	0.016**	0.014	0.020**	0.012*	0.023**	0.014*
Poor social support	0.007	0.010	0.006	0.007	0.005	0.006	0.004ł	0.016*ł
Poor social integration	-0.004	-0.007	-0.002	-0.011	-0.004	-0.004	-0.003	-0.007
Indirect effect on physical frailty through allostatic load:								
Low physical activity	0.005*	0.003	0.008*	0.005	0.010*	0.006*	0.007	0.006*
Depressive symptoms	0.002*	0.001	0.003*	0.002	0.003*	0.002*	0.001	0.003*
Cognitive impairment	0.003	0.004	0.003*	0.005	0.007*	0.002	0.002	0.006*
Poor social support	0.002	-0.001	0.001	0.001	0.002	<0.001	0.002	0.001*
Poor social integration	<0.001	0.001	-0.001	0.004	0.000	0.001	0.001	<0.001

* Indicates p-value <0.05 but >=0.0125

** Indicates p-value <0.0125 (to take into account Bonferroni's correction for 4 comparison models)

ł Indicates moderation with p-value <0.05 but >=0.0125

N=4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old)

For subgroups, N = [a]2,819 [b]1,819 [c]3,324 [d]1,314 [e]2,275 [f]2,363 [g]2,244 [h]2,394

Table 9. Sensitivity analyses to explore data being missing not at random (MNAR): standardized coefficients from latent growth curve models

Predictor	MAR: using FIML	MNAR: using shared parameter model
Effects of time-invariant predictors (wave 2) on physical frailty intercept factor		
Older age	0.563*	0.586*
Female gender	0.419*	0.191*
Obesity	0.101*	0.126*
Underweight	0.051*	0.042
Smoking history	0.038	0.045*
High alcohol intake	-0.101*	-0.118*
Low education	0.147*	0.167*
Low wealth	0.113*	0.132*
Effects of time-invariant predictors (wave 2) on physical frailty slope factor		
Older age	0.288	0.367*
Female gender	0.062	0.059
Obesity	0.156	0.104
Underweight	-0.040	0.053
Smoking history	-0.058	-0.072
High alcohol intake	0.019	0.067
Low education	-0.058	-0.028
Low wealth	0.100	0.063
Effects of lagged time-varying predictors (waves 1, 2, and 4) on physical frailty factor (waves 2, 4, and 6)		
Chronic disease	0.236*	0.178*
Allostatic load	0.108*	0.067*
Low physical activity	0.189*	0.145*
Depressive symptoms	0.115*	0.099*
Cognitive impairment	0.182*	0.097*
Poor social support	0.067*	0.059*
Poor social integration	0.007	-0.016

8.3 Further Thoughts

Although predictors of physical frailty with effects in early or mid-life such as obesity, low education, and wealth are identified in this study, the main purpose here is to uncover conditions that increase risk of developing physical frailty or its worsening when a person is already in late life. Gratifyingly, the effects of a number such conditions in lifestyle-related, psychological, and social domains have been identified. These include low physical activity, depressive symptoms, cognitive impairment, poor social support, and poor social integration. Given the potential for their modification by interventions in older people, these conditions deserve attention in the formulation of health and social strategies. While prevention of chronic disease is already an established component of these strategies in most places, allostatic load is more complex entity that requires a multi-pronged approach to address its different components.

Notwithstanding efforts directed at preventing or slowing down the progression of physical frailty in older people, we can only expect reduction of physical frailty to be achieved in part. Even with the most appropriate health and social interventions, many older people will still continue to develop physical frailty with advancing age. Thus, it is imperative that we also turn our attention to examining the effects of physical frailty. Understanding the pathways from physical frailty to these adverse outcomes will be the focus of the rest of my thesis.

9 Fourth Paper

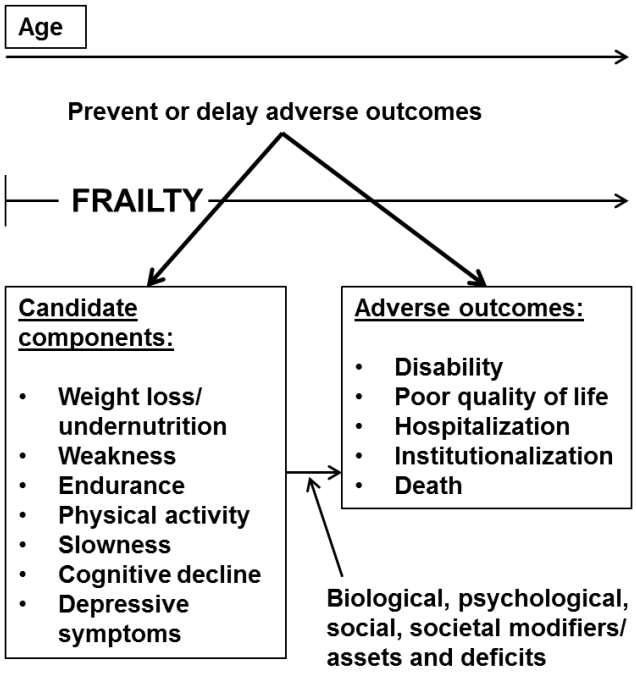
9.1 Introduction

Having identified the predictors of physical frailty and their moderated and indirect effects, I will now proceed to explore key adverse outcomes of physical frailty in older people, namely death and activity limitation. In the fourth paper, I will focus on its effect on death. We already know that frailty increases the risk of death (Buchman et al., 2009; Cawthon et al., 2007; Gu et al., 2009; A. B. Mitnitski et al., 2004; Rockwood et al., 2011). What is less clear are *for whom* physical frailty has stronger effect on death, and *how* physical frailty leads to death. In other words, there is less evidence available on moderators and indirect effects of physical frailty on death. A good understanding of pathways from physical frailty to death can inform public health and social policy on appropriate strategies for improving longevity in older people. To this end, the fourth paper seeks to examine the negative effects of physical frailty on longevity, and pays attention to moderators and indirect effects.

The research aim is to explore the validity of a framework of pathways from frailty to death by quantifying the relationship of physical frailty with multidimensional conditions on these pathways. I will seek to answer the research question: “Which physical, psychological, and social conditions moderate or mediate the effect of physical frailty on death in older people?”

For the conceptual model for pathways from physical frailty to death, I will again adopt the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004). The right side of the working framework on pathways to frailty is now the focus of this paper, and is reproduced in Figure 9.1 (page 153). As for the third paper, physical frailty is specified with three indicators rather than the seven components proposed in this framework (box on the left in Figure 9.1). That aside, the challenge is to identify the biological, psychological, and social conditions represented by the assets and deficits (lower right corner of Figure 9.1), which moderate the effect of physical frailty on death (arrow to that path). The foregoing literature review identified that in the Canadian Study of Health and Aging, death rates for those aged over 75 years who exercised were similar to those aged from 65 to 75 years who did not exercise. This effect was seen across gender and different degrees of frailty, but with the largest health benefits of exercise found among those participants who were more frail at baseline (Hubbard et al., 2009a). Apart from this, good evidence on specific conditions influencing the effect of frailty on death is not found.

Figure 9.1: Pathways from frailty to its adverse effects adapted from the working framework of the proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004)



Guided by this limited evidence, I will examine the role of low physical activity as a moderator of the effect of physical frailty on death. In line with the categories of conditions put forth in Figure 9.1, I will also explore the possibility that psychological and social conditions such as depressive symptoms, poor social support, and poor social integration assume roles as moderators. In addition, I will explore the possible mediating roles of physical and psychological conditions such as low physical activity, depressive symptoms, and cognitive impairment on these pathways.

Physical frailty will again be measured by its three indicators, namely slowness, weakness, and exhaustion at wave 2. Unlike in the third paper and for the sake of simplicity, I will not incorporate the measurement model for physical frailty in the full model, but rather will use unique physical frailty factor scores for each respondent that are derived from confirmatory factor analysis. Death across waves 3 to 5 is the outcome of interest. Given that this is a binary outcome at three time intervals, I will use discrete time survival analysis to estimate the effect of physical frailty. A rich set of physical, psychological, and social predictors (wave 2) of death will be included as control variables in the model. In addition, and as mentioned, selected conditions will be included in the models as moderators and mediators of the effect of physical frailty.

To examine moderation, I will include interaction variables of physical frailty with other predictors, one at a time in successive models to screen for significant effects. Probing of significant moderated effects will be performed to estimate the effect of physical frailty on death at different levels of the moderating variable.

For indirect effects, the methodological considerations are more complex. In the tradition of regression-based mediation analysis, I will use the product of coefficients to estimate the magnitude of these indirect effects. Sobel's test will be used to test their statistical significiance (Sobel, 1982). Of note, these mediation analyses stand on five assumptions. The first three are the adequate control for physical frailty-death, physical frailty-mediator, and mediator-death confounding, which would apply to any observational study. To address test assumptions, I will employ a series of sensitivity analyses to explore the potential impact of residual unmeasured confounding. Parameters of an unmeasured confounder, represented by a "phantom" latent variable, that would be required to shift the estimated effect of physical frailty to a non-significant level will be identified (VanderWeele, 2015). The idea is to estimate how sensitive the results are to unmeasured confounding. The fourth assumption is that there should not be any mediator-death confounder that is itself affected by physical frailty. However, testing for the violation of this assumption would require more complicated modeling (Daniel et al., 2013) that is beyond the ambit of this paper. The fifth assumption requires that there is no physical frailty-mediator moderation. This is accounted for by inclusion of physical frailty-mediator interaction in the model.

The following paper examines pathways from physical frailty to death. As before, some of the foregoing key points are unavoidably repeated as this is a self-contained journal article. References specifically for this paper are yet again provided in a separate list just before the Supplementary Materials (page 177 to 180). Relevant Mplus input files are provided in the Appendix. At the time of writing, this paper is being considered for publication in a gerontology journal.

9.2 Impact of physical frailty on longevity: identifying pathways in the English Longitudinal Study of Ageing

Joint work with Associate Professor Jouni Kuha (Departments of Statistics and Methodology, London School of Economics) and Professor Michael Murphy (Department of Social Policy, London School of Economics)

Abstract

We seek to examine the negative impact of physical frailty on longevity in older people, and to identify *for whom* its effect is stronger, and understand *how* it exerts its effect. For 4,638 respondents aged 65 to 89 years of the English Longitudinal Study of Ageing, confirmatory factor analysis for physical frailty using three indicators, namely slowness, weakness, and exhaustion is performed to obtain unique factor scores. Using discrete time survival analysis, we estimate the effect of physical frailty factor score on death over three waves (6 years), while exploring moderation and mediation by key physical, psychological, and social conditions. We confirm that higher levels of physical frailty significantly increase death risk, even after accounting for the effects of a rich set of multidimensional predictors. This effect extends across gender and age, except for those aged at least 75 years. However, it is significantly weaker among those with more cognitive impairment. Moreover, there are non-significant trends towards this effect being stronger among those with high consumption of alcohol and poor social integration, but weaker among those with obesity. More importantly, significant indirect effects of physical frailty on death act through low physical activity and cognitive impairment. Based on our findings, low physical activity and cognitive impairment are mediators, while high alcohol consumption and poor social integration are possible moderators on pathways from physical frailty to death. Efforts to address these conditions represent opportunities to mitigate at least in part the negative impact of physical frailty on longevity in older people.

Key words: aged, death, mediators, moderators, discrete time survival analysis, physical activity, depression

Introduction

Frailty is widely regarded as the multidimensional loss of an individual's body system reserves that in turn results in vulnerability to developing adverse health-related outcomes (Espinoza & Walston, 2005; Lally & Crome, 2007; Pel-Littel et al., 2009). It is conceptualized as a transitional state between robustness and functional decline (Lang et al., 2009) that is associated with increased risk of death, disability, falls, hospitalization, and institutionalization (Daniels et al., 2012; Ensrud et al., 2009; Ensrud et al., 2008; Jones et al., 2005; Kiely et al., 2009; Pilotto et al., 2012; Woo et al., 2012). Although long recognized as an important condition in older people, frailty has been defined in various ways ranging from a frailty phenotype with five components (Fried et al., 2001) to a frailty index that adopts a multiple deficit accumulation approach (Rockwood & Mitnitski, 2007). Some extent of consensus on its operational definition has only recently been achieved (Morley et al., 2013). Nonetheless, different definitions are probably best suited for different purposes (Martin & Brighton, 2008).

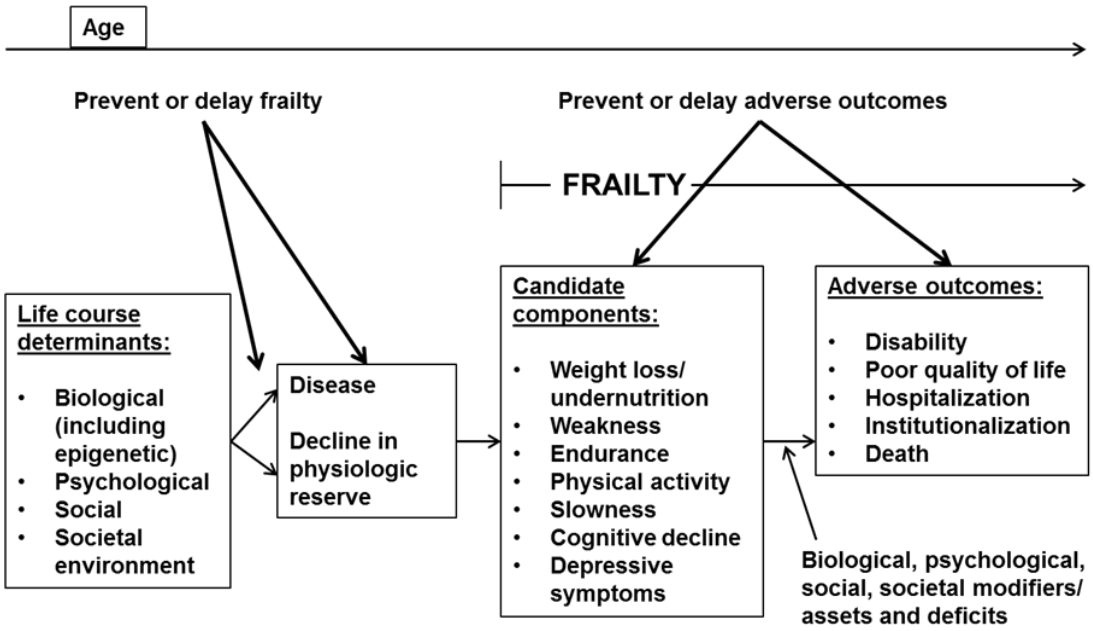
Across a spectrum of definitions applied, the prevalence of frailty is estimated to be about 10% among people aged 65 years or older (Collard et al., 2012). In the United Kingdom alone, the number of those in this age group was 11.6 million in 2015 (ONS, 2016), suggesting that approximately 1.2 million older people across the country are frail. The potential adverse outcomes of frailty and the size of its problem combine to create significant health and social impact for ageing populations. Thus, frailty plays a central role in influencing the well-being of older people and holds major public health importance (Woo et al., 2006).

Previous research indicates that frailty increases the risk of mortality in older people (Buchman et al., 2009; Cawthon et al., 2007; Gu et al., 2009; Mitnitski et al., 2004). However, the precise mechanisms by which frailty exerts this effect are unclear. There is sparse knowledge on precise pathways from frailty to eventual death. Better understanding of these pathways including identification of moderators and mediators on these pathways is needed to inform rational public health and social policy with respect to organizing effective population-level interventions that could potentially reduce the impact of frailty on premature death.

To conceptualize pathways from frailty to mortality, a good starting point is the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004). An adapted and simpler version is shown in Figure 1. In the right half of this figure, biological, psychological, social, and societal assets and deficits are represented as moderators on the pathway from frailty to adverse outcomes including death. These assets and deficits represent potential targets for intervention to reduce the adverse impact of frailty. More recently, Gobbens et al proposed the integral concept of frailty (Gobbens et al., 2010) and developed a similar set of frailty pathways that were in essence adapted from those of the Canadian working framework. Other frailty pathways have been proposed but are largely restricted to the biological sphere, and are therefore less suitable for a broader investigation of the effects of

frailty. Thus, the Canadian working framework offers a useful foundation on which to build a conceptual model for pathways from frailty to death.

Figure 1. Working framework of the Canadian Initiative for Frailty and Aging (adapted from Bergman, 2004 with modifications)

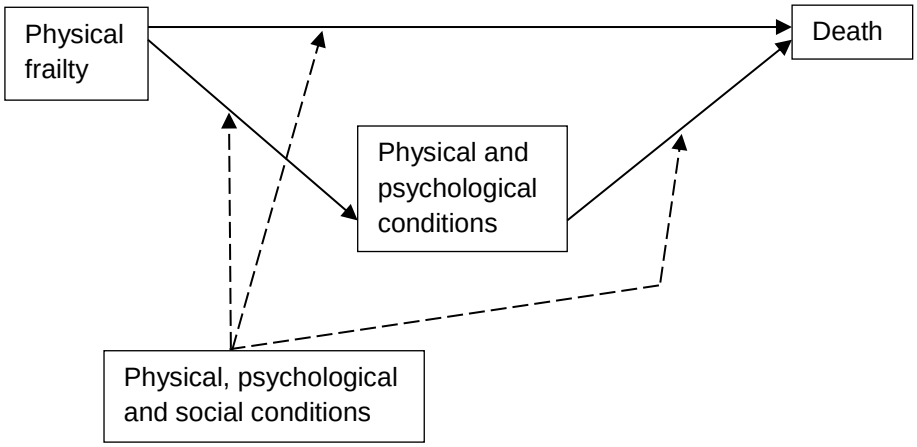


With a conceptual model of frailty pathways available, the challenge then is to identify a frailty specification that is suitable for investigation of these pathways. In his seminal work, Strawbridge recognized the multidimensional nature of frailty and conceptualized frailty as involving problems in at least two from among physical, nutritive, cognitive, and sensory domains (Strawbridge et al., 1998). More recently, the view of frailty being multidimensional has been expressed in part by the development of frailty identifiers that measure deficits across more than a single domain (Bielderman et al., 2013; Gobbens et al., 2010; Rockwood, 2005). However, some of the multidimensional elements in these frailty specifications are themselves hypothesized to be key conditions on pathways from frailty to its adverse outcomes. Having these elements as part and parcel of the frailty specification complicates the task of teasing out important relationships between frailty and these conditions. As an alternative, the integral concept of frailty explicitly defines frailty as having three distinct domains, namely physical, psychological, and social (Gobbens et al., 2010). Being able to specify frailty based on a single domain facilitates its disentanglement from conditions related to its other two domains. This in turn facilitates less constrained exploration of the relationship of frailty with physical, psychological, and social conditions that may operate as mediators or moderators of its effect.

Among these three frailty domains, physical frailty offers the most promising choice as a frailty specification for investigation of its pathways. There are a few reasons for this. Firstly, physical frailty is far better understood and a more established concept than psychological or social frailty are. Secondly, physical frailty contributes most to prediction of adverse outcomes among these three frailty domains (Gobbens et al., 2012). Finally, there exists an excellent prototype for physical frailty in the Cardiovascular Health Study (CHS) frailty phenotype (Fried et al., 2001). It conceptualizes physical frailty as having five components, namely, unintentional weight loss, weak hand grip strength, self-reported exhaustion, slow walking speed, and low physical activity level.

Our conceptual model for investigating the effect of physical frailty on death is shown in Figure 2. In this model, indirect effects through physical and psychological mediators are included in addition to the direct effect. Furthermore, the moderation of these direct and indirect effects by physical, psychological, and social conditions is also incorporated (dotted lines). Thus, we base these pathways on those of the Canadian working framework, but advance beyond to include indirect effects.

Figure 2. Conceptual model for investigation of pathways from physical frailty to death



Following on from the foregoing discussion, our study aims to identify moderators and mediators of the relationship between physical frailty and death. We ask the following research questions:

1) Which physical, psychological, and social conditions moderate the effect of physical frailty on death?
2) Which physical and psychological conditions mediate the effect of physical frailty on death?
3) Do key psychological and social conditions moderate the mediated effects (moderated mediation) of physical frailty on death?

In addition, we ask if there are any gender- and age-specific effects of physical frailty on death.

To answer these questions, we use panel data from the English Longitudinal Study of Ageing (ELSA). ELSA is a longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013). It offers a broad range of reliable and multidimensional data across biennial waves beginning from 2002, and is currently still ongoing.

Methods

Data

Our study population comprises 4,638 respondents aged 65 to 89 years at wave 2 (2004) of ELSA (Marmot et al., 2015). Those aged 90 years and above are excluded given that their age is uniformly coded as “90”, and that their number is small. All participants gave informed consent. Ethical approval for ELSA was granted by the Multicentre Research and Ethics Committee. Ethical oversight for this study is provided by procedures of the London School of Economics Ethics Policy.

Physical frailty is specified by three indicators drawn from those of the CHS frailty phenotype (Fried et al., 2001), namely slowness, weakness, and exhaustion. *Slowness* is the average gait speed (in m/s) of two attempts at walking 2.4 m, but with values reversed through multiplication by -1. *Weakness* is derived from the dominant hand grip strength in kg, which is multiplied by 1.5 in the case of women, and then reversed. The differential handling of raw grip strength values in men and women is based on gender-specific and population-independent cut-off values for grip strength previously proposed for the CHS frailty phenotype criteria (Saum et al., 2012). *Exhaustion* is a binary variable based on a positive response to at least one of two items of the Center for Epidemiologic Studies Depression (CES-D) Scale on whether the respondent “felt everything they did during the past week was an effort” and “could not get going much of the time in the past week” (Radloff, 1977). It has been previously argued and demonstrated that the physical frailty specification with these three indicators has face, content, construct, and concurrent validity (Ding, 2016). Using confirmatory factor analysis (CFA) with these three indicators, unique physical frailty factor scores for wave 2 are derived for each respondent. These factor scores are then used for subsequent analyses.

Death is the outcome of interest. It is represented by a set of three binary variables at waves 3 to 5, each of which are assigned a value of one if death occurs in the time interval following the preceding wave, zero if still alive, and censored if death occurs at or prior to the preceding wave. Other predictors of death at wave 2 are drawn from deficit categories listed in the Canadian working framework. Beyond *age* and *gender*, physical predictors include *obesity* (binary: body mass index at least 30 kg/m^2 compared with normal, defined as less than 30 kg/m^2 but more than 20 kg/m^2), being *underweight* (binary: body mass index 20 kg/m^2 or less compared with normal, defined as less than 30 kg/m^2 but more than 20 kg/m^2), *low physical activity* (four levels of increasing intensity activity related to occupation and exercise), *chronic disease* (count of conditions from 0 to 14), *allostatic load* (score of 0 to 9), *smoking* history (binary: whether ever smoked), and *high alcohol intake* (binary: whether had alcohol drink almost every day in the past 12 months). Allostatic load is a measure of the physiological dysregulation in multiple body systems (Gruenewald et al., 2009), and is specified by nine biomarkers including blood pressure readings, anthropometric measurements, and blood tests

for cholesterol levels, glucose control, and inflammatory markers. For each biomarker, a score of one is awarded for values beyond a cut-off level reflecting high risk, with a score of zero given if otherwise. The total score reflects the allostatic load.

Psychological predictors include *depressive symptoms*, which is based on a count of six out of eight items (score of 0 to 6) of the CES-D Scale (Radloff, 1977). The two omitted items are those already used to measure exhaustion as a physical frailty indicator. *Cognitive impairment* is derived from a cognitive index based on the combined memory and executive function test performance (score of 0 to 49), which is then reversed.

Social predictors include *low education* (binary: no qualifications compared with any qualification), and *low wealth* (binary: lowest 2 deciles compared with highest 8 deciles of non-pension wealth). Additionally, *poor social integration*, reflecting social isolation, is based on the combined score on five items (score of 0 to 14) concerning whether participants have no spouse and partner living with them, had little contact with children, had little contact with other family members, had little contact with friends, and were not a member of any organization, club or society. Contact includes meeting, phoning, or writing or email. The composite scoring mode is adapted from previous work (Banks et al., 2010). Finally, *poor social support*, in terms of deficient emotional support, and reflecting negative social interaction with family and friends, is measured by the combined scores on whether there is lack of positive support, and occurrence of negative support (score of 0 to 54). Lack of positive support is measured by negative answers to questions on “understand the way you feel”, “can rely on if you had a serious problem”, and “can open up to them if you need to talk” with respect to children, other family members, and friends. Negative support is measured by positive answers to questions on whether children, other family members, and friends "criticizes the respondent", "lets the respondent down", and "gets on the nerves of respondent". The composite scoring mode is again based on that of the previous study mentioned (Banks et al., 2010).

Statistical analyses:

A series of structural equation models that examine the effect of physical frailty on death using discrete time survival analysis, and which include combinations of moderated and mediated effects, are constructed. The hazard of death $h(t)$ is the probability of death occurring at time interval t given that death has not occurred before t, and is expressed as

$$h(t) = 1 / (1+\exp(T_t))$$

where T is the estimate of the linear predictor (“threshold” or intercept) for the binary event of death time interval t, obtained from logistic regression, and given a set of explanatory variables where their values are zero. To obtain this estimate for the average respondent, physical frailty factor score and all other variables are rescaled so that their zero values represent their means. To do so for respondents with physical frailty factor scores one standard deviation above or below the mean, their factor score values are similarly rescaled so that their zero values

represent these defined values. Their corresponding survival probability at time *t* or *s*(*t*) is given by 1 - *h*(*t*) multiplied by those in the previous time points (Newsom, 2015). Thus,

$$s(t) = \Pi(1 - h(t))$$

The discrete time survival model examines death at waves 3, 4, and 5. Physical frailty, moderators and mediators of its effect, as well as other predictors of death are all measured at wave 2. The mathematical formulas are provided in the Supplementary Materials.

Model 1 concerns prediction of death by physical frailty factor scores at wave 2 controlled for gender, age, and multidimensional predictors, namely chronic disease, allostatic load, obesity, being underweight, low physical activity, smoking, high alcohol intake, depressive symptoms, cognitive impairment, low education, low wealth, poor social support, and poor social integration measured at the same wave. The regression coefficients represent the log odds of death for one standard deviation increase in continuous predictors, and from zero to one for binary predictors. Gender- and age-specific effects are estimated by including interactions of physical frailty with gender and age respectively in the model, and then probing these interactions. The latter procedure involves estimating the effect of physical frailty on death separately for men and women, and at specific ages, which are given by:

pf + (pf-g*Gender)

pf + (pf-a*Age)

where *pf* is the coefficient for physical frailty, *pf-g* is the coefficient for the interaction of physical frailty with gender, *Gender* is the value assigned for male or female, *pf-a* is the coefficient for the interaction of physical frailty with age, and *Age* is the value for specific ages. Differences between effect estimates across gender and age are tested for statistical significance of moderation using the Wald test. Model 2 explores moderation of the effect of physical frailty on death by ten selected conditions at wave 2 namely, obesity, low physical activity, allostatic load, smoking, high alcohol intake, depressive symptoms, cognitive impairment, low wealth, poor social support, and poor social integration, by including in turn their respective interaction variables in the model. These lifestyle-related, psychological, and social variables are chosen a priori given that they represent potentially modifiable conditions. Probing of these interaction effects and tests for statistical significance of differences across categories of these potential moderators are then performed in the same way as for gender and age.

Model 3 extends Model 1 by including indirect effects through low physical activity, depressive symptoms, and cognitive impairment measured at wave 2. Although it would be ideal to use values of these mediators at a subsequent time point (say, wave 3), doing so would place them within the time frame for the outcome, namely waves 3 to 5, which will be problematic. We included treatment-mediator interaction variables to relax the assumption of the absence of treatment-mediator interaction (Muthén & Asparouhov, 2015). Estimates of indirect effects are derived using the product of coefficients method. Since the logistic regression is used to predict the binary outcome, computing comparable coefficients for these two types of models to obtain the product of coefficients has been suggested (Mackinnon & Dwyer, 1993). However, where the mediator is continuous, which is the case here, it has been proposed that the indirect effect

can be obtained through the product of coefficient method using the physical frailty coefficient from linear regression where the mediator is the outcome, and the mediator coefficient from logistic regression where death is the outcome (MacKinnon et al., 2007). The latter procedure is adopted here. Sobel's test for significance testing is applied (Sobel, 1982). As in Model 1, gender- and age-specific effects are also estimated by including interactions of physical frailty, and then probing these interaction effects. Estimates of the indirect effect of physical frailty on death according to gender and age are given by:

(pf + (pf-g*Gender))*m

(pf + (pf-a*Age))*m

where *pf* is the coefficient for physical frailty, *pf-g* is the coefficient for the interaction of physical frailty with gender, and *pf-a* is the coefficient for the interaction of physical frailty with age, for the effect on the mediator. *Gender* is the value assigned for male or female, and *Age* is the value for specific ages. Finally, *m* is the coefficient for the mediator for its effect on death. Model 4 explores moderation of these indirect effects (moderated mediation) by poor social support, and poor social integration through including their respective interaction variables for the physical frailty-mediator and mediator-death effects, and then again probing the interaction effects as for gender and age. These two social variables are selected a priori on the basis that they may be potentially modifiable conditions that influence indirect effects of physical frailty. Yet again, tests for significance of moderation across gender, age, poor social support, and poor social integration are performed using the Wald test.

Sensitivity analyses are conducted to explore the potential impact of residual confounding due to unmeasured variables including genetic influences and social conditions in early life. The adopted approach is that of identifying the parameters of an unmeasured confounder that would be required to shift the estimated effect of physical frailty to a non-significant level (VanderWeele, 2015). To implement these, we create and include a "phantom" latent variable in Model 1. Its correlation with physical frailty is fixed at 0.1 (low) and effect on death is varied starting from that equivalent to the effect of physical frailty on death, and then increasing this in turn by its multiples (that is, two times, three times, and so on). The point at which the effect of physical frailty on death is rendered non-significant is sought. The procedure is repeated with correlation of the "phantom" latent variable with physical frailty set to 0.3, and then finally to 0.5. For Model 3, the correlation of the "phantom" latent variable with the three mediators is added to the foregoing procedure and then varied accordingly. The end product of these analyses are tables of "corrected" estimates when implementing a range of sensitivity parameters (VanderWeele, 2015).

Missing values are handled by full information maximum likelihood (FIML), which operates under the assumption of missing at random (MAR). It is analogous to multiple imputation, but without actual creation of imputation datasets. Rather, the missing data is handled within the analysis model using maximum likelihood estimation, which identifies population parameters having the highest probability of producing the sample data. It uses all available data to generate their estimates and assumes multivariate normality. To facilitate this procedure for

predictor variables, their means will be estimated. Mplus version 7.4 (Muthén & Muthén, 1998-2012) is used to perform discrete time survival analysis, while STATA version 14.1 is used for all other analyses. Statistical significance is generally assessed at the 5% level. Where Bonferroni's correction is implemented to account for multiple comparisons when testing ten separate moderated effects in Model 2, statistical significance is assessed at the 0.5% level. Similarly, to test two separate moderated effects in Model 4, statistical significance is assessed at the 2.5% level.

Results

Table 1 describes the characteristics of our study population. There is complete data on death, age, and gender. Missing values due to death or loss to follow-up occur in less than 10% of cases for majority of other variables, with the highest proportion being about 50% for allostatic load. The mean age of respondents is 74 years, and approximately 55% are women. Physical frailty levels are on average higher in women and those aged 75 years and above. Death occurs by wave (year) 3 (2006), 4 (2008), and 5 (2010) among 6.0%, 12.8% and 20.1% of respondents respectively. This means that mortality is 6 to 7% within each successive wave with this figure being higher in men than women (7 to 8% vs. 5 to 6%) and in those aged 75 years and above at baseline than those younger (10 to 11% vs. 3 to 4%).

Table 1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses

Variables	All	By gender		By Age group	
		Male	Female	< 75 years	>= 75 years
General:					
Mean age, years (SD)	74.0 (6.3)	73.5 (6.2)	74.3 (6.4)	69.3 (2.8)	80.2 (3.9)
Female, n/N (%)	2,568/4,638 (55.4)	-	-	1,399/2,643 (52.9)	1,169/1,995 (58.6)
Physical frailty:					
Mean average walking speed, m/sec (SD):	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
Hand grip strength, kg (SD)	25.9 (10.2)[6]	33.4 (8.9)[7]	19.6 (6.1)[8]	28.4 (10.2)[9]	22.2 (8.2)[10]
Exhaustion, n/N (%):	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
Mean physical frailty factor score (SD):	0.01 (0.17)[11]	-0.03 (0.16)[12]	0.03 (0.17)[13]	-0.05 (0.16)[14]	0.08 (0.15)[15]
Physical:					
Obesity, n/N (%)	1,018/3,976 (25.6)	400/1,783 (22.4)	618/2,193 (28.2)	662/2,328 (28.4)	356/1,648 (21.6)
Mean chronic disease count [out of 14] (SD)	1.9 (1.4)[16]	1.8 (1.4)[17]	2.0 (1.4)[18]	1.8 (1.4)[19]	2.1 (1.5)[20]
Mean allostatic load score [out of 9] (SD)	2.1 (1.6)[21]	2.3 (1.6)[22]	2.0 (1.5)[23]	2.0 (1.6)[24]	2.3 (1.5)[25]
Mean low physical activity level, [0 of 3] (SD)	1.4 (0.8)[26]	1.3 (0.8)[27]	1.4 (0.8)[28]	1.2 (0.8)[29]	1.6 (0.8)[30]

Smoking history, n/N (%)	2,963/4,634 (63.9)	1,567/2,069 (75.7)	1,396/2,565 (54.5)	1,649/2,639 (62.5)	681/1,995 (65.9)
Heavy alcohol intake, n/N (%)	1,249/3,871 (32.3)	720/1,742 (41.3)	529/2,129 (24.9)	792/2,344 (33.8)	457/1,527 (29.9)
Psychological:					
Mean CESD-8 score [0 to 8] (SD)	1.7 (2.0)[31]	1.3 (1.7)[32]	1.9 (2.1)[33]	1.5 (1.9)[34]	1.9 (2.0)[35]
Mean cognitive impairment score [0 to 49] (SD)	18.9 (6.5)[36]	19.3 (6.4)[37]	18.5 (6.5)[38]	17.1 (6.0)[39]	21.4 (6.3)[40]
Social:					
Low education, n (%)	2,256/4,618 (48.9)	885/2,061 (41.5)	1,401/2,557 (54.8)	1,158/2,630 (44.0)	1,098/1,998 (55.2)
Low wealth, n (%)	980/4,557 (21.5)	365/2,022 (18.1)	615/2,535 (24.3)	454/2,584 (17.6)	526/1,973 (26.7)
Mean poor social support score [0 to 54] (SD)	13.7 (7.0)[41]	14.7 (7.0)[42]	12.9 (6.8)[43]	13.9 (7.0)[44]	13.3 (6.8)[45]
Mean poor social integration score [0 to 14] (SD)	6.6 (2.5)[46]	6.7 (2.6)[47]	6.5 (2.5)[48]	6.4 (2.5)[49]	7.0 (2.6)[50]
Death:					
By wave 3 (2006), n/N (%)	278/4,638 (6.0)	147/2,070 (7.1)	131/2,568 (5.1)	83/2,643 (3.1)	195/1,995 (9.8)
By wave 4 (2008), n/N (%)	593/4,368 (12.8)	314/2,070 (15.2)	279/2,568 (10.9)	191/2,643 (7.2)	402/1,995 (20.2)
By wave 5 (2010), n/N (%)	932/4,638 (20.1)	483/2,070 (23.3)	449/2,568 (17.5)	289/2,643 (10.9)	643/1,995 (32.2)

CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)

Unless indicated otherwise, N=4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old).

N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]3,869 [7]1,760 [8]2,109 [9]2,276 [10]1,593 [11]4,547 [12]2,019 [13]2,528 [14]2,609 [15]1,938 [16]4,608 [17]2,052 [18]2,556 [19]2,617 [20]1,991 [21]2,264 [22]1,043 [23]1,221 [24]1,414 [25]850 [26]4,565 [27]2,032 [28]2,533 [29]2,610 [30]1,955 [31]4,479 [32]1,987 [33]2,492 [34]2,586 [35]1,893 [36]4,348 [37]1,945 [38]2,403 [39]2,545 [40]1,803 [41]3,339 [42]1,529 [43]1,810 [44]2,068 [45]1,271 [46]3,267 [47]1,506 [48]1,761 [49]2,035 [50]1,232

Among multidimensional predictors at wave 2, there are minor gender-specific differences in levels of chronic disease, allostatic load, low physical activity, cognitive impairment, and weak social network. However, differences are more marked for obesity, depressive symptoms, low wealth, and low education, which are more common or have higher levels in women. In addition, women have lower prevalence of smoking and heavy alcohol consumption, and better social support. Those aged 75 years and older have more chronic disease, allostatic load,

depressive symptoms, and cognitive impairment, while having lower physical activity, education, and wealth, as well as poorer social integration than those younger. Fewer in this older age group have obesity and heavy alcohol intake, while more have smoked.

Estimates for hazard of death are derived from the threshold values at the three time points and shown in the Supplementary Materials (Table 5). With mean physical frailty factor score and at mean values for other predictors, the hazard of death across the three time periods increases from 0.040 to 0.069, while the survival probability decreases from 0.960 to 0.845. However, when physical frailty factor score is one standard deviation below the mean, the corresponding hazard of death is lower (0.033 to 0.057), while the survival probability is correspondingly higher (0.967 to 0.871). In contrast, for physical frailty factor score at one standard deviation above the mean, the hazard of death is higher (0.050 to 0.084), while the survival probability is correspondingly lower (0.950 to 0.812). Hazard of death across time is graphically illustrated in Figure 3, while survival probability is shown in Figure 4. The interpretation of these findings is that with an increase of one standard deviation in physical frailty factor score from the mean value, the hazard of death is approximately 20% higher, when other predictors are held at their mean values.

Figure 3. Death hazard estimates at waves 3 to 5 derived from discrete time survival analysis: comparison of different levels of physical frailty holding constant the effects of other predictors at their mean values

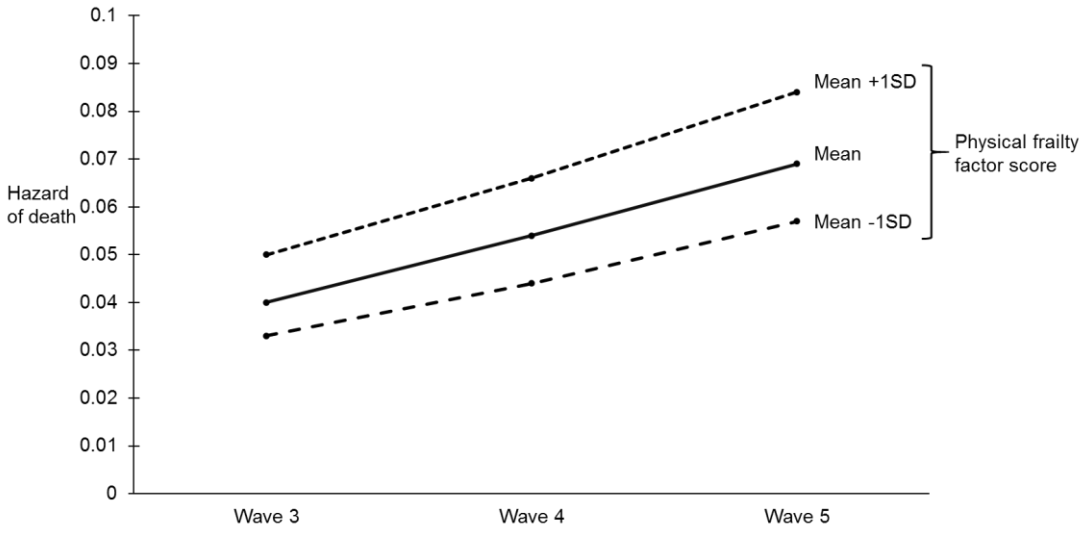


Figure 4. Survival probability estimates at waves 3 to 5 derived from discrete time survival analysis: comparison of different levels of physical frailty holding constant the effects of other predictors at their mean values

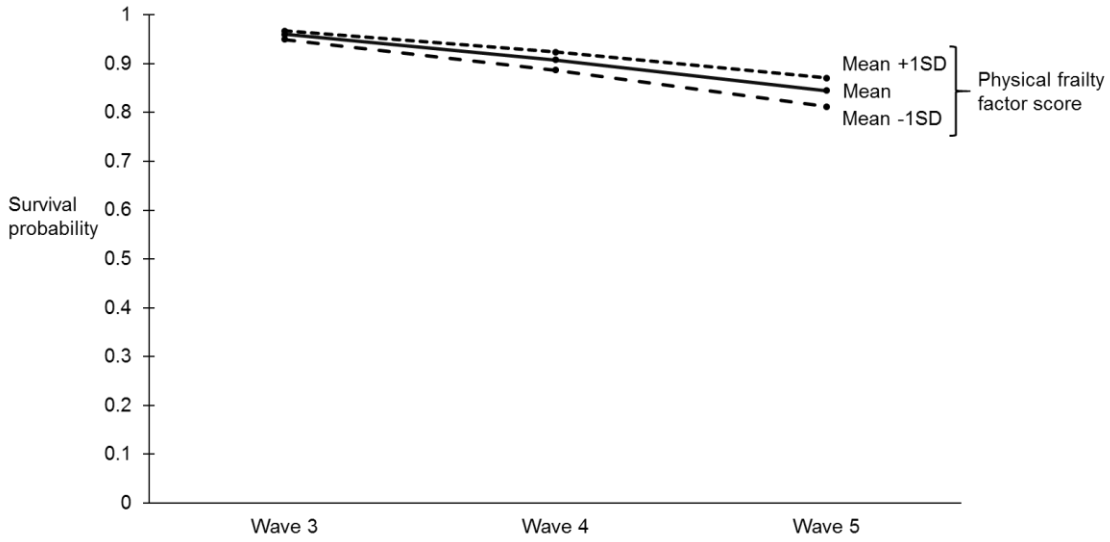


Table 2 provides the standardized coefficients for prediction of death across waves 3 to 5 obtained from discrete time survival analysis (Model 1). For the whole group, physical frailty significantly predicts hazard of death over the following 3 waves after controlling for other key multidimensional predictors. More precisely, one standard deviation increase of the physical factor score predicts 24% increase in the odds of death. Interestingly when standardized coefficients are compared in the Supplementary Materials (Table 6), the effect size of physical frailty on death is smaller than the corresponding effects of older age and female gender, similar in magnitude to those of smoking, being underweight, and low physical activity, but larger than those of other predictors. More precisely, the effect size of physical frailty is approximately 40% that of age, which has a standard deviation of approximately 6 years. Thus, in more concrete terms, the effect of one standard deviation increase in physical frailty factor score on death is approximately equivalent to the effect of increase in age of 2.5 years. This is stronger for women and those younger, with non-significant effects at 85 years of age as indicated by the coefficients in the second and third panels in Table 2. Given these findings, physical frailty is a significant and relatively strong predictor of death over the following 6 years, except among very old people.

In addition, Table 2 shows that the effect of physical frailty decreases as the level of cognitive impairment increases as indicated by the coefficients in the fourth panel (Model 2). In fact, the difference in this effect is three-fold comparing that at level of cognitive impairment score one standard deviation above to that one standard deviation below the mean value. Thus, cognitive

impairment exerts a negative moderating influence on the effect of physical frailty on death, which is statistically significant at the 0.5% level when accounting for multiple comparisons. On the other hand, none of the other conditions have significant moderating influence on the effect of physical frailty. However, there are non-significant trends towards stronger effect of physical frailty among those having high alcohol intake and poor social integration, but weaker effect among those with obesity. Details of their effects are in the Supplementary Materials (Table 7).

Table 2. Main and moderated effects of physical frailty (wave 2) on hazard of death (waves 3 to 5) while controlling for other predictors (wave 2) using discrete time survival analysis with interactions and probing of effects: coefficients for log odds and odds ratio of death

		Log odds of death	Odds ratio of death
All		0.213*	1.237*
Gender:	Men	0.171*	1.186*
	Women	0.260*	1.297*
Age**	65 years	0.416*	1.516*
	75 years	0.242*	1.274*
	85 years	0.067	1.070
Cognitive impairment ɬ	Low	0.383***	1.467***
	Average	0.256***	1.292***
	High	0.130****	1.139****

For cognitive impairment, values one standard deviation below the mean are designated as “low” and values one standard deviation above the mean as “high”. The mean value is designated as “average”.

* Indicates p-value <0.05

** Indicates that p-value <0.05 for moderation

*** Indicates p-value <0.005 (Bonferroni’s correction for 10 multiple comparisons)

**** Indicates p-value <0.05 but >=0.005

ɬ Indicates that p-value <0.005 for moderation

Values of log odds and the odds ratio of death are for one standard deviation increase in physical frailty factor score. Estimated effects are controlled for age, gender, chronic disease, allostatic load, smoking, high alcohol intake, obesity, being underweight, low physical activity, depressive symptoms, cognitive impairment, low education level, low wealth, poor social support, and poor social integration.

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

Mediation effects are inferred from the product of coefficients for physical frailty-mediator and mediator-death effects. In the first panel of Table 3, the coefficients for the mediated or indirect effects through low physical activity and cognitive impairment are positive and statistically significant, while that through depressive symptoms is not (Model 3). The interpretation is that the effect of physical frailty on death acts indirectly through low physical activity and cognitive

impairment. As indicated by coefficients in the second and third panels of Table 3, these indirect effects are stronger in the younger group. However, that through cognitive impairment is stronger in women, while those through the other two mediators are stronger in men. Only the difference in indirect effect through low physical activity across age is statistically significant. On the other hand, coefficients in the fourth and fifth panels of table 3 show minimal and non-significant differences across high and low levels of poor social support and poor social integration, indicating that these two conditions do not moderate these indirect effects (Model 4).

Table 3. Mediation (indirect effects) of physical frailty on hazard of death (waves 3 to 5) by low physical activity, depressive symptoms, and cognitive impairment including moderated effects (moderated mediation) using discrete time survival analysis: coefficients for log odds and odds ratio of death

		Mediator		
		Low physical activity	Depressive symptoms	Cognitive impairment
All		0.085*	-0.008	0.053*
Gender:	Men	0.084*	-0.007	0.057*
	Women	0.085*	-0.009	0.050*
Age:	65 years***	0.072*	-0.008	0.054*
	75 years	0.087*	-0.009	0.054*
	85 years***	0.103*	-0.009	0.054*
Poor social support:	Low	0.084**	-0.007	0.049**
	Average	0.085**	-0.008	0.053**
	High	0.085**	-0.009	0.057**
Poor social integration:	Low	0.080**	-0.006	0.048**
	Average	0.084**	-0.008	0.053**
	High	0.089**	-0.010	0.059**

* Indicates statistical significance at 5% level

** Indicates statistical significance at 2.5% level (Bonferroni's correction for multiple comparisons for 2 separate models)

*** Indicates statistically significance at the 5% level for moderation of indirect effects (only through low physical activity)

Mean values are used as cut-off points for stratification of depressive symptoms, social support, and social integration into two categories.

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

Finally, the results of sensitivity analyses that simulate the effect of unmeasured confounding (represented by a "phantom" variable) on the effect of physical frailty on hazard of death are

provided by “corrected” estimates in Table 4. When there is no unmeasured confounding, the log odds of death is 0.214 (first column of first row) which is consistent with Table 2. However, if correlation of an unmeasured confounder with physical frailty is 0.1, then the estimate remains significant, but decreases to 0.184 (second column of second row) when the effect of the unmeasured confounder on death is equivalent to that of physical frailty on death. The estimate remains significant, but further decreases to 0.151 and 0.122 (third and fourth columns of second row) when the effect of the unmeasured confounder on death is equivalent to two-fold and three-fold that of physical frailty on death respectively. When the latter increases to four-fold, the estimate decreases to 0.095 (fifth column of second row), and is now not significant. Next, if correlation of the unmeasured confounder with physical frailty is increased to 0.2, then the estimate remains significant, but decreases to 0.145 (second column of third row) when the effect of the unmeasured confounder on death is equivalent to that of physical frailty on death. When the latter increases to two-fold, the estimate decreases to 0.072 (third column of third row) and is non-significant. Finally, if correlation of the unmeasured confounder with physical frailty is further increased to 0.3, then the estimate remains significant, but decreases to 0.105 (second column of fourth row) when the effect of the unmeasured confounder on death is equivalent to that of physical frailty on death. When the latter increases to two-fold, the estimate decreases to -0.008 (third column of fourth row) and is clearly not significant. Together, these results indicate that for the effect of physical frailty on death to be rendered non-significant, an unmeasured confounder would either need to have between two to four times the effect of physical frailty, depending on whether its correlation with physical frailty is moderate (0.3) or very low (0.1) respectively. Thus, our estimated effect of physical frailty is relatively robust to unmeasured confounding.

Table 4. “Corrected” estimates of the effect of physical frailty (wave 2) on hazard of death (waves 3 to 5) over different sensitivity parameters using discrete time survival analysis: coefficients for log odds of death

Correlation of the unmeasured confounder with physical frailty	Effect of the unmeasured confounder on death in terms of multiples of the uncorrected effect of physical frailty on death				
	0X	1X	2X	3X	4X
0	0.214*	-	-	-	-
0.1	-	0.184*	0.151*	0.122*	0.095
0.2	-	0.145*	0.072	-	-
0.3	-	0.105*	-0.008	-	-

* Indicates statistical significance at 5% level

Shaded cells indicate that “corrected” estimates for the effect of physical frailty on death remain positive and significant.

Missing values are handled by full information maximum likelihood (FIML).

N = 4.638

Similarly, “corrected” estimates of indirect effects for ranges of sensitivity parameters are provided in the Supplementary Materials (Table 8). For the indirect effect of physical frailty on death through low physical activity to be rendered non-significant, the effect of an unmeasured confounder on death would need to be three times that of physical frailty when its correlations with physical frailty and low physical activity are moderate (0.3). On the other hand, for the indirect effect through cognitive impairment to be rendered non-significant, the corresponding effect of an unmeasured confounder on death would need only need to be equivalent to two times that of physical frailty when its correlations with physical frailty and low physical activity are also moderate (0.3). These results suggest that the indirect effect through low physical activity is also relatively robust to unmeasured confounding, although it is less so for that through cognitive impairment.

Discussion

For community-dwelling older people in England, increasing physical frailty levels independently predict death over the following six years. In other words, the risk of death from physical frailty remains even after accounting for other concurrent physical, psychological, and social predictors. Overall, its effect size ranks in the intermediate band among those of a rich set of multidimensional predictors. It is worth highlighting that we identify the incremental or marginal effects of physical frailty over and above those of other predictors of death. Notably, the effect of physical frailty is stronger among women and those who are younger. However, this effect is not significant among those who are very old. Our findings are consistent with previous work demonstrating that a frailty index had a greater negative effect on survival in women compared with men (Bartley et al., 2016; Mitnitski et al., 2004), and in lower compared higher age categories (Gu et al., 2009) among older people. For men and those very old, it is likely that conditions other than physical frailty have a larger role in predicting death. Nonetheless, we confirm that physical frailty has a distinct and sizeable impact on limiting longevity in older people, except those who are very old.

To answer the question on *for whom* its effect is stronger, we observe that the effect of physical frailty on death is negatively moderated by cognitive impairment. Beyond this, we are unable to demonstrate significant moderation by other conditions in physical, psychological and social domains suggested in the Canadian working framework (Bergman et al., 2004). The latter finding parallels recent work demonstrating that psychosocial resources do not modify the effect of frailty on death (Hoogendijk et al., 2014). Despite this, it would be pertinent not to dismiss interesting trends observed even though they did not achieve statistical significance, given the greater statistical power typically needed to demonstrate moderation. Among these trends, physical frailty appears to have stronger effects in those who have high consumption of alcohol and poor social integration, but weaker effects among those with obesity. In the search for modifiers of the effect of physical frailty on longevity, our findings provide possible directions for future work, particularly in exploring the role of social integration.

Returning to cognitive impairment, its negative moderation of the effect of physical frailty on death has not been reported previously. If replicated elsewhere, this finding may provide valuable insight on the complexity of pathways involved with respect to the relationship between physical frailty and other predictors. To explain this unexpected finding, we note that older people with more cognitive impairment are themselves at higher risk for death (see Table 5 of the Supplementary Materials). It is possible that physical frailty adds less to the risk of death in situations where there already is more cognitive impairment. To an extent, the evidence on the stage of dementia being a stronger predictor of death than the frailty index supports this explanation (Kelaiditi et al., 2016).

Equally interesting, the effect of physical frailty is weaker among those with obesity compared with those who are not, although this difference does not reach statistically significant levels.

However, in contrast to cognitive impairment, obesity itself predicts lower risk of death (see Table 2). The reduction of death risk among obese older people has been described as the "obesity paradox" (Strandberg et al., 2013), and is a vigorously debated subject. Placing our findings in this context, we deduce that the inter-relationships between weight, physical frailty, and death are likely to be more complex than those represented by the pathways we specified. Thus, until the evidence is clearer, obesity should certainly not be viewed in a positive light in terms of enhancing longevity in older persons with physical frailty.

Beyond prediction and moderation, we demonstrate mediated effects of physical frailty and answer at least in part the question on *how* physical frailty exerts its effect on death. Its significant indirect effects on death through low physical activity and cognitive impairment are the major findings of our study. Given that low physical activity has a close relationship with frailty (Fried et al., 2001), and that it predicts lower life expectancy (Nazroo et al., 2008; Stessman et al., 2009), it is quite plausible that low physical activity could act as a mediator. In addition, we have already seen that cognitive impairment predicts death. Coupled with the knowledge that physical frailty predicts future cognitive impairment (Auyeung et al., 2011), it also seems quite plausible that cognitive impairment is a mediator. The implication of these findings is that low physical activity and cognitive impairment are possible target conditions for intervention for older people who are physically frail where enhancing longevity is concerned.

Overall, our findings add to the existing body of evidence supporting health and social policies that promote greater physical activity and attempt to prevent cognitive decline in the bid to enhance longevity in older people through modifying the adverse impact of physical frailty. Given that participation in physical activity is low in older people despite public education on its benefits, implementation of multi-modal means of encouraging more physical activity need to be considered (McPhee et al., 2016). Preventing cognitive impairment is a more challenging endeavor. Current evidence suggests that cognitive training, and perhaps physical activity and dietary omega-3 tatty acids may have a role (Plassman et al., 2010). Beyond encouraging physical activity, advice on maintaining or boosting mental activity and encouraging fish consumption are common components of health promotion efforts directed at older people, although the extent of their take up has been less studied. In addition, our findings suggest that addressing high alcohol consumption and poor social integration among older people with physical frailty are potential areas of focus for further investigation. From a broader perspective, addressing these conditions may already be recognized as sensible objectives of health and social policies. In fact, initiatives that are consistent with these objectives may already been implemented in many settings. Nonetheless, frailty-specific evidence such as from this study may assist in bolstering support for the initiation, continuation, or even further expansion of such programs in the face of public resource constraints.

There are a few methodological limitations of our study that are worth mentioning. Firstly, dependence on observational data imposes limits on the interpretation of findings. That said, the advantage of using longitudinal data allows us to ensure that cause precedes effect.

Moreover, inclusion of a broad range of physical, psychological, and social conditions in these models permits us to control for their effects and to argue that the influence of omitted variables is unlikely to be large enough to change our major conclusions. Indeed, our sensitivity analyses suggest that estimated effects of physical frailty on death are relatively robust to potential unmeasured confounding. Secondly, the use of secondary data restricts the way key variables are specified, particularly those concerning lifestyle habits or social conditions. However, this is compensated in part by the availability of rich and credible data available in ELSA. In addition, we benefit from the work of others who have elegantly operationalized the measurement of complex social constructs such as social support and integration (Banks et al., 2010), and then demonstrated the utility of these specifications. Thirdly, more than 20% of values are missing for allostatic load, low social support, and low social integration. We argue that handling on the MAR assumption is reasonable given that we include a broad range of predictors that provide information for the FIML procedure. Nonetheless, the potential influence of missing values needs to be borne in mind when interpreting negative findings for these three predictors. Lastly, five assumptions are needed if we are to inject any extent of causal interpretation into our mediation analysis (VanderWeele, 2016). The first three are adequate control for the physical frailty-death, physical frailty-mediator, and mediator-death confounding, which would apply to any observational study. As mentioned, controlling for a wide range of multidimensional predictors of death in our statistical models increases the possibility that these assumptions hold. In addition, our sensitivity analyses suggest that residual confounding is not likely to change our results in any important way. The fourth is that there should not be any mediator-death confounder that is itself affected by physical frailty. Addressing any violation of this assumption would entail performing more complicated modeling (Daniel et al., 2013) that is beyond the ambit of our study. Thus, we acknowledge that our findings stand on this assumption. The fifth requires that there is no physical frailty-mediator moderation. To address this assumption, we include physical frailty-mediator interactions in our mediation models and thus, obtain estimates of indirect effects while taking these into account. Finally, we conduct multiple comparisons through performing separate models when exploring moderation, thereby increasing the risk of discovering significant effects purely by chance. To minimize this risk, we restrict our analyses to a reduced set of most plausible effects informed by the conceptual framework adopted, and use Bonferroni's method of correction for multiple comparisons when testing for statistical significance of moderated effects.

In summary, the evidence from ELSA confirms that physical frailty increases the risk of death in older people beyond that conferred by a rich set of multidimensional predictors. More importantly, it suggests that low physical activity and cognitive impairment are mediators, and high alcohol intake and poor social integration are possible moderators on pathways from physical frailty to death. Thus, in terms of mitigating the negative impact of physical frailty on longevity, implementation of interventions that address these conditions merit consideration as population health and social strategies. This is of course in addition to efforts directed at reducing physical frailty in the first place.

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Supplementary Materials

Mathematical equations for the statistical models

Let y_i denote the factor score of the continuous factor for death across wave 3 to 5 in the discrete time survival model, p_i be the physical frailty factor score at wave 2, and x_i represents a time-invariant predictor for individuals i = 1..., n.

The discrete time survival model with continuous factor is

$$y_i = \beta_0 + \beta_1 p_i + \beta_2 x_i + \varepsilon_i$$

Here, the coefficient β_1 describes the associations between physical frailty and death, while β_2 describes the associations between the time-invariant predictor and death. The estimated coefficients β_1 and β_2, are shown in Table 2.

Moderation: Here, we consider the interaction between physical frailty and a time-invariant predictor. Thus, the corresponding discrete time survival model with continuous factor is

$$y_i = \beta_0 + \beta_1 p_i + \beta_2 x_i + \beta_3 p_i * x_i + \varepsilon_i$$

where $p_i * x_i$ is the variable for interaction. The estimated coefficient β_3 describes this interaction.

Mediation: Here we use the results of standard linear path analysis applied to the discrete time survival model. For simplicity of notation in introducing the idea, consider the case where m_i is a mediator of the effect of p_i on y_i, so that

$$y_i = \beta_0 + \beta_1 p_i + \beta_2 x_i + \beta_3 m_i + \varepsilon_i$$

Suppose further that

$$m_i = \lambda_0 + \lambda_1 p_i + \delta_i.$$

Then the model given p_i and x_i only, averaging over the distribution of m_i, is

$$y_i = \beta_0 + \beta_{*1} pi + \beta_2 x_i + \varepsilon_{*i}$$

where $\varepsilon_{*i} = (\varepsilon_i + \beta_3 \delta_i)$ and $\beta^*_1 = \beta_1 + \beta_3 \lambda_1$. Here β_{*1} is the total effect of the variable z_i on the death factor, β_1 is the direct effect of p_i, and $\beta_3 \lambda_1$ the indirect effect of p_i mediated via m_i.

Table 5. Estimated unstandardized thresholds (or intercepts) from discrete time survival analysis with corresponding hazard, and survival probability in the three time periods for different physical frailty factor score values and at mean values for other predictors

	Thresholds			Hazard			Survival probability		
Physical frailty factor score	- 1SD	Mean	+ 1SD	- 1SD	Mean	+ 1SD	- 1SD	Mean	+ 1SD
Wave 3	3.381	3.167	2.953	0.033	0.040	0.050	0.967	0.960	0.950
Wave 4	3.083	2.869	2.654	0.044	0.054	0.066	0.924	0.908	0.887
Wave 5	2.813	2.599	2.385	0.057	0.069	0.084	0.871	0.845	0.812

N = 4.638

Table 6. Effects of physical frailty (wave 2) and other predictors (wave 2) on hazard of death (waves 3 to 5) while controlling for each other using discrete time survival analysis: standardized coefficients for log odds and odds ratio of death

	Log odds of death	Odds ratio of death
Physical frailty*	0.214	1.239
Age*	0.518	1.679
Female gender*	-0.548	0.578
Chronic disease*	0.153	1.165
Allostatic load*	0.133	1.142
Smoking history*	0.257	1.293
High alcohol intake	0.029	1.029
Obesity*	-0.311	0.733
Underweight*	0.237	1.267
Low physical activity*	0.252	1.287
Depressive symptoms	-0.012	0.988
Cognitive impairment*	0.156	1.169
Low education level	0.003	1.003
Low wealth	0.005	1.005
Poor social support	-0.028	0.972
Poor social integration	0.078	1.081

* Indicates statistical significance at 5% level

Values of log odds or the odds ratio of death are for one standard deviation increase in continuous predictors or the increase from zero to one for the binary predictors (female gender, obesity, smoking, high alcohol intake, low educational level, and low wealth).

Missing values are handled by full information maximum likelihood (FIML).

N = 4.638

Table 7. Main and moderated effects of physical frailty (wave 2) on hazard of death (waves 3 to 5) while controlling for other predictors (wave 2) using discrete time survival analysis: coefficients for log odds and odds ratio of death

		Log odds of death	Odds ratio of death
All		0.213*	1.239*
Smoking	No	0.184*	1.202*
	Yes	0.227**	1.255**
High alcohol intake	No	0.168**	1.183**
	Yes	0.316**	1.372**
Low physical activity	Less	0.299**	1.348**
	Average	0.238**	1.269**
	More	0.177**	1.194**
Obesity	No	0.250**	1.284**
	Yes	0.073	1.076
Allostatic load	Low	0.216*	1.242*
	Average	0.213**	1.237**
	High	0.210*	1.233*
Depressive symptoms	Low	0.222**	1.249**
	Average	0.214**	1.238**
	High	0.206**	1.228**
Cognitive impairment***	Low	0.383**	1.467**
	Average	0.256**	1.292**
	High	0.130*	1.139*
Poor social support	Low	0.214**	1.239**
	Average	0.213**	1.238**
	High	0.212**	1.237**
Poor social integration	Low	0.170*	1.186*
	Average	0.218**	1.243**
	High	0.265**	1.303**
Low wealth	No	0.222**	1.249**
	Yes	0.192*	1.212*

For continuous variables (depressive symptoms, cognitive impairment, low social support, low social integration, and low physical activity), values one standard deviation below the mean are designated as “low” and values one standard deviation above the mean as “high”. The exception is low wealth where lower 2 deciles of total non-pension wealth are designated as “Yes” and higher 8 deciles as “No”. Binary variables are obesity, underweight, smoking, high alcohol intake, and low wealth.

* Indicates statistical significance at the 5% level but not at the 0.5% level

** Indicates statistical significance at the 0.5% level (Bonferroni’s correction for 10 multiple comparisons)

*** Indicates statistical significance at the 0.5% level for moderation (Bonferroni’s correction for 10 multiple comparisons)

Values of log odds or the odds ratio of death are for one standard deviation increase (for continuous variables) or values from 0 to 1 (for binary variables) in the main or moderated effects. The estimated effects are controlled for age, gender, chronic disease, allostatic load, smoking history, high alcohol

intake, obesity, low physical activity, depressive symptoms, cognitive impairment, low education level, low wealth, poor social support, and poor social integration.
Missing values are handled by full information maximum likelihood (FIML).
N = 4.638

Table 8. "Corrected" estimates of the indirect effects of physical frailty (wave 2) on hazard of death (waves 3 to 5) over different sensitivity parameters using discrete time survival analysis: coefficients for log odds of death

Mediator of indirect effect	Correlation of unmeasured confounder with mediator	Correlation of unmeasured confounder with physical frailty						
		0	0.1			0.3		
		Effect of the unmeasured confounder on death in terms of multiples of the uncorrected effect of physical frailty on death						
		0X	1X	2X	3X	1X	2X	3X
Low physical activity	0	0.085*	-	-	-	-	-	-
	0.1	-	0.078*	0.072*	0.066*	0.077*	0.071*	0.065*
	0.3	-	0.061*	0.038*	0.016	0.061*	0.038*	0.015
Depressive symptoms	0	-0.008	-	-	-	-	-	-
	0.1	-	-0.015	-0.021	-0.027	-0.015	-0.021	-0.027*
	0.3	-	-0.028	-0.047*	-0.067*	-0.028*	-0.047*	-0.067*
Cognitive impairment	0	0.053*	-	-	-	-	-	-
	0.1	-	0.044*	0.038*	0.032*	0.044*	0.038*	0.033*
	0.3	-	0.031*	0.012	-0.006	0.032*	0.013	-0.006

* Indicates statistical significance at 5% level

Shaded cells indicate that "corrected" estimates for the effect of physical frailty on death remain positive and significant.

Missing values are handled by full information maximum likelihood (FIML).

N = 4.638

9.3 Further Thoughts

We have seen that pathways from physical frailty to death include indirect effects through low physical activity and cognitive impairment. This brings about opportunities for interventions to reduce the impact of physical frailty on death by modifying these two conditions in older people. However, besides longevity, other aspects of their lives matter to older people. Among the prominent themes from narratives on what older people view as most important is their desire for independence. This means having the ability to do activities are important to them (Redding et al., 2014). It also involves having good health and mobility to continue doing activities that enhance their quality of life (Gabriel & Bowling, 2004). This concerns the length of healthy life or *healthspan*, as opposed to mere length of life or *lifespan*. Increasing healthspan not only requires delaying the physiological decline that results in disease and disability (Crimmins, 2015), but also involves mitigating their negative effects in older people.

In view of the centrality of independence for older people, I will proceed to complete my thesis by examining the relationship between physical frailty and functional disability. Thus, the final paper focuses on pathways from physical frailty to activity limitation.

10 Fifth Paper

10.1 Introduction

As mentioned, being able to walk and perform self-care activities independently matters to older people. Functional disability certainly reduces the quality of life in older people (Murphy et al., 2007 ; Walker & Lowenstein, 2009). Unfortunately, being physical frail increases an older person's risk of functional disability (Avila-Funes et al., 2008; Romero-Ortuno et al., 2011; Woo et al., 2006). While that may be the case, it is important to understand whether this risk is influenced by other physical, psychological, and social conditions. In other words, we need to identify moderators of the effect of physical frailty on functional disability. Furthermore, it is important to understand how physical frailty confers this risk by identifying mediators of its indirect effects. Where these moderators and mediators are potentially modifiable lifestyle-related, psychological, and social conditions, they represent target conditions for interventions that aim to mitigate the negative effects of physical frailty on functional independence in older people.

With these in mind, the research aim of the fifth paper is to explore pathways from physical frailty to functional disability. I will seek to answer the research question: "Which physical, psychological, and social conditions moderate or mediate the effect of physical frailty on functional disability in older people?" To this end, I will yet again adopt the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) as the conceptual model. The right side of this working framework as illustrated in Figure 9.1 (page 153) is relevant. Potential moderators and mediators will be drawn from the categories of conditions listed in the bottom right hand corner of this figure. Before that, a suitable definition of functional disability is required.

In the latest WHO classification of disability, three levels of functioning are defined. They are impairment, activity limitation, and participation restriction (ICF, 2002). Typically, activity limitation is measured in terms of needing assistance in basic and instrumental activities of daily living (BADL and IADL). BADL items include bathing, dressing, toileting, transferring, feeding and walking (Katz et al., 1963), while those of instrumental IADL involve performance of more complex tasks ranging from preparing meals and taking medications to managing money and going shopping (Lawton & Brody, 1969). Activity limitation exerts a negative impact on older people. Those with increasing levels of activity limitation have lower levels of well-being manifested by higher prevalence of depression, less life satisfaction, poorer quality of life, and more loneliness even after stratifying according to age (Demakakos et al., 2010). Thus, activity limitation defined by difficulty in performing BADL, is the outcome of interest for this paper.

As similar to the fourth paper, physical frailty is measured by its three indicators, namely slowness, weakness, and exhaustion, with unique physical frailty factor scores derived for each respondent. However, since examining change is the focus of this paper, physical frailty scores will be specified as a time-varying variable at waves 2, 4, and 6, instead of only at wave 2. Activity limitation at waves 2, 4, and 6 is the outcome. It is defined as the number out of six basic activities of daily living (BADL) items performed with difficulty (score of 0 to 6). As for the previous two papers, a rich set of physical, psychological, and social predictors of activity limitation will be included as control variables. In addition, selected conditions will also be specified as moderators or mediators of the effect of physical frailty.

To estimate the effect of physical frailty on activity limitation across time, I will use autoregressive cross-lagged models (ACLM) over waves 2, 4, and 6 of ELSA data. ACLM is useful for examining whether one variable predicts another by taking advantage of temporal precedence of the first over the second variable. The fundamental idea of the lagged model is to estimate the effect of the cause (physical frailty) measured at an earlier time point on the effect (activity limitation) at a later point, while controlling for the earlier value of the effect variable (lagged activity limitation). Doing so allows control of pre-existing differences, as well as removal of stable aspects of the effect variable. Consequently, the cross-lagged effect represents the effect of the cause on *change* in the outcome (Newsom, 2015). Since interest is solely on the effect of physical frailty on change in activity limitation, and not on the opposite, a series of autoregressive cross-lagged models will be constructed where the attention is on unidirectional rather than bidirectional effects.

The following paper examines pathways from physical frailty to activity limitation. Yet again, some of the foregoing key points are unavoidably repeated as this is a self-contained journal article. Its references are again in a separate list just before the Supplementary Materials (pages 211 to 214). Relevant Mplus input files are provided in the Appendix. At the time of writing, this paper is being considered for publication in a gerontology journal.

10.2 Pathways from physical frailty to activity limitation in older people: identifying moderators and mediators in the English Longitudinal Study of Ageing

Joint work with Associate Professor Jouni Kuha (Departments of Statistics and Methodology, London School of Economics) and Professor Michael Murphy (Department of Social Policy, London School of Economics)

Abstract

Physical frailty increases the risk of future activity limitation, which in turn compromises independent living of older people and limits their healthspan. Thus, we seek to identify moderators and mediators on pathways from physical frailty to activity limitation in older people, including gender- and age-specific effects. From data of the English Longitudinal Study of Ageing, unique physical frailty factor scores of 4,638 respondents aged 65 to 89 years are obtained from confirmatory factor analysis of physical frailty, which is specified by three indicators, namely slowness, weakness, and exhaustion. Using a series of autoregressive cross-lagged models, we estimate the effect of physical frailty factor score on activity limitation *change*, including its moderation by social conditions, and indirect effects through physical and psychological conditions. We find that physical frailty significantly worsens the activity limitation trajectory, and this effect is significantly stronger with older age. Physical frailty also has significant indirect effects through low physical activity, depressive symptoms, and cognitive impairment. In turn, the indirect effects of physical frailty through low physical activity and cognitive impairment are stronger with older age. Sensitivity analyses suggest that these effects vary in their robustness to unmeasured confounding. We conclude that low physical activity, depressive symptoms, and cognitive impairment are potentially modifiable mediators on pathways from physical frailty to activity limitation in older people, including those who are very old. This evidence offers support for population-level interventions that address these conditions to mitigate the effect of physical frailty on activity limitation, and thereby enhance healthspan.

Key words: disability, pathways, physical activity, depression, cognition, cross-lagged

Introduction

Frailty is widely regarded as the multidimensional loss of an individual's body system reserves that results in vulnerability to developing adverse health-related outcomes (Espinoza & Walston, 2005; Lally & Crome, 2007; Pel-Littel et al., 2009). It is conceptualized as a transitional state between robustness and functional decline (Lang et al., 2009) that is associated with increased risk of death, disability, falls, hospitalization, and institutionalization (Daniels et al., 2012; Ensrud et al., 2009; Ensrud et al., 2008; Jones et al., 2005; Kiely et al., 2009; Pilotto et al., 2012; Woo et al., 2012). Although long recognized as an important condition in older people, frailty has been defined in various ways ranging from a frailty phenotype with five components (Fried et al., 2001), to a frailty index that adopts a multiple deficit accumulation approach (Rockwood & Mitnitski, 2007). Some extent of consensus on its operational definition has only recently been achieved (Morley et al., 2013). Nonetheless, different definitions are probably best suited for different purposes (Martin & Brighton, 2008).

Across a spectrum of definitions applied, the prevalence of frailty is estimated to be about 10% among people aged 65 years or older (Collard et al., 2012). In the United Kingdom alone, the number of those in this age group was 11.6 million in 2015 (ONS, 2016), permitting the estimation that approximately 1.2 million older people across the country are frail. The potential adverse outcomes of frailty and its size of problem combine to create significant health and social impact for ageing populations. Consequently, frailty plays a central role in influencing the well-being of older people and holds major public health importance (Woo et al., 2006).

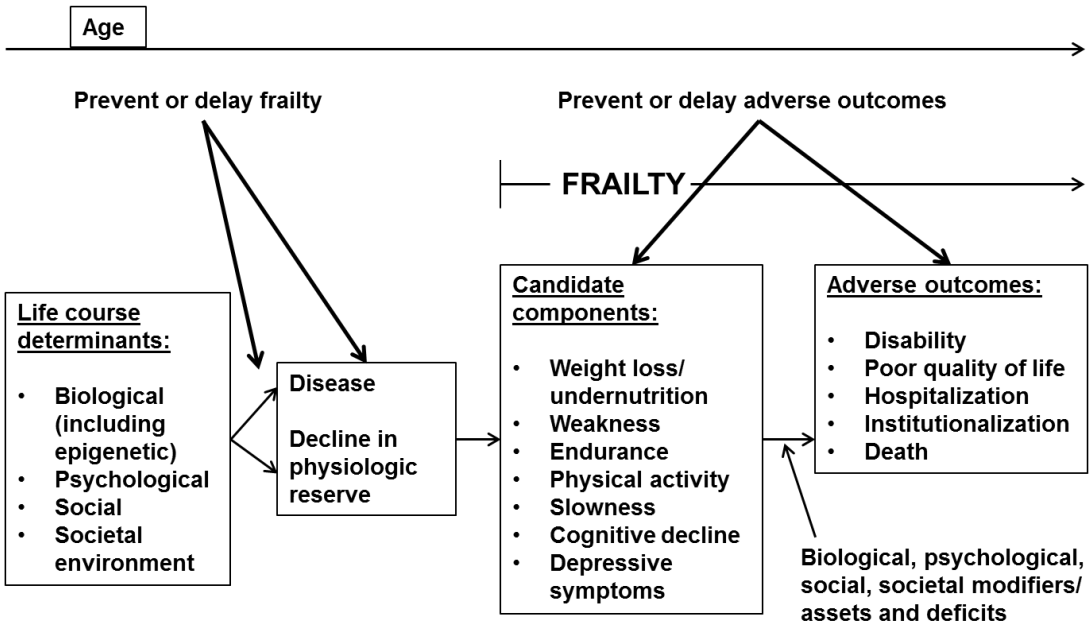
As an adverse outcome of frailty, functional disability reduces the quality of life in older people (Murphy et al., 2007 ; Walker & Lowenstein, 2009). The latest WHO classification of disability defined three levels of functioning. They are impairment, activity limitation, and participation restriction (ICF, 2002). Typically, activity limitation is measured in terms of needing assistance in basic and instrumental activities of daily living (BADL and IADL). BADL items include bathing, dressing, toileting, transferring, feeding and walking (Katz et al., 1963), while those of instrumental IADL involve performance of more complex tasks ranging from preparing meals and taking medications, to managing money and going shopping (Lawton & Brody, 1969). Activity limitation exerts a negative impact on older people. Those with increasing levels of activity limitation have lower levels of well-being, which manifests as higher prevalence of depression, less life satisfaction, poorer quality of life, and more loneliness, even after stratifying for age (Demakakos et al., 2010). Moreover, activity limitation compromises healthspan, which is measured by length of healthy life (Crimmins, 2015), and is equally if not more important than lifespan for many older people.

Frailty and functional disability, represented here by activity limitation, are considered distinct entities with some degree of overlap (Fried et al., 2004). More importantly, frailty indicators predict future activity limitation in terms of BADL and IADL dependence among community-dwelling older people (Avila-Funes et al., 2008; Gobbens et al., 2012b; Romero-Ortuno et al.,

2011; Vermeulen et al., 2011). However, the precise mechanisms by which frailty exerts this effect are less clear. Particularly, there is sparse knowledge on pathways from frailty to eventual activity limitation. Better understanding of these pathways including the identification of moderators and mediators on them can inform public health and social policy with respect to organizing effective population-level interventions that could potentially minimize the impact of frailty where it already occurs. This may in turn slow down or even delay the onset of activity limitation in older people.

To conceptualize pathways from frailty to activity limitation, a good starting point is the working framework proposed by the Canadian Initiative on Frailty and Aging (Bergman et al., 2004) which is simplified and shown in Figure 1. In the right half of this figure, biological, psychological, social, and societal assets and deficits are represented as moderators on the pathway from frailty to adverse outcomes which include disability. These assets and deficits represent potential target conditions for intervention to reduce the negative impact of frailty. More recently, the integral concept of frailty (Gobbens et al., 2010b) developed a similar set of frailty pathways adapted from those of the Canadian working framework. Other frailty pathways have also been proposed, but are largely restricted to the biological sphere, and are therefore less suitable for a broader investigation of the effects of frailty. Thus, the Canadian working framework offers a useful foundation on which to build a conceptual model for pathways from frailty to activity limitation.

Figure 1. Working framework of the Canadian Initiative for Frailty and Aging (adapted from Bergman, 2004 with modifications)

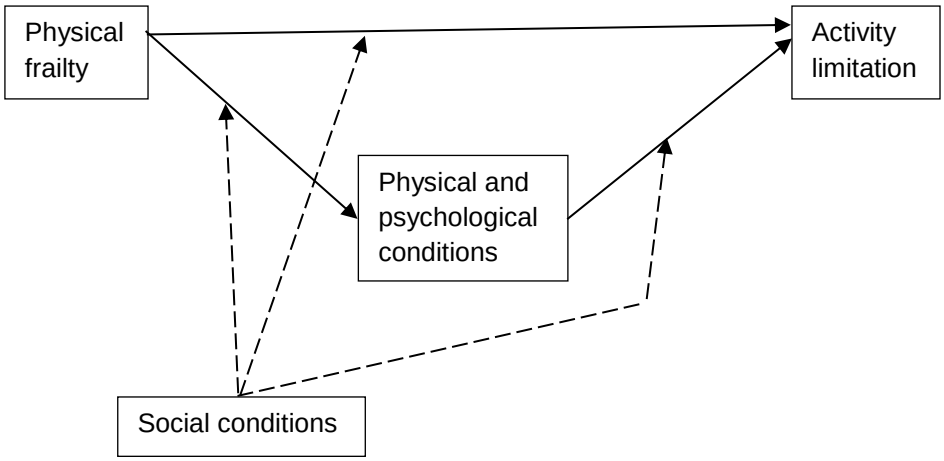


With a conceptual model of frailty pathways available, the challenge is then to identify a frailty specification that is suitable for investigation of these pathways. In his seminal work, Strawbridge recognized the multidimensional nature of frailty and conceptualized frailty as involving problems in at least two from among physical, nutritive, cognitive, and sensory domains (Strawbridge et al., 1998), More recently, the view of frailty being multidimensional has been expressed in part through the development of frailty identifiers that measure deficits across more than a single domain (Bielderman et al., 2013; Gobbens et al., 2010b; Rockwood, 2005). However, some of the multidimensional elements in these frailty specifications are also hypothesized to be key conditions on pathways from frailty to its adverse outcomes. Having these elements as part and parcel of the frailty specification complicates the task of teasing out the relationship between frailty and these key deficits. As an alternative, the integral concept of frailty explicitly specifies frailty as having three distinct domains namely physical, psychological, and social (Gobbens et al., 2010a). Being able to specify frailty based on a single domain facilitates its disentanglement from conditions related to the other two domains. This in turn facilitates less constrained exploration of the relationship of frailty with physical, psychological, and social conditions that may turn out to be mediators or moderators of its effect.

Among these three frailty domains, physical frailty offers the most promising choice as a frailty specification for the investigation of related pathways. There are a number of reasons for this. Firstly, physical frailty is far better understood than psychological or social frailty. Secondly, physical frailty contributes most to prediction of disability among the three frailty domains (Gobbens et al., 2012a). Finally, there exists an excellent prototype for physical frailty in the CHS frailty phenotype (Fried et al., 2001). It conceptualizes physical frailty has having five components. Our previous work argues that specifying physical frailty with three of the five indicators namely walking speed, grip strength, and report of exhaustion retains face and content validity. In addition, we demonstrate construct and concurrent validity for this physical frailty specification (Ding, 2016). In the light of these points, physical frailty specified by these three indicators holds promise for the investigation of pathways from frailty to activity limitation.

Our conceptual model for investigating the relationship of physical frailty with activity limitation is shown in Figure 2. In this model, indirect or mediated effects through physical and psychological conditions are included in addition to the direct effect. Furthermore, moderation of these effects by social conditions is also incorporated (dotted lines). We base these hypothesized pathways in part on the Canadian working framework, while advancing beyond to also include indirect effects. These pathways are also consistent with current thinking that posits psychosocial resources as possible moderators and mediators of the effects of frailty (Dent & Hoogendijk, 2015).

Figure 2. Conceptual model for investigation of pathways from physical frailty to activity limitation



Thus, the overarching aim of our study is to identify and estimate the effects of physical, psychological, and social conditions that have roles as moderators and mediators of the relationship between physical frailty and future activity limitation in older people. Under this broad aim, we seek to answer three research questions:

1) Does the effect of physical frailty on activity limitation vary across different levels of key social conditions?
2) Does physical frailty have an indirect effect on activity limitation through key lifestyle and psychological conditions?
3) Do the effects of physical frailty on activity limitation vary across gender and age?

To answer these questions, we use longitudinal data from the English Longitudinal Study of Ageing (ELSA). ELSA is a longitudinal survey of a representative sample of the English population aged 50 years and older living in their homes at baseline (Steptoe et al., 2013). It offers a broad range of reliable and multidimensional data across biennial waves beginning from 2002, and is still ongoing.

Methods

Data

Our study population comprises 4,638 older respondents aged 65 to 89 years at wave 2 (2004) of ELSA (Marmot et al., 2015). Those aged 90 years and older are excluded given that their age is uniformly coded as “90”, and that their number is small. All participants gave informed consent. Ethical approval for ELSA was granted by the Multicentre Research and Ethics Committee. Ethical oversight for this study is provided by procedures of the London School of Economics Ethics Policy.

Physical frailty is specified by three indicators drawn from those of the CHS frailty phenotype (Fried et al., 2001), namely slowness, weakness, and exhaustion. *Slowness* is the average gait speed (in m/s) of two attempts at walking 2.4 m, but with values reversed through multiplication by -1. *Weakness* is the dominant hand grip strength in kg, which is multiplied by 1.5 for women. The differential handling of raw grip strength values in men and women is based on gender-specific and population-independent cut-off values for grip strength previously proposed for the CHS frailty phenotype criteria (Saum et al., 2012). After that, reversal of all values is achieved by multiplying them by -1. *Exhaustion* is a binary variable based on a positive response to at least one of two items in the Center for Epidemiologic Studies Depression Scale (CES-D) scale on whether the respondent “felt everything they did during the past week was an effort” and “could not get going much of the time in the past week” (Radloff, 1977). We have previously argued and demonstrated that the combination of these three indicators is preferred to represent the physical frailty construct from among other permutations of the five components of the CHS frailty phenotype (Ding, 2016). Given that measures for these indicators are only available at waves 2, 4, and 6, we measured physical frailty at these time points. Confirmatory factor analysis (CFA) with these three indicators across waves 2, 4, and 6 is performed, while assuming and thereby imposing scalar (strong) invariance, where all loadings and intercepts are held constant across time. From CFA, unique physical frailty factor scores for waves 2, 4, and 6 are obtained for each respondent, and then used for the subsequent regression analyses.

Activity limitation is the outcome of interest and is defined by the number out of six BADL items performed with difficulty (score of 0 to 6). As we focus on physical function, IADL is not used because its performance requires additional cognitive competency. Other predictors of activity limitation are drawn from the multidimensional categories listed in the Canadian working framework (Bergman et al., 2004). Beyond *age* and *gender*, physical predictors, namely *obesity* (binary: body mass index (BMI) of 30 kg/m^2 or more with reference to normal, defined by BMI less than 30 kg/m^2 but more than 20 kg/m^2), being *underweight* (binary: BMI of 20 kg/m^2 or less with reference to normal, defined by BMI less than 30 kg/m^2 but more than 20 kg/m^2), *low physical activity* (four levels of decreasing intensity activity related to occupation and exercise), *chronic disease* (count of conditions from 0 to 14), *allostatic load* (score of 0 to 8), *smoking*

(binary: whether ever smoked), and *high alcohol intake* (binary: whether had alcohol drink almost every day in the past 12 months). Allostatic load is a measure of physiological dysregulation in multiple body systems (Gruenewald et al., 2009), and is specified by eight biomarkers including blood pressure readings, anthropometric measurements, and blood tests for cholesterol levels, glucose control, and inflammatory markers. For each biomarker, a score of one is awarded for values beyond a cut-off level reflecting high risk, with a score of zero given if otherwise. The total score defines allostatic load.

Psychological predictors include *depressive symptoms*, which are measured by a count of six out of eight items (score of 0 to 6) of the CES-D Scale (Radloff, 1977). The two omitted items are those already used to specify exhaustion as a physical frailty indicator. *Cognitive impairment* is measured by reversing a cognitive index based on the combined memory and executive function test performance (score of 0 to 49).

Social predictors include *low education* (binary: no qualifications compared with any qualification), and *low wealth* (binary: lowest 2 deciles compared with highest 8 deciles of non-pension wealth). Additionally, *low social integration*, reflecting social isolation, is based on a combined score on five items (score of 0 to 14) concerning whether participants have no spouse and partner living with them, had little contact with children, had little contact with other family members, had little contact with friends, and were not a member of any organization, club or society. Contact includes meeting, phoning, or writing or email. Its composite scoring procedure is adapted from that of a previous study (Banks et al., 2010). Finally, *poor social support*, in terms of deficient emotional support, and reflecting negative social interaction with family and friends is measured by the combined scores on whether there is lack positive support, and the occurrence of negative support (score of 0 to 54). Lack of positive support is measured by negative answers to questions on “understand the way you feel”, “can rely on if you had a serious problem”, and “can open up to them if you need to talk” with respect to children, other family members, and friends. Negative support is measured by positive answers to questions on whether children, other family members, and friends "criticizes the respondent", "lets the respondent down", and "gets on the nerves of respondent". Its composite scoring procedure is again based on that of the aforementioned study (Banks et al., 2010).

Statistical analyses:

A series of autoregressive cross-lagged models over waves 2, 4, and 6 of ELSA data are created to examine the effect of physical frailty on activity limitation change, and include moderated and mediated effects. Details of models and their equations are provided in the Supplementary Materials.

Model 1 predicts activity limitation *change* by physical frailty controlling for other predictors, namely gender, age, obesity, underweight state, chronic disease, allostatic load, smoking history, high alcohol intake, low educational level, low wealth, poor social integration, and poor

social support at wave 2. Both physical frailty and activity limitation are included at waves 2, 4, and 6 with auto-regressive effects for activity limitation (waves 2 and 4 predicting waves 4 and 6 respectively) and physical frailty (wave 2 predicting wave 4). Cross-lagged effects of physical frailty at waves 2 and 4 predicting activity limitation change at waves 4 and 6 respectively are included. Equivalent effects are constrained to be equal across time. Here, the cross-lagged effect of physical frailty on activity limitation change is the focus of estimation. In addition, stratified analyses according to gender and age group (at least 75 years and less than 75 years) are performed to obtain gender- and age group-specific estimates of the effect of physical frailty. Model 2 extends Model 1 by examining moderation of the effect of physical frailty by poor social support and poor social integration through stratified analyses according to values below the mean and those at least the mean. Differences between effect estimates across gender, age, poor social support, and poor social integration categories are tested for statistical significance of moderation using the Wald test.

Model 3 extends Model 1 by including mediation of the indirect effects of physical frailty on activity limitation *change* by low physical activity, depressive symptoms, and cognitive impairment. For the indirect effect of physical frailty (wave 2) on activity limitation change (wave 4), the mediators are either at wave 3 (cognitive impairment) or wave 4 (low physical activity and depressive symptoms). Correspondingly, for the indirect effect of physical frailty (wave 4) on activity limitation change (wave 6), the mediators are either at wave 4 (cognitive impairment) or wave 6 (low physical activity and depressive symptoms). Cognitive impairment at waves 3 and 4 are used because the full cognitive index is not available at waves 5 and 6. Mediation effects are inferred from the product of coefficients for the physical frailty-mediator and mediator-activity limitation effects, using Sobel's test to test for significance (Sobel, 1982). Absence of physical frailty-mediator interaction is assumed. Stratified analyses according to gender and age group are also performed. Finally, Model 4 is an extension of Model 3 with the addition of analyses for moderation of mediated effects (moderated mediation or conditional indirect effects) (Preacher et al., 2007) by poor social support, and poor social integration through stratified analyses as for Model 2. Yet again, differences between indirect effect estimates across gender, age, poor social support, and poor social integration categories are tested for statistical significance of moderation using the Wald test. Full details of the model specifications are given in the Supplementary Material.

Sensitivity analyses are performed to relax three important assumptions in our analyses and then to observe whether there are important changes in the results. Firstly, physical frailty-mediator interaction is also included in Model 3, relaxing the assumption of its absence. Secondly, we relax the assumption that there is no unmeasured confounding when estimating the physical frailty-mediator, mediator-activity limitation, and physical frailty-activity limitation effects. This is accomplished by including continuous latent variables ("phantom" variables) with varying magnitude of effect on physical frailty, activity limitation, and mediators in the model. This is to simulate the presence of unmeasured confounders and estimate the magnitude of their effects that would sufficient to cause the effects of physical frailty and

mediators to be non-significant (VanderWeele, 2016). Thirdly, we relax the assumption that the activity limitation has an approximately normal distribution, given that this variable is measured by number of BADL items performed with difficulty, which can be considered as count data. In anticipation that this distribution is right skewed with a large proportion of zero values, negative binomial regression will be also performed for its prediction to check if there are any important differences in the results in doing so (Zaninotto & Falaschetti, 2011). In addition, we restrict our analyses to respondents who have available values for activity limitation at wave 6, thereby excluding those contributing to attrition across time. The purpose is to provide alternative analyses to those implementing maximum likelihood for the whole study population, which in turn assumes that missing values are MAR.

Missing values are handled under the assumption of missing at random (MAR) by full information maximum likelihood (FIML), which a procedure that is analogous to multiple imputation but without actual creation of imputation datasets. Rather, the missing data is handled within the analysis model using maximum likelihood estimation, which identifies population parameters having the highest probability of producing the sample data. It uses all available data to generate their estimates and assumes multivariate normality. It is also implemented for predictor variables by treating them as dependent variables through estimating their sample means. Mplus version 7.4 (Muthén & Muthén, 1998-2012) is used to perform the autoregressive cross-lagged analyses, while STATA version 14.1 is used for all other analyses. Statistical significance is assessed at the 5% level, except for examination of moderated effects by the two social predictors, where it is assessed at the 2.5% level on account of Bonferroni's correction for multiple comparisons.

Results

Table 1 describes the characteristics of the study population including physical frailty indicators, factor scores, frailty status, and activity limitation across waves 2, 4, and 6. In addition, predictors at wave 2 are also shown. Additional information on mediators at waves 2, 4, and 6 is also provided by the Supplementary Materials (Table 4). The mean age is 74 years and women comprise approximately 55 percent. Activity limitation increases on over time with 27% needing assistance in one or more basic activities of living (BADL) item at wave 2 to 30% at wave 6. Correspondingly, the mean number of BADL items requiring assistance also increases from 0.51 to 0.70 from waves 2 to 6. There is more difficulty with BADL among women and those aged at least 75 years. Physical frailty increases over time as measured by factor scores (-0.02 to 0.02) and proportion categorized as having frailty (20% to 25%). Thus, increasing levels of activity limitation parallel increasing physical frailty in the study population. Moreover, physical frailty levels and proportions of respondents who are frail are higher among women and in the older group. Among physical, psychological, and social conditions at wave 2, there are minor gender-specific and age-specific differences with a few exceptions. Obesity is more common among women and in the younger group. Both history of smoking and high alcohol intake are more common among men. On the other hand, women and those in the older group have more depressive symptoms, while the latter also have more cognitive impairment.

Table 1. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses

Variables	All	By gender		By Age group	
		Male	Female	< 75 years	>= 75 years
General:					
Mean age, years (SD)	74.0 (6.3)	73.5 (6.2)	74.3 (6.4)	69.3 (2.8)	80.2 (3.9)
Female, n/N (%)	2,568/4,638 (55.4)	-	-	1,399/2,643 (52.9)	1,169/1,995 (58.6)
Physical frailty:					
Mean average walking speed, m/sec (SD)	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
Hand grip strength, kg (SD)	25.9 (10.2)[6]	33.4 (8.9)[7]	19.6 (6.1)[8]	28.4 (10.2)[9]	22.2 (8.2)[10]
Exhaustion, n/N (%)	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
Frailty by Frailty Index, n/N (%):					
Wave 2	717/3,647 (19.7)	236/1,639 (14.4)	481/2,008 (24.0)	322/2,207 (14.6)	395/1,440 (27.4)

	Wave 4	507/2,371 (21.4)	158/1,051 (15.0)	349/1,320 (26.4)	279/1,571 (17.8)	228/800 (28.5)
	Wave 6	438/1,774 (24.7)	145/768 (18.9)	293/1,006 (29.1)	285/1,325 (21.5)	153/449 (34.1)
Mean physical frailty factor score (SD):	Wave 2	-0.02 (0.81)[11]	-0.21 (0.76)[12]	0.12 (0.80)[13]	-0.28 (0.78)[14]	0.32 (0.71)[15]
	Wave 4	0.01 (0.80)[11]	-0.18 (0.78)[12]	0.15 (0.78)[13]	-0.25 (0.78)[14]	0.35 (0.68)[15]
	Wave 6	0.02 (0.76)[11]	-0.15 (0.74)[12]	0.16 (0.74)[13]	-0.22 (0.75)[14]	0.35 (0.64)[15]
Physical:						
Obesity, n/N (%)		1,018/3,976 (25.6)	400/1,783 (22.4)	618/2,193 (28.2)	662/2,328 (28.4)	356/1,648 (21.6)
Underweight, n/N (%)		117/3,689 (3.2)	42/1,661 (2.5)	75/2,028 (3.7)	59/2,226 (2.7)	58/1,463 (4.0)
Mean chronic disease count [0 to 14] (SD)		1.9 (1.4)[16]	1.8 (1.4)[17]	2.0 (1.4)[18]	1.8 (1.4)[19]	2.1 (1.5)[20]
Mean allostatic load score [0 to 8] (SD)		2.0 (1.5)[21]	1.9 (1.5)[22]	2.1 (1.5)[23]	1.9 (1.5)[24]	2.1 (1.5)[25]
Mean low physical activity level [0 to 3] (SD)		1.2 (0.9)[26]	1.1 (0.9)[27]	1.3 (0.9)[28]	1.0 (0.9)[29]	1.4 (0.9)[30]
Smoking history, n/N (%)		2,963/4,634 (63.9)	1,567/2,069 (75.7)	1,396/2,565 (54.5)	1,649/2,639 (62.5)	681/1,995 (65.9)
Heavy alcohol intake, n (%)		1,249/3,871 (32.3)	720/1,742 (41.3)	529/2,129 (24.9)	792/2,344 (33.8)	457/1,527 (29.9)
Psychological:						
Mean CESD-8 score [0 to 8] (SD)		1.7 (2.0)[31]	1.3 (1.7)[32]	1.9 (2.1)[33]	1.5 (1.9)[34]	1.9 (2.0)[35]
Mean cognitive impairment score [0 to 49] (SD)		27.5 (6.3)[36]	26.3 (6.4)[37]	25.5 (6.5)[38]	24.1 (6.0)[39]	28.4 (6.3)[40]
Social:						
Low education, n (%)		2,256/4,618 (48.9)	885/2,061 (41.5)	1,401/2,557 (54.8)	1,158/2,630 (44.0)	1,098/1,998 (55.2)
Low wealth, n (%)		980/4,557 (21.5)	365/2,022 (18.1)	615/2,535 (24.3)	454/2,584 (17.6)	526/1,973 (26.7)
Mean poor social support score [0 to 54] (SD)		13.7 (7.0)[41]	14.7 (7.0)[42]	12.9 (6.8)[43]	13.9 (7.0)[44]	13.3 (6.8)[45]
Mean poor social integration score [0 to 14] (SD)		6.6 (2.5)[46]	6.7 (2.6)[47]	6.5 (2.5)[48]	6.4 (2.5)[49]	7.0 (2.6)[50]

Activity limitation:					
Mean number of BADL items performed with difficulty [0 to 6] (SD):					
Wave 2 (2004)	0.51 (1.08)[51]	0.47 (1.03)[52]	0.55 (1.11)[53]	0.40 (0.96)[54]	0.66 (1.19)[55]
Wave 4 (2008)	0.58 (1.17)[56]	0.52 (1.13)[57]	0.63 (1.20)[58]	0.45 (1.04)[59]	0.79 (1.33)[60]
Wave 6 (2012)	0.70 (1.37)[61]	0.63 (1.32)[62]	0.75 (1.40)[63]	0.53 (1.18)[64]	1.07 (1.65)[65]
At least one BADL item performed with difficulty, n (%):					
Wave 2 (2004)	1,246/4,635 (26.9)	510/2,070 (24.6)	736/2,565 (28.7)	563/2,641 (21.3)	683/1.994 (34.3)
Wave 4 (2008)	917/3,127 (29.3)	336/1,356 (27.0)	551/1,771 (31.1)	457/1,916 (23.8)	460/1,211 (38.0)
Wave 6 (2012)	730/2,402 (30.4)	280/1,023 (27.4)	450/1,379 (32.6)	408/1,642 (24.9)	322/760 (42.4)

Frail status by Frailty Index (FI): FI >=0.25

CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)

BADL: basic activities of daily living

Unless indicated otherwise, N = 4,638 (all), 2,070 (male), 2,568 (female), 2,643 (less than 75 years old), and 1,995 (at least 75 years old).

N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]3,869 [7]1,760 [8]2,109 [9]2,276 [10]1,593 [11]4,560 [12]2,025 [13]2,535 [14]2,616 [15]2,025 [16]4,608 [17]2,052 [18]2,556 [19]2,617 [20]1,991 [21]2,319 [22]1,064 [23]1,255 [24]1,436 [25]883 [26]4,567 [27]2,032 [28]2,535 [29]2,611 [30]1,956 [31]4,479 [32]1,987 [33]2,492 [34]2,586 [35]1,893 [36]4,349 [37]1,946 [38]2,403 [39]2,546 [40]1,803 [41]3,339 [42]1,529 [43]1,810 [44]2,068 [45]1,271 [46]3,267 [47]1,506 [48]1,761 [49]2,035 [50]1,232 [51]4,635 [52]2,070 [53]2,565 [54]2,641 [55]1,994 [56]3,127 [57]1,356 [58]1,771 [59]1,916 [60]1,211 [61]2,402 [62]1,023 [63]1,379 [64]1,642 [65]760

Table 2 provides linear regression coefficients where physical frailty factor scores are standardized (Models 1 and 2). Physical frailty significantly predicts activity limitation *change* two years later controlling for other key predictors. More precisely, one standard deviation increase in physical frailty predicts increase in activity limitation change of almost 0.25 BADL items performed with difficulty (first panel of coefficients) over this time interval. Although this effect appears small in absolute terms, it is notable that physical frailty has by far the largest magnitude of effect on activity limitation change compared with other predictors when their standardized coefficients are compared in the Supplementary Materials (Table 5). In fact, the magnitude of effect for physical frailty is almost 2.5 times that of older age, which has the next largest significant effect. Viewed alternatively, one standard deviation increase in physical frailty predicts increase in activity limitation change that is equivalent to over two-fold that of the average increase observed in the study population, which is in the order of 0.1 BADL items performed with difficulty over two years (see Table 1). This effect of physical frailty is stronger for men compared with women, but not significantly so (second panel of coefficients). However,

this effect is significantly stronger among those in the older group compared with those younger (third panel of coefficients). Furthermore, the effect of physical frailty on activity limitation change has mild and non-significant differences across higher and lower levels of poor social support and poor social integration (fourth and fifth panels of coefficients).

Table 2. Main and moderated effects of physical frailty on activity limitation change controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: standardized regression coefficients for physical frailty factor score and its interactions variables

Outcome: activity limitation		Coefficient estimate
Physical frailty		0.234*
Physical frailty - gender:	Men	0.254*
	Women	0.219*
Physical frailty - age**:	<75 years	0.190*
	>=75 years	0.312*
Physical frailty - poor social support:	Low level	0.230***
	High level	0.244***
Physical frailty - poor social integration:	Low level	0.207***
	High level	0.257***

Physical frailty: factor scores standardized according to standard deviation of wave 2 values
Physical frailty - gender, Physical frailty - age, Physical frailty - poor social support, and Physical frailty - poor social integration: respective interactions with physical frailty factor scores
Low level: one standard deviation below the mean value
High level: one standard deviation above the mean value
All effects are controlled for lagged activity limitation, gender, age, chronic disease, allostatic load, body mass index (BMI) category, smoking history, alcohol intake level, educational level, wealth level, social support level, and social integration level.
* p-value <0.05
** p-value <0.05 for difference between two groups
*** p-value <0.025 (Bonferroni's correction for multiple comparisons for 2 separate moderation models)
Missing values are handled by full information maximum likelihood (FIML).
N = 4,638

Extension of the models to include mediation effects of physical frailty on activity limitation *change* (Model 3) yields interesting results which are shown in Table 3. Low physical activity, depressive symptoms, and cognitive impairment are all significant mediators (first panel), with their respective indirect effects being equivalent in magnitude to approximately 30%, 8%, and 4% that of the total effect indicated in Table 2. There are no differences in these indirect effects across gender (second panel). On the other hand, indirect effects of physical frailty through low physical activity and cognitive impairment are significantly stronger with older age, whereas that

through depressive symptoms is not (third panel). In addition, indirect effects are not significantly different across strata defined by poor social support and poor social integration levels (fourth and fifth panels), indicating that there is no significant moderation of the indirect effects by these two conditions (Model 4). However, a trend in the indirect effect through depressive symptoms being more than 1.5 times stronger with higher compared with lower levels of poor social support is noted.

Table 3. Mediation and moderated mediation of physical frailty on activity limitation controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: product of coefficients estimates

Outcome: activity limitation		Mediator		
		Low physical activity	Depressive symptoms	Cognitive impairment
All		0.070*	0.019*	0.009*
Gender:	Male	0.079*	0.019*	0.012*
	Female	0.062*	0.019*	0.009*
Age**:	<75 years	0.051*	0.011*	0.005*
	>=75 years	0.086*	0.030*	0.017*
Poor social support:	Low level	0.068****	0.015***	0.013****
	High level	0.073****	0.024****	0.006
Poor social integration:	Low level	0.067****	0.022****	0.010****
	High level	0.073****	0.017****	0.009****

All effects are controlled for lagged activity limitation, gender, age, chronic disease, allostatic load, body mass index (BMI) category, smoking history, alcohol intake level, educational level, wealth level, social support level, and social integration level

Low level: one standard deviation below mean value

High level: one standard deviation above mean value

Coefficients of physical frailty are standardized.

* p-value <0.05

** p-value <0.05 for difference between two groups (only where the mediator is low physical activity or cognitive impairment, but not depressive symptoms)

*** p-value <0.05 but >=0.025

**** p-value <0.025 (Bonferroni's correction for multiple comparisons for 2 separate moderation models)

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

Sensitivity analyses yield informative results. Firstly, repeat analyses that include physical frailty-mediator interactions in the model obtain estimates of 0.075, 0.017, and 0.009 for the indirect effects mediated through low physical activity, depressive symptoms, and cognitive impairment respectively. These estimates are very similar to those obtained in models

excluding these interactions, indicating that including the latter only has trivial impact. Secondly, additional analyses that simulate the presence of an unmeasured confounder indicate that the magnitude of its effect on activity limitation change needs to be equivalent to three-fold that of the strongest among other predictors (age) for the effect of physical frailty on activity limitation change at a low level (0.3) of correlation between the unmeasured confounder and physical frailty to be rendered non-significant as shown in Table 4. This suggests that the estimated effect of physical frailty on activity limitation change is relatively robust to any unmeasured confounding.

Table 4. Sensitivity analysis with simulation of unmeasured confounder of relationship between physical frailty and activity limitation using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: linear regression coefficients

Correlation between unmeasured confounder and physical frailty	Effect size of unmeasured confounder on activity limitation (comparison with that of strongest predictor of activity limitation)			
	0X	1X	2X	3X
0	0.234*	-	-	-
0.1 (very low)	-	0.182*	0.132*	0.083*
0.3 (low)	-	0.172*	0.096*	0.015

* p-value <0.05

Coefficients are interpreted as change in activity limitation score for a one standard deviation increase in physical frailty factor score.

Shaded areas indicate that the effect of physical frailty on activity limitation remains positive and significant.

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

On the other hand, for indirect effects through low physical activity and depressive symptoms, correlation of an unmeasured confounder with mediators only needs to be 0.3 for them to be rendered non-significant, and in the opposite direction (for that through low physical activity), even at correlation with physical frailty of only 0.1 and effect on activity limitation just equivalent to that of the strongest among other predictors (chronic disease). Moreover, the indirect effect through cognitive impairment is rendered non-significant at correlation of an unmeasured confounder with the mediator and physical frailty of 0.1 and 0.3 respectively, and its effect on activity limitation again equivalent to that of the strongest among other predictors (chronic

diease). These results are shown in the Supplementary Materials (Table 7), and suggest that estimated indirect effects may be more sensitive to correlation of any unmeasured confounder with mediators. Thirdly, given the large proportion of zero values and right skewed distribution for activity limitation, negative binomial regression is also performed as an alternative to linear regression for Model 1. The results are approximately equivalent to those of linear regression (not shown). In view of this, the analyses for Models 1 to 4 represent our final findings. Lastly, repeat analyses for 2,402 respondents who have complete values for activity limitation at wave 6 obtain similar and significant estimates of the main and indirect effects of physical frailty, albeit with slightly lower magnitudes compared those for the analysis of the whole study population that assume MAR for missing values (results not shown).

Discussion

For community-dwelling older people in England, increasing levels of physical frailty independently predict more activity limitation *change* two years later. This means that the significantly worse activity limitation trajectory that is conferred by physical frailty remains even after taking into account the effects of a broad set of concurrent physical, psychological, and social predictors. This confirms previous work by others (Lang et al., 2007; Vermeulen et al., 2011). In terms of magnitude, one standard deviation increase in physical frailty level predicts increase in activity limitation change over two years that is more than two-fold that of the population average. By any measure, this is a strong effect. However, our findings go beyond mere prediction. We find that this negative effect is mediated by low physical activity, depressive symptoms, and cognitive impairment. In addition, the effect of physical frailty is stronger with older age. Finally, the indirect effects of physical frailty on activity limitation through low physical activity and cognitive impairment are stronger with older age. In other words, the pathways from physical frailty to activity limitation appear to be more complex and involve mediation by physical and psychological conditions, which in turn is influenced by age. Notably, our findings add to the frailty pathways hypothesized in the Canadian working framework by identifying mediators on those pathways. To our knowledge, this is the first report concerning indirect effects of physical frailty on activity limitation trajectory in older people.

The indirect effects we uncover provide insight on *how* physical frailty exerts its effect on activity limitation change. From our results, we infer that low physical activity mediates almost one third of the effect of physical frailty, whereas depressive symptoms and cognitive impairment do so much less. Low physical activity has previously been demonstrated to worsen activity limitation (Landi et al., 2007), with the exercise being shown to have the opposite desirable effect (Chou et al., 2012). Thus, the relatively large contribution of low physical activity to mediation is not surprising given that individuals who are physically frail are likely to have less physical activity, which in turn increases risk of activity limitation. However, the precise mechanism by which depressive symptoms and cognitive impairment mediate the effect of physical frailty on activity limitation change is less clear. Nevertheless, we know that physical frailty increases the risk of depression (Collard et al., 2015; Mezuk et al., 2012), which in turn increases the risk of activity limitation (Bruce et al., 1994). Furthermore, physical frailty predicts incident cognitive impairment (Canevelli et al., 2015). However, previous research yielded mixed results as to whether cognitive impairment had additional impact on disability for those who are already physically frail (Ament et al., 2014; Avila-Funes et al., 2009).

On the other hand, our findings go only to a limited extent to indicate *for whom* the effect of physical frailty on activity limitation change is stronger. It is quite expected that the effect of physical frailty, including its indirect effects, would be stronger among those who are older, given the additional physiological decline that occurs with older age that is not captured by physical frailty and other predictors and are therefore subsumed under it. Nevertheless, this finding suggests that the effect of physical frailty on activity limitation, including those mediated

by low physical activity and cognitive impairment not only remains, but may even be strongerl in very old people. Although previous research demonstrated that social support in the form of positive social interaction protects against functional decline in older people (Unger et al., 1997), we did not observe this moderating effect. However, there is some suggestion that the indirect effect through depressive symptoms may be stronger with poorer social support. It is plausible that better social support, particularly in terms of emotional support through positive social interaction, may to some extent protect against activity limitation because of its psychological benefits, but we could not demonstrate a significant moderating effect. On the other hand, psychosocial resources may not protect against functional decline in physically frail older people to the degree as may be expected (Hoogendijk et al., 2014). That said, the relationship between these two conditions could be more complex, given that negative social exchanges have been shown to predict depression in ELSA respondents (Stafford et al., 2011). Nonetheless, alternative definitions of social support could be considered in further work investigating its influence on the effect of physical frailty on activity limitation.

The described mediators on pathways from physical frailty to activity limitation may lend themselves to modification by population-level interventions that hold promise for addressing the larger public health implications of frailty on the healthspan of older people. Specifically, low physical activity, depressive symptoms, and cognitive impairment represent potential interventional opportunities for health and social programs that typically comprise behavioural and therapeutic components. At the very least, the evidence assembled here should go some distance in justifying the conduct of experimental or quasi-experimental trials testing interventions that encourage and facilitate physical activity, prevent depressive symptoms, delay the onset or slow down the progression of cognitive impairment, with the expressed objective of mitigating activity limitation resulting from physical frailty among older people. While it is possible that poor social support may have a moderating effect, addressing it is a more challenging task. Since social interactions are largely conducted at the personal level, it is hard to see how formal programs and policies can directly influence them. Instead, public education that raises awareness that positive interactions with frail older people may reduce the risk of activity limitation could be explored.

From a broader perspective, addressing low physical activity, depressive symptoms, and cognitive impairment may already be recognized as sensible objectives of health and social policies. However, ongoing initiatives with these objectives may benefit from the additional frailty-specific evidence assembled here, in terms of bolstering support for their continuation or even expansion.

We acknowledge two major limitations of our study. Firstly, dependence on observational data imposes limits on causal inference. That said, use of longitudinal data permits specification of cause preceding effect in our models. Moreover, inclusion of a broad range of multidimensional deficits in these models allows us to argue that the effects of any omitted variables are unlikely to be large and influential in changing the major conclusions of this study. In addition, our

sensitivity analyses suggest that at least some of our results relatively robust to model misspecification due to any unmeasured confounders. Notwithstanding this, our findings may offer the best available evidence on the possible mechanisms underlying the effect of physical frailty on activity limitation, in the absence of confirmation from experiments utilizing randomized or geographically-based treatment assignment. Next, the use of secondary data restricts the way key variables are specified, particularly those concerning lifestyle habits or social conditions. Fortunately, the availability of rich and credible data available in ELSA affords the opportunity to create these variables, or adopt the definitions developed by others.

In conclusion, the evidence from ELSA suggests that low physical activity, depressive symptoms, and cognitive impairment have roles as mediators of the effect of physical frailty on activity limitation. Indirect effects through low physical activity and cognitive impairment are stronger with advancing age. Beyond these, poor social support may be a moderator on pathways from physical frailty to activity limitation. In terms of minimizing activity limitation resulting from physical frailty in older people, population health and social measures addressing these four conditions merit consideration for further investigation or even implementation. These measures can augment health promotion efforts directed at reducing physical frailty in the first place, thereby contributing to the wider effort of improving the healthspan of older people, including those who are very old.

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Supplementary Materials

Mathematical equations for the statistical models with corresponding graphical representation

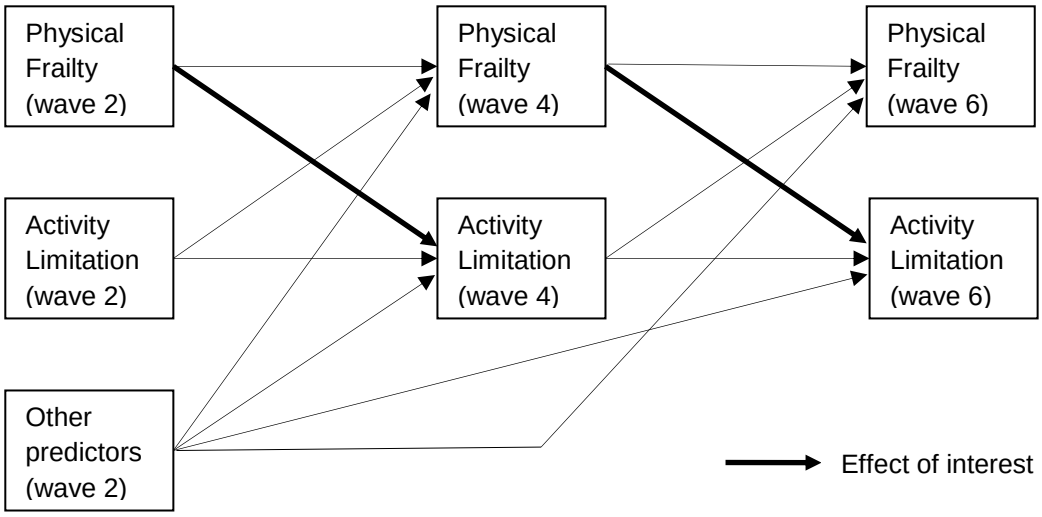
Model 1:

Let y_{ti} denote activity limitation defined by number of items of basic activities of daily living performed with difficulty (score 0 to 6) across waves 2, 4, and 6, $y_{t\text{-}1i}$ be the lagged activity limitation, p_{ti} be the physical frailty factor score across waves 2, 4, and 6, and x_i represents a time-invariant predictor at t =1 (wave 2) for individuals i = 1..., n at t = 2 and 3 (waves 4 and 6).

The equation for the effect of interest in the autoregressive cross-lagged model is:

$$y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_1 p_{t\text{-}1i} + \beta_2 x_i + \varepsilon_{ti}$$

The coefficient β_1 describes the effect of lagged physical frailty factor score on activity limitation, while β_2 describes the effect of time-invariant predictors on activity limitation and β_0 is the intercept. The focus is on the estimated coefficient β_1 which is shown in Table 2. A graphical representation of this model is:



For gender- and age-specific effects, stratified analyses of two subgroups according to gender, age group use the same equation.

Model 2:

The equation for Model 1 applies for stratified analyses of two subgroups according to moderating variables, namely poor social support and poor social integration.

Model 3:

Suppose m_i is a mediator of the effect of $p_{t\text{-}1i}$ on y_{ti}, so that:

$$y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_1 p_{t\text{-}1i} + \beta_2 x_i + \beta_4 m_{ti} + \varepsilon_{ti}$$

Suppose further that

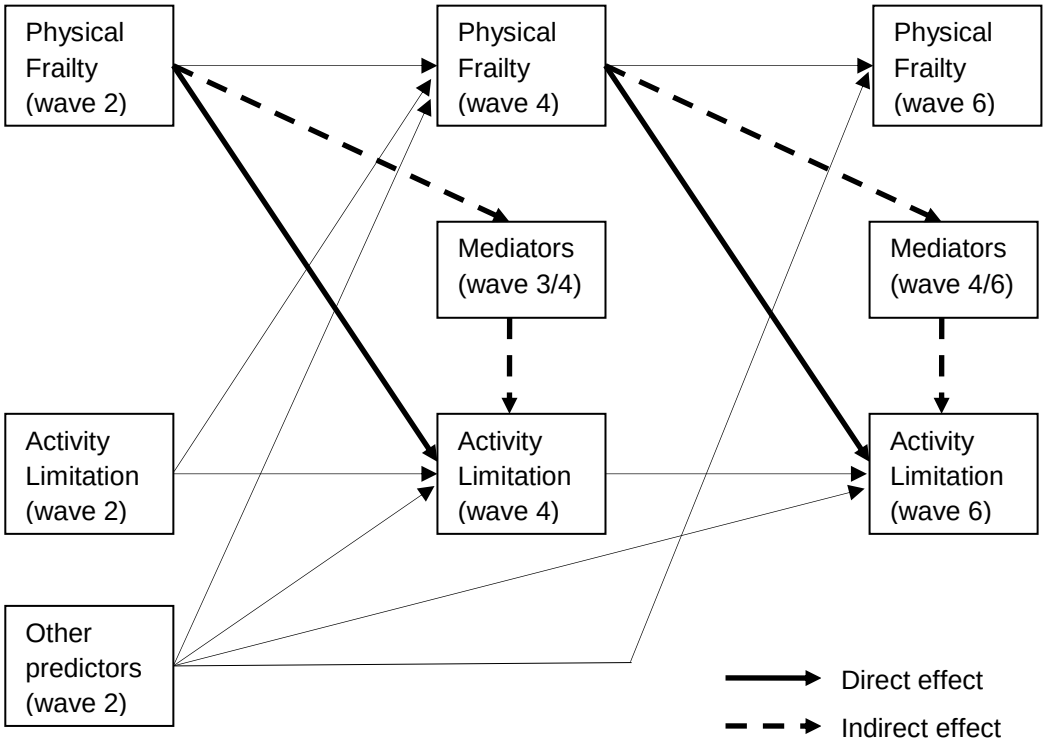
$$m_{ti} = \lambda_0 + \lambda_1 p_{t\text{-}1i} + \delta_{ti}$$

Then the model given $p_{t\text{-}2i}$ and x_i only, averaging over the distribution of m_{ti}, is

$$Y_{ti} = \beta_0 + y_{t\text{-}1i} + \beta_{*1} p_{t\text{-}1i} + \beta_2 x_i + \varepsilon_{*ti}$$

where $\varepsilon_{*ti} = (\varepsilon_{ti} + \beta_4 \delta_{ti})$ and $\beta_{*1} = \beta_1 + \beta_4 \lambda_1$

Here, β_{*1} is the total effect of $p_{t\text{-}1i}$ on activity limitation, β_1 is the direct effect of $p_{t\text{-}1i}$, and $\beta_4 \lambda_1$ is the indirect effect of $p_{t\text{-}1i}$ mediated via m_{ti}.



For gender- and age-specific effects, stratified analyses of two subgroups according to gender, age group use the same equation.

Model 4:

The equation for Model 3 applies for stratified analyses of two subgroups according to moderating variables, namely poor social support and poor social integration.

Table 5. Characteristics of English Longitudinal Study of Ageing (ELSA) wave 2 respondents aged 65 to 89 years included in analyses: physical frailty-related and other time varying variables across different waves

Variables		All	By gender		By Age group	
			Male	Female	< 75 years	>= 75 years
Physical frailty-related:						
Mean average walking speed,						
m/sec (SD):	Wave 2	0.8 (0.3)[1]	0.9 (0.3)[2]	0.8 (0.3)[3]	0.9 (0.3)[4]	0.7 (0.3)[5]
	Wave 4	0.8 (0.3)[6]	0.8 (0.3)[7]	0.7 (0.3)[8]	0.8 (0.3)[9]	0.7 (0.2)[10]
	Wave 6	0.8 (0.3)[11]	0.8 (0.3)[12]	0.7 (0.3)[13]	0.8 (0.3)[14]	0.6 (0.2)[15]
Hand grip strength (dominant						
hand), kg (SD):	Wave 2	25.9 (10.2)[16]	33.4 (8.9)[17]	19.6 (6.1)[18]	28.4 (10.2)[19]	22.2 (9.0)[20]
	Wave 4	24.3 (10.2)[21]	32.0 (9.0)[22]	18.2 (6.2)[23]	26.6 (10.3)[24]	20.4 (8.6)[25]
	Wave 6	22.8 (9.5)[26]	29.6 (8.8)[27]	17.5 (5.9)[28]	24.4 (9.6)[29]	18.9 (7.9)[30]
Exhaustion, n/N (%):						
	Wave 2	1,490/4,510 (33.0)	568/1,997 (28.4)	922/2,513 (36.7)	728/2,596 (28.0)	762/1,914 (39.8)
	Wave 4	955/2,977 (32.1)	327/1,290 (25.4)	628/1,687 (37.2)	518/1,868 (27.7)	437/1,109 (39.4)
	Wave 6	632/1,962 (32.2)	218/848 (25.7)	414/1,114 (37.2)	401/1,402 (28.6)	231/560 (41.3)
Physical:						
Mean low physical activity						
level, n (%):	Wave 2	1.2 (0.9)[31]	1.1 (0.9)[32]	1.3 (0.9)[33]	1.0 (0.9)[34]	1.4 (0.9)[35]
	Wave 4	1.3 (1.0)[36]	1.2 (1.0)[37]	1.4 (0.9)[38]	1.1 (0.9)[39]	1.7 (1.0)[40]
	Wave 6	1.4 (1.0)[41]	1.3 (1.0)[42]	1.6 (0.9)[43]	1.2 (0.9)[44]	1.9 (0.9)[45]
Psychological:						
Mean CESD-8 score						
[0 to 8] (SD):	Wave 2	1.7 (2.0)[46]	1.3 (1.7)[47]	1.9 (2.1)[48]	1.5 (1.9)[49]	1.9 (2.0)[50]
	Wave 4	1.5 (1.9)[51]	1.1 (1.7)[52]	1.8 (2.0)[53]	1.3 (1.8)[54]	1.8 (2.0)[55]
	Wave 6	1.0 (1.4)[56]	0.8 (1.2)[57]	1.2 (1.5)[58]	0.9 (1.3)[59]	1.2 (1.5)[60]
Mean cognitive impairment						
score [0 to 49] (SD):						
	Wave 2	27.5 (6.3)[61]	26.3 (6.4)[62]	25.5 (6.5)[63]	24.1 (6.0)[64]	28.4 (6.3)[65]
	Wave 3	25.7 (6.6)[66]	26.0 (6.5)[67]	25.5 (6.8)[68]	24.0 (6.1)[69]	28.4 (6.5)[70]
	Wave 4	25.6 (6.8)[71]	25.8 (6.6)[72]	25.5 (6.9)[73]	24.0 (6.2)[74]	28.6 (6.7)[75]

Frail status: Frailty Index >=0.25

CESD-8: Center for Epidemiologic Studies Depression Scale (8 items)

N = [1]4,096 [2]1,826 [3]2,266 [4]2,400 [5]1,692 [6]2,649 [7]1,182 [8]1,467 [9]1,705 [10]944 [11]1,688 [12]754 [13]934 [14]1,254 [15]434 [16]3,869 [17]1,760 [18]2,109 [19]2,276 [20]1,593 [21]2,531 [22]1,115 [23]1,416 [24]1,621 [25]910 [26]1,868 [27]820 [28]1,048 [29]1,339 [30]529 [31]4,567 [32]2,032 [33]2,535 [34]2,611 [35]1,956 [36]3,125 [37]1,355 [38]1,770 [39]1,915 [40]1,210 [41]2,404 [42]1,023 [43]1,381 [44]1,643 [45]761 [46]4,479 [47]1,987 [48]2,492 [49]2,586 [50]1,893 [51]2,960 [52]1,285 [53]1,675 [54]1,859 [55]1,101 [56]2,215 [57]947 [58]1,268 [59]1,557 [60]658 [61]4,349 [62]1,946 [63]2,403 [64]2,546 [65]1,803 [66]2,605 [67]1,145 [68]1,460 [69]1,680 [70]925 [71]3,375 [72]1,492 [73]1,883 [74]2,041 [75]1,334

Table 6. Effects of physical frailty on activity limitation controlling for other predictors using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: standardized regression coefficients for predictors at wave 2

Outcome: Activity Limitation	Coefficient estimate
Lagged activity limitation	0.572**
Physical frailty	0.234**
Female	-0.085**
Older age	0.097**
Chronic disease	0.079**
Allostatic load	-0.007
Obesity	0.043
Underweight state	0.195
Smoking history	-0.021
High alcoholic intake	<0.001
Low wealth	0.017
Low educational level	-0.004
Poor social support	0.052*
Poor social interaction	-0.022

Coefficients are standardized for continuous predictors. Thus, coefficients are interpreted as change in activity limitation score for a one standard deviation increase in continuous predictors, or from zero to one for binary predictors (female gender, obesity, underweight state, smoking, high alcohol intake, low wealth, and low educational level).

* p-value <0.05 but >=0.01

** p-value <0.01

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

Table 7. Sensitivity analysis with simulation of unmeasured confounder of indirect effects of physical frailty on activity limitation using the autoregressive cross-lagged model over waves 2, 4, and 6 of the English Longitudinal Study of Ageing: linear regression coefficients

Mediator	Correlation between unmeasured confounder and mediators	Correlation between unmeasured confounder and physical frailty	Effect size of unmeasured confounder on activity limitation (comparison with that of strongest predictor of activity limitation)		
			0X	1X	3X
Low physical activity	0	0	0.70*	-	-
	0.1 (very low)	0.1 (very low)	-	0.042*	0.038*
		0.3 (low)	-	0.026*	0.024*
	0.3 (low)	0.1 (very low)	-	-0.030*	-0.024*
		0.3 (low)	-	-0.074*	-0.066*
Depressive symptoms	0	0	0.19*	-	-
	0.1 (very low)	0.1 (very low)	-	0.014*	0.013*
		0.3 (low)	-	0.010*	0.009*
	0.3 (low)	0.1 (very low)	-	0.002	0.001
		0.3 (low)	-	-0.004*	-0.003*
Cognitive impairment	0	0	0.09*	-	-
	0.1 (very low)	0.1 (very low)	-	0.004*	0.003*
		0.3 (low)	-	0.001	0.001
	0.3 (low)	0.1 (very low)	-	-0.010*	-0.004
		0.3 (low)	-	-0.019*	-0.015*

* p-value <0.05

Coefficients are interpreted as change in activity limitation score for a one standard deviation increase in physical frailty factor score.

Shaded areas indicate that effect of physical frailty on activity limitation remains positive and significant.

Missing values are handled by full information maximum likelihood (FIML).

N = 4,638

10.3 Further Thoughts

Based on the evidence from ELSA, pathways from physical frailty to activity limitation are not simple and merely direct, but involve indirect effects through three mediators, namely low physical activity, depressive symptoms, and cognitive impairment. Just as for pathways to physical frailty and death, these mediators pertain to the physical and psychological dimensions. Notably, these indirect effects extend to, and are even stronger among very old people, at least where low physical activity and cognitive impairment are mediators. More importantly, addressing these conditions through health and social interventions represent opportunities for influencing pathways from physical frailty to activity limitation

11 Closing Discussion

11.1 Methodological Aspects

Through examining pathways to frailty and its outcomes, I utilize three different techniques of analyzing longitudinal data from ELSA. In the third paper, latent growth curves allow estimation of both intra-individual change of physical frailty and inter-individual differences in that change. In the fourth paper, discrete time survival analysis permits estimation of the effects of physical frailty on death as a binary outcome measured at two-yearly intervals. Finally, in the fifth paper, autoregressive cross lagged models afford the opportunity to estimate the effect of physical frailty on activity limitation change.

Further, I construct statistical models largely within the structural equation modeling framework. In doing so, latent variables with multiple indicators represent the physical frailty construct. These are either incorporated as the measurement component of the full statistical model (measurement model), or as manifest (or observed) variables of physical frailty factor scores derived from the measurement model. The major advantage of incorporating the measurement model in the third paper is that this handles measurement error better. This in turn translates to improved ability to detect any significant effects. On the other hand, doing so inevitably increases the complexity of the statistical models, resulting in longer computational time, and on occasion, non-convergence. In the light of this drawback, I elected to use physical frailty scores derived from the measurement model in the fourth and fifth papers.

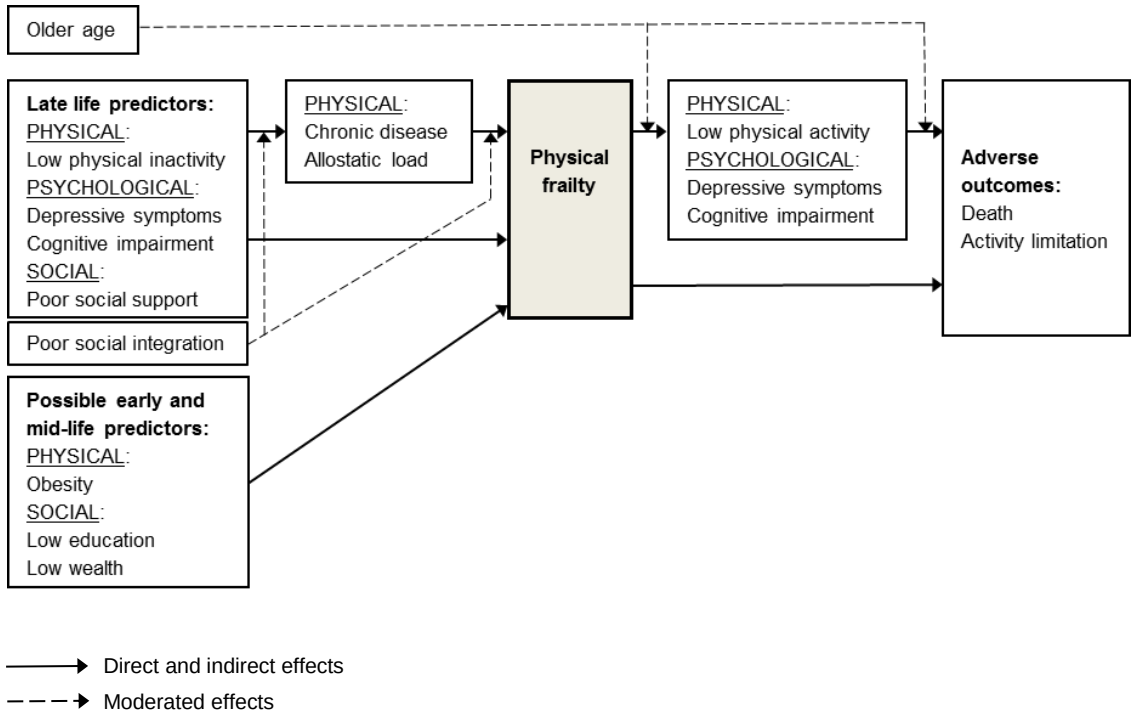
Finally, it is worth highlighting that for the core analyses throughout these three papers, I use standard regression methods and have largely not drawn on concepts from the potential outcomes framework for causal inference (Little & Rubin, 2000). Instead, I have only introduced limited ideas from the causal inference literature when performing mediation analyses in the fourth and fifth papers (Muthén & Asparouhov, 2015). Thus, I rely on temporal relationships in longitudinal data and a rich set of multidimensional conditions as control variable for qualified and cautious causal interpretation of findings in these three papers. Certainly, there is potential to extend the current work by using the potential outcomes framework. However, such an endeavor is worthy of a separate project well beyond this thesis.

11.2 Substantive Implications

I have investigated pathways to frailty and its adverse outcomes using an approach that is guided by the working framework proposed by the Canadian Initiative for Frailty and Aging (Bergman et al., 2004). The evidence from ELSA assembled from these three papers supports the validity of this framework of frailty pathways by confirming the roles of several physical, psychological, and social conditions as predictors on pathways to physical frailty. Beyond this, additional indirect effects on pathways from physical frailty to its adverse outcomes through key mediators are demonstrated. However, moderated effects on these pathways are observed to a

lesser extent. In the effort to construct a composite picture of these pathways, Figure 11.1 summarizes the major positive effects on frailty pathways based on the evidence from ELSA, while using the working framework of the Canadian Initiative on Frailty and Aging as the template.

Figure 11.1. Summary of evidence on frailty pathways from the English Longitudinal Study of Ageing using the working framework of the Canadian Initiative on Frailty and Aging as the template



It is worth highlighting that when attempting to unpack the complexity of these pathways, the picture that emerges is at times unexpected, thereby raising more questions. For example, on pathways to physical frailty, several conditions such as smoking, obesity, and low wealth did not predict physical frailty change as expected. As mentioned, it is likely that their major influence on physical frailty is exerted well before later life when ELSA respondents are eligible to enter our study. In support of this explanation, obesity, low education, and low wealth have significant effects on initial physical frailty measured at start of follow-up, but not on physical frailty change during the follow-up period. In addition, moderation by low physical activity, depressive symptoms, poor social support, and poor social integration is not statistically significant. As alluded to, higher statistical power needed for moderation may be at least in part a possible explanation for these negative findings, which is a common theme that extends

across the last three papers. In the case of pathways to adverse outcomes, negative moderation of the effect of physical frailty on death by cognitive impairment is unanticipated. As discussed, a possible explanation is that physical frailty adds less to the risk of death due to the competing effect of more severe cognitive impairment. In addition, lack of moderation of the effects of physical frailty on death and activity limitation change by social conditions is somewhat surprising. Besides the issue of statistical power required, this situation may be related in part to the way complex social constructs are operationalized. Alternatively, and as alluded to, it may be that these social conditions do not truly have significant impact on physical frailty and its adverse outcomes as has been widely assumed (Hoogendijk et al., 2014).

Overall, the unexpected findings suggest that multiple mechanisms involving indirect pathways and moderators have yet to be discovered on frailty pathways. More poignantly, the findings from these three papers are likely to represent the “tip of the iceberg” where the relationship of physical frailty with physical, psychological, and social conditions is concerned. Indeed, the assembling of evidence from ELSA in this thesis should be viewed as the initial steps in the arguably intriguing process of understanding frailty pathways more precisely. There is certainly much more to learn by unravelling the mechanisms at work on these pathways. To this end, two aspects are relevant for future work. The first pertains to the identification of conditions on pathways that are yet unmeasured. The second involves the specification of additional relationships on frailty pathways, particularly those involving mediation and moderation.

Given the findings of my thesis, I would like to offer some suggestions for further research. Firstly, where data permits, inclusion of other relevant lifestyle-related and environmental conditions would be helpful. Examples include dietary habits, and neighborhood characteristics (Lang et al., 2008). Secondly, revision of the measurement of key constructs such as cognition, social support, and social interaction is worth exploring. Thirdly, alternative specifications of relationships between key conditions on frailty pathways including additional indirect effects and moderation could be considered, as this may facilitate obtaining more complete answers to questions on *for whom* these effects are stronger and *how* they exert their effects. These are the most interesting and relevant questions with respect to better understanding complex frailty pathways. They, in turn, can inform more optimally the development of health and social strategies to address physical frailty at the population level. Fourthly, examination of the effect of physical frailty on other outcomes such as health care utilization and nursing home admission is needed to better comprehend how its wider negative impact may be mitigated. Finally, replication of our findings in other older populations would be helpful in providing assurance of their applicability beyond England, and indeed, if possible, across continents.

12 Final Conclusions

In summary, pathways to frailty and its adverse effects are more complex than is immediately apparent. Overall, the evidence on frailty pathways from ELSA is broadly consistent with those proposed by the working framework of the Canadian Initiative for Frailty and Aging. Several key physical, psychological, and social conditions have different roles on these pathways.

On pathways to physical frailty, low physical activity, depressive symptoms, cognitive impairment, and poor social support all predict future physical frailty during late life. In addition, obesity, low education, and low wealth are likely to be early to mid-life conditions that predict physical frailty in late life. Furthermore, chronic disease and allostatic load mediate the indirect effects of low physical activity, depressive symptoms, and cognitive impairment on future physical frailty. Finally, poor social integration moderates the indirect effect of poor social support through chronic disease.

On pathways to its adverse outcomes, physical frailty increases the risk of death independent of a broad range of physical, psychological, and social predictors. This effect extends across gender and age, but not to those who are very old. There is suggestion that effect of physical frailty may be stronger among those with high consumption of alcohol and with poor social integration. More importantly, the effect of physical frailty on death is exerted indirectly through low physical activity and cognitive impairment. Furthermore, physical frailty worsens the activity limitation trajectory, with this effect being stronger with older age. This effect is also exerted indirectly through low physical activity, depressive symptoms, and cognitive impairment. In turn, the indirect effect of physical frailty through low physical activity is stronger with older age and possibly, poor social support.

Thus, physical, psychological, and social conditions play key roles on frailty pathways, whether as predictors, moderators, mediators, or their combinations. More importantly, they represent potentially modifiable target conditions for population-level interventions that may not only slow the progression of physical frailty, but also mitigate its effects on death and activity limitation in older people. More detailed examination of their specific roles is warranted to achieve more precise understand frailty pathways. To this end, I hope that the findings of my thesis will serve as a springboard for further research on frailty pathways by others. Nevertheless, for certain conditions, such as low physical activity, depressive symptoms, cognitive impairment, and poor social support, the evidence of their influence on these pathways from ELSA is arguably strong enough to consider implementing programs to address them as part of broad efforts to enhance both the lifespan and healthspan of older people.

13 References

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14 Appendix

14.1 Literature search strategies

Search Terms

For MEDLINE using PubMed and then modified for other search portals:

Frailty identifiers
(frailty[Text Word]) AND (index*[Text Word] OR indices[Text Word] OR deficit*[Text Word] OR phenotyp*[Text Word] OR construct*[Text Word] OR concept*[Text Word] OR measure*[Text Word] OR identifi*[Text Word] OR indicator*[Text Word] OR instrument*[Text Word] OR score*[Text Word] OR scale*[Text Word] OR syndrom*[Text Word] OR state*[Text Word] OR component*[Text Word] OR diagnos*[Text Word] OR definition*[Text Word] OR model*[Text Word] OR framework*[Text Word]) AND (Humans[Mesh] AND aged[MeSH])

Frailty pathways
(frailty[Text Word]) AND (chronic[Text Word] OR comorbidity[Text Word] OR socioeconomic[Text Word] OR social*[Text Word] OR support[Text Word] OR access*[Text Word] OR medical*[Text Word] OR "health care"[Text Word] OR healthcare[Text Word] OR diet*[Text Word] OR nutrition[Text Word] OR exercise*[Text Word] OR "physical activity"[Text Word] OR "physical inactivity"[Text Word] OR smoking[Text Word] OR lifestyle[Text Word] OR environment*[Text Word] OR biological*[Text Word] OR psychosocial*[Text Word] OR "life course"[Text Word] OR cogniti*[Text Word] OR dementi*[Text Word] OR mood[Text Word] OR depressi*[Text Word] OR caus*[Text word] OR path*[Text Word] OR mediat*[Text Word] OR moderat*[Text Word] OR modif*[Text Word] OR determinant*[Text Word]) AND (Humans[Mesh] AND aged[MeSH])

Sources of literature

Electronic databases

1) Health
   - MEDLINE via PubMed
   - Cochrane Library
     - Cochrane Database of Systematic Reviews (CDSR)
     - Cochrane Central Register of Controlled Trials (CENTRAL)

2) Social sciences
   - Campbell Library

3) Multi-disciplinary

- Web of Science

Hand searched documents

1) Identified from references of papers selected from electronic databases

14.2 Scoring systems for key variables

Chronic disease

Condition	Definition
Hypertension (High blood pressure)	Whether ever reported high blood pressure
Angina	Whether ever reported angina
Myocardial Infarction (Heart attack)	Whether ever reported myocardial infarction
Congestive Heart Failure	Whether ever reported congestive heart failure
Arrhythmia (Abnormal heart rhythm)	Whether ever reported arrhythmia
Diabetes Mellitus	Whether ever reported diabetes
Stroke	Whether ever reported stroke
Asthma	Whether ever reported asthma
Arthritis	Whether ever reported arthritis
Osteoporosis	Whether ever reported osteoporosis
Cancer	Whether ever reported cancer
Parkinson's Disease	Whether ever reported Parkinson's Disease
Psychiatric disorders	Whether ever reported psychiatric disorders
Dementia	Whether ever reported dementia

Note: Presence of each comorbid condition is assigned a score of 1. The total score is from 0 to 14.

Allostatic load

Allostatic load is the physiological dysregulation in multiple body systems and is specified by nine biomarkers including blood pressure readings, anthropometric measurements, and blood tests for cholesterol levels, glucose control, and inflammatory markers. These biomarkers are:

Biomarker	**Definition**
Systolic blood pressure	whether >150 mmHg or not
Diastolic blood pressure	whether >80 mmHg or not
Glycosylated haemoglobin level	whether >5.8% or not
Serum triglyceride level	whether >2.2 mmol/l or not
Serum c-reactive protein level	whether >4.7 mg/l or not
Serum fibrinogen level	whether >3.7 umol/l or not
Peak expiratory flow rate	whether <232 l/min or not
Waist-hip ratio	whether >0.9588534 or not

Note: For each biomarker, a score of one is awarded for values beyond a cut-off level reflecting high risk (75^{th} percentile), with a score of zero given if otherwise.

Low resilience

Low resilience is measured in relation to three facets of adversity.

1) Objective financial adversity: defined as being in the lowest quintile of total non-pension wealth.
2) Self-perceived financial adversity is the report of sometimes or more often having too little money to spend on needs.
3) Widowhood is the change of marital status from being married or single in wave 1 to being widowed in wave 2.

The criterion for establishing resilience under these three facets of adversity is a Center for Epidemiologic Studies Depression Scale (CES-D) score of three or less.

Facet	Criterion for adversity satisfied	Criterion for resilience satisfied	Score
Objective financial adversity	Yes	Yes	-1
	No	No	0
	No	Yes	0
	Yes	No	1
Self-perceived financial adversity	Yes	Yes	-1
	No	No	0
	No	Yes	0
	Yes	No	1
Widowhood	Yes	Yes	-1
	No	No	0
	No	Yes	0
	Yes	No	1

Note: Summing up separate scores for the three facets, a total score ranging from -3 to 3 is obtained where higher scores indicate lower resilience.

Poor social integration

Item	Scoring
Living with spouse for partner	Whether having no spouse or partner living with them (1)
Little contact with children	Whether contact by meeting, phoning, or email is: - at least once per week (0) - once or twice a month (1) - once every few months (2) - once or twice a year or less (3)
Little contact with other family members	Whether contact by meeting, phoning, or email is: - at least once per week (0) - once or twice a month (1) - once every few months (2) - once or twice a year or less (3)
Little contact with friends	Whether contact by meeting, phoning, or email is: - at least once per week (0) - once or twice a month (1) - once every few months (2) - once or twice a year or less (3)
Low membership of non-religious organizations, clubs or societies	Whether having membership of the following groups or organizations (number): 1) Political party, trade union or environmental groups 2) Tenants groups, resident groups, neighbourhood watch 3) Charitable associations 4) Education, arts or music groups or evening classes 5) Social Clubs 6) Sports clubs, gyms, exercise classes - 0 (0) - 1 or 2 (1) - 3 or 4 (2) - 5 or 6 (3)
Not a member of a religious group	Whether not a member of any church or other religious group (1)

Note: Individual scores for each item are indicated in brackets. The total score (0 to 14) is a measure of the extent of social isolation.

Poor social support

Item	Scoring
Lack of positive support	Answers to questions on whether children: “understand the way you feel” - a lot (0) - some (1) - a little (2) - not at all (3) “can rely on if you had a serious problem” - a lot (0) - some (1) - a little (2) - not at all (3) “can open up to them if you need to talk” - a lot (0) - some (1) - a little (2) - not at all (3) In turn, answers for these questions are also sought with respect to other family members, and friends. Total score: 0 to 27
Negative support	Answers to questions on whether children: "criticizes the respondent" - a lot (3) - some (2) - a little (1) - not at all (0) "lets the respondent down" - a lot (3) - some (2) - a little (1) - not at all (0) "gets on the nerves of respondent" - a lot (3) - some (2) - a little (1) - not at all (0) In turn, answers for these questions are also sought with respect to other family members, and friends. Total score: 0 to 27

Note: Individual scores for each item are indicated in brackets. The total score (0 to 54) is a measure of the extent of deficient emotional support or negative social interaction.

Frailty Index (30 items)

Item	Definition
Chronic illness: Hypertension	Whether ever reported high blood pressure
Chronic illness: Myocardial Infarction	Whether ever reported myocardial infarction
Chronic illness: Congestive heart failure	Whether ever reported congestive heart failure
Chronic illness: Diabetes Mellitus	Whether ever reported diabetes
Chronic illness: Stroke	Whether ever reported stroke
Chronic illness: Arthritis	Whether ever reported arthritis
Chronic illness: Cancer	Whether ever reported cancer
Chronic illness: Obesity	BMI: WHO definition of obesity (>=30) or underweight (<18.5)
Psychological condition: Dementia	Whether ever reported dementia
Psychological condition: Feeling depressed (CESD)	Whether…felt depressed much of the time during the past week
Psychological condition: Feeling effortful (CESD)	Whether…felt everything they did during the past week was an effort
Psychological condition: Feeling happy (CESD): reverse	Whether…happy much of the time during the past week (reverse)
Psychological condition: Feeling lonely (CESD)	Whether…felt lonely much of the time during the past week
Psychological condition: Could not get going (CESD)	Whether…could not get going much of the time during the past week
Poor self-rated health	Whether self-rated health reported as “poor”
Mobility: walking 100 yards	Difficulty walking 100 yards
Mobility: getting up from chair	Difficulty getting up from chair after sitting long periods
Mobility: climbing stairs	Difficulty climbing one flight stairs without resting
Mobility: lifting weights	Difficulty lifting or carrying weights over 10 pounds
BADL: dressing	Difficulty dressing, including putting on shoes and socks
BADL: walking	Difficulty walking across a room
BADL: bathing	Difficulty bathing or showering
BADL: eating	Difficulty eating, such as cutting up food
BADL: toileting	Difficulty using the toilet, including getting up or down
IADL: shopping	Difficulty shopping for groceries
IADL: taking medication	Difficulty taking medications
IADL: doing housework	Difficulty doing work around house and garden
IADL: managing finances	Difficulty managing money, eg paying bills, keeping track expenses
Weak grip strength	Weak grip strength (1st measurement dominant hand) using gender-specific cut-offs (male: <30kg female: <20 kg)

Note: Positive response or finding for each item is assigned a score of 1. The total score is divided by 30 to obtain the frailty Index (0 to 1).

14.3 Mplus input files

Paper 1:

```
Title: CFA for physical frailty with 4 indicators
Data: File is physical frailty.dat;
Variable:
   Names are
         id sex slow weak exhaust wtloss;
   Usevariables are
         slow weak exhaust wtloss;
   Categorical are
         exhaust wtloss;
   Auxiliary = id;
   Missing are ALL (-9999);
  Analysis:
   Estimator = mlr;
  Model:
   pffactor BY slow weak exhaust wtloss;
  Output:
   stand sampstat;
  Savedata:
   File is CFA.4indicators.dat;
   Save = fscores;

! id = identification number; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion;
wtloss = weight loss; lowphyac = low physical activity;
! An additional Variable command is inserted for separate analyses of men and women:
   Useobservations are
     sex EQ 1; and then sex EQ 2;
where sex EQ 1 for men, and sex EQ 2 for women.

! To use the wlsmv estimator instead of mlr, the Analysis command is omitted.
```

```
Title: CFA for physical frailty with three indicators (including exhaustion)
Data: File is physical frailty.dat;
Variable:
   Names are
         id sex slow weak exhaust wtloss;
   Usevariables are
         slow weak exhaust;
   Categorical are
         exhaust;
   Auxiliary = id;
   Missing are ALL (-9999);
 Analysis:
   Estimator = mlr;
 Model:
   pffactor BY slow weak exhaust;
 Output:
   stand sampstat;
 Savedata:
   File is CFA.3indicators.exhaust.dat;
   Save = fscores;

! id = identification number; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion;
wtloss = weight loss; lowphyac = low physical activity;
! An additional Variable command is inserted for separate analyses of men and women:
   Useobservations are
     sex EQ 1; and then sex EQ 2;
where sex EQ 1 for men, and sex EQ 2 for women.

! To use the wlsmv estimator instead of mlr, the Analysis command is omitted.
```

```
Title: CFA for physical frailty with three indicators (including weight loss)
Data: File is physical frailty.dat;
Variable:
   Names are
         id sex slow weak exhaust wtloss;
   Usevariables are
         slow weak wtloss;
   Categorical are
         wtloss;
   Auxiliary = id;
   Missing are ALL (-9999);
 Analysis:
   Estimator = mlr;
 Model:
   pffactor BY slow weak wtloss;
 Output:
   stand sampstat;
 Savedata:
   File is CFA.3indicators.wtloss.dat;
   Save = fscores;

! id = identification number; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion;
wtloss = weight loss; lowphyac = low physical activity;
! An additional Variable command is inserted for separate analyses of men and women:
   Useobservations are
     sex EQ 1; and then sex EQ 2;
where sex EQ 1 for men, and sex EQ 2 for women.

! To use the wlsmv estimator instead of mlr, the Analysis command is omitted.
```

Paper 2:

! In addition to the input files for Paper 1, the following file is used.

```
Title: CFA for physical frailty with 5 indicators
Data: File is physical frailty.dat;
Variable:
   Names are
         id sex slow weak exhaust wtloss lowphyac;
   Usevariables are
         slow weak exhaust wtloss lowphyac;
   Categorical are
         exhaust wtloss lowphyac;
   Auxiliary = id;
   Missing are ALL (-9999);
 Analysis:
   Estimator = mlr;
 Model:
   pffactor BY slow weak exhaust wtloss lowphyac;
 Output:
   stand sampstat;
 Savedata:
   File is CFA.5indicators.dat;
   Save = fscores;

! id = identification number; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion;
wtloss = weight loss; lowphyac = low physical activity;
! An additional Variable command is inserted for separate analyses of men and women:
   Useobservations are
     sex EQ 1; and then sex EQ 2;
where sex EQ 1 for men, and sex EQ 2 for women.
```

Paper 3:

! **Model 1**

```
Title: Latent growth curve model for prediction of physical frailty with multiple indicators
Data: File is physical frailty1.dat;
Define:
    age_c65 = age_w2 - 65;
Variable:
  Names are
    id sex age_w2 sex slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6
    exhau_w6 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2
    loedu_w2 bmi_30 bmi_20 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4
  Usevariables are
    slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6 exhau_w6
    cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2 loedu_w2
    bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 sex age_c65;
  Categorical are
    exhau_w2 exhau_w4 exhau_w6;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  pffac_w2 BY slow_w2 (s)
  weak_w2 (w)
  exhau_w2 (e);
  [slow_w2] (si);
  [weak_w2] (wi);
  [exhau_w2$1] (ei);
  pffac_w4 BY slow_w4 (s)
  weak_w4 (w)
  exhau_w4 (e);
  [slow_w4] (si);
  [weak_w4] (wi);
  [exhau_w4$1] (ei);
  pffac_w6 BY slow_w6 (s)
  weak_w6 (w)
  exhau_w6 (e);
  [slow_w6] (si);
  [weak_w6] (wi);
  [exhau_w6$1] (ei);
  slow_w2 WITH slow_w4;
  slow_w2 WITH slow_w6;
```

```
  slow_w4 WITH slow_w6;
  weak_w2 WITH weak_w4;
  weak_w2 WITH weak_w6;
  weak_w4 WITH weak_w6;
  i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
  i WITH s;
  i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
  s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
  pffac_w2 ON cesd6_w1 (ces)
  lowpa_w1 (lop)
  cogni_w1(cog)
  pssu_w1 (pss)
  psin_w1 (psi)
  cd14_w2 (cd)
  allo8_w2 (all);
  pffac_w4 ON cesd6_w2 (ces)
  lowpa_w2 (lop)
  cogni_w2(cog)
  pssu_w2 (pss)
  psin_w2 (psi)
  cd14_w4 (cd)
  allo8_w4 (all);
  pffac_w6 ON cesd6_w4 (ces)
  lowpa_w4 (lop)
  cogni_w4(cog)
  pssu_w4 (pss)
  psin_w4 (psi)
  cd14_w6 (cd)
  allo8_w6 (all);
  [bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
  loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
  cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
Output:
  stand sampstat cinterval;
```

! The suffixes, _w1, _w2, _w4, and _w6 indicate that variables are measured at waves 1, 2, 4, and 6 respectively.
! id = identification number; age = age; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pffac = physical frailty factor;

```
Title: Latent growth curve model for prediction of physical frailty with multiple indicators and stratified by
gender
Data: File is physical frailty1.dat;
Define:
    age_c65 = age - 65;
Variable:
  Names are
    id sex age_w2 sex slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6
    exhau_w6 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2
    loedu_w2 bmi_30 bmi_20 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4
  Usevariables are
    slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6 exhau_w6
    cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2 loedu_w2
    bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 age_c65;
Categorical are
    exhau_w2 exhau_w4 exhau_w6;
    Classes = c(2);
  Knownclass = c(sex = 1-2);
  Missing are ALL (-9999);
Analysis:
  Type = mixture;
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  %overall%
  pffac_w2 BY slow_w2 (s)
  weak_w2 (w)
  exhau_w2 (e);
  [slow_w2] (si);
  [weak_w2] (wi);
  [exhau_w2$1] (ei);
  pffac_w4 BY slow_w4 (s)
  weak_w4 (w)
  exhau_w4 (e);
  [slow_w4] (si);
  [weak_w4] (wi);
  [exhau_w4$1] (ei);
  pffac_w6 BY slow_w6 (s)
  weak_w6 (w)
  exhau_w6 (e);
  [slow_w6] (si);
  [weak_w6] (wi);
  [exhau_w6$1] (ei);
  slow_w2 WITH slow_w4;
```

```
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces)
lowpa_w1 (lop)
cogni_w1(cog)
pssu_w1 (pss)
psin_w1 (psi)
cd14_w2 (cd)
allo8_w2 (all);
pffac_w4 ON cesd6_w2 (ces)
lowpa_w2 (lop)
cogni_w2(cog)
pssu_w2 (pss)
psin_w2 (psi)
cd14_w4 (cd)
allo8_w4 (all);
pffac_w6 ON cesd6_w4 (ces)
lowpa_w4 (lop)
cogni_w4(cog)
pssu_w4 (pss)
psin_w4 (psi)
cd14_w6 (cd)
allo8_w6 (all);
[bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
%c#1%
pffac_w2 BY slow_w2 (s1)
weak_w2 (w1)
exhau_w2 (e1);
[slow_w2] (si1);
[weak_w2] (wi1);
[exhau_w2$1] (ei1);
pffac_w4 BY slow_w4 (s1)
weak_w4 (w1)
exhau_w4 (e1);
[slow_w4] (si1);
[weak_w4] (wi1);
[exhau_w4$1] (ei1);
pffac_w6 BY slow_w6 (s1)
```

```
weak_w6 (w1)
exhau_w6 (e1);
[slow_w6] (si1);
[weak_w6] (wi1);
[exhau_w6$1] (ei1);
slow_w2 WITH slow_w4;
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces1)
lowpa_w1 (lop1)
cogni_w1(cog1)
pssu_w1 (pss1)
psin_w1 (psi1)
cd14_w2 (cd1)
allo8_w2 (all1);
pffac_w4 ON cesd6_w2 (ces1)
lowpa_w2 (lop1)
cogni_w2(cog1)
pssu_w2 (pss1)
psin_w2 (psi1)
cd14_w4 (cd1)
allo8_w4 (all1);
pffac_w6 ON cesd6_w4 (ces1)
lowpa_w4 (lop1)
cogni_w4(cog1)
pssu_w4 (pss1)
psin_w4 (psi1)
cd14_w6 (cd1)
allo8_w6 (all1);
[bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
%c#2%
pffac_w2 BY slow_w2 (s1)
weak_w2 (w1)
exhau_w2 (e1);
[slow_w2] (si1);
[weak_w2] (wi1);
[exhau_w2$1] (ei1);
pffac_w4 BY slow_w4 (s1)
```

```
  weak_w4 (w1)
  exhau_w4 (e1);
  [slow_w4] (si1);
  [weak_w4] (wi1);
  [exhau_w4$1] (ei1);
  pffac_w6 BY slow_w6 (s1)
  weak_w6 (w1)
  exhau_w6 (e1);
  [slow_w6] (si1);
  [weak_w6] (wi1);
  [exhau_w6$1] (ei1);
  slow_w2 WITH slow_w4;
  slow_w2 WITH slow_w6;
  slow_w4 WITH slow_w6;
  weak_w2 WITH weak_w4;
  weak_w2 WITH weak_w6;
  weak_w4 WITH weak_w6;
  i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
  i WITH s;
  i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
  s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
  pffac_w2 ON cesd6_w1 (ces1)
  lowpa_w1 (lop1)
  cogni_w1(cog1)
  pssu_w1 (pss1)
  psin_w1 (psi1)
  cd14_w2 (cd1)
  allo8_w2 (all1);
  pffac_w4 ON cesd6_w2 (ces1)
  lowpa_w2 (lop1)
  cogni_w2(cog1)
  pssu_w2 (pss1)
  psin_w2 (psi1)
  cd14_w4 (cd1)
  allo8_w4 (all1);
  pffac_w6 ON cesd6_w4 (ces1)
  lowpa_w4 (lop1)
  cogni_w4(cog1)
  pssu_w4 (pss1)
  psin_w4 (psi1)
  cd14_w6 (cd1)
  allo8_w6 (all1);
  [bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
  loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
  cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
Output:
  stand sampstat cinterval;
```

! The suffixes, _w1, _w2, _w4, and _w6 indicate that variables are measured at waves 1, 2, 4, and 6 respectively.
! id = identification number; age = age; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pffac = physical frailty factor;

```
Title: Latent growth curve model for prediction of physical frailty with multiple indicators and stratified by
age group
Data: File is physical frailty1.dat;
Define:
    IF age GE 75 THEN age75 = 2;
    IF age LT 75 THEN age75 = 1;
    age_c65 = age - 65;
Variable:
  Names are
    id sex age_w2 sex slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6
    exhau_w6 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2
    loedu_w2 bmi_30 bmi_20 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4
  Usevariables are
    slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6 exhau_w6
    cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2 loedu_w2
    bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 sex age_c65;
Categorical are
    exhau_w2 exhau_w4 exhau_w6;
    Classes = c(2);
  Knownclass = c(age75 = 1-2);
  Missing are ALL (-9999);
Analysis:
  Type = mixture;
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  %overall%
  pffac_w2 BY slow_w2 (s)
  weak_w2 (w)
  exhau_w2 (e);
  [slow_w2] (si);
  [weak_w2] (wi);
  [exhau_w2$1] (ei);
  pffac_w4 BY slow_w4 (s)
  weak_w4 (w)
  exhau_w4 (e);
  [slow_w4] (si);
  [weak_w4] (wi);
  [exhau_w4$1] (ei);
  pffac_w6 BY slow_w6 (s)
  weak_w6 (w)
  exhau_w6 (e);
  [slow_w6] (si);
  [weak_w6] (wi);
```

```
[exhau_w6$1] (ei);
slow_w2 WITH slow_w4;
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces)
lowpa_w1 (lop)
cogni_w1(cog)
pssu_w1 (pss)
psin_w1 (psi)
cd14_w2 (cd)
allo8_w2 (all);
pffac_w4 ON cesd6_w2 (ces)
lowpa_w2 (lop)
cogni_w2(cog)
pssu_w2 (pss)
psin_w2 (psi)
cd14_w4 (cd)
allo8_w4 (all);
pffac_w6 ON cesd6_w4 (ces)
lowpa_w4 (lop)
cogni_w4(cog)
pssu_w4 (pss)
psin_w4 (psi)
cd14_w6 (cd)
allo8_w6 (all);
[bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
%c#1%
pffac_w2 BY slow_w2 (s)
weak_w2 (w)
exhau_w2 (e);
[slow_w2] (si);
[weak_w2] (wi);
[exhau_w2$1] (ei);
pffac_w4 BY slow_w4 (s)
weak_w4 (w)
exhau_w4 (e);
[slow_w4] (si);
[weak_w4] (wi);
```

[exhau_w4$1] (ei);
pffac_w6 BY slow_w6 (s)
weak_w6 (w)
exhau_w6 (e);
[slow_w6] (si);
[weak_w6] (wi);
[exhau_w6$1] (ei);
slow_w2 WITH slow_w4;
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces)
lowpa_w1 (lop)
cogni_w1(cog)
pssu_w1 (pss)
psin_w1 (psi)
cd14_w2 (cd)
allo8_w2 (all);
pffac_w4 ON cesd6_w2 (ces)
lowpa_w2 (lop)
cogni_w2(cog)
pssu_w2 (pss)
psin_w2 (psi)
cd14_w4 (cd)
allo8_w4 (all);
pffac_w6 ON cesd6_w4 (ces)
lowpa_w4 (lop)
cogni_w4(cog)
pssu_w4 (pss)
psin_w4 (psi)
cd14_w6 (cd)
allo8_w6 (all);
[bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
%c#2%
pffac_w2 BY slow_w2 (s1)
weak_w2 (w1)
exhau_w2 (e1);
[slow_w2] (si1);
[weak_w2] (wi1);

[exhau_w2$1] (ei1);
pffac_w4 BY slow_w4 (s1)
weak_w4 (w1)
exhau_w4 (e1);
[slow_w4] (si1);
[weak_w4] (wi1);
[exhau_w4$1] (ei1);
pffac_w6 BY slow_w6 (s1)
weak_w6 (w1)
exhau_w6 (e1);
[slow_w6] (si1);
[weak_w6] (wi1);
[exhau_w6$1] (ei1);
slow_w2 WITH slow_w4;
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces1)
lowpa_w1 (lop1)
cogni_w1(cog1)
pssu_w1 (pss1)
psin_w1 (psi1)
cd14_w2 (cd1)
allo8_w2 (all1);
pffac_w4 ON cesd6_w2 (ces1)
lowpa_w2 (lop1)
cogni_w2(cog1)
pssu_w2 (pss1)
psin_w2 (psi1)
cd14_w4 (cd1)
allo8_w4 (all1);
pffac_w6 ON cesd6_w4 (ces1)
lowpa_w4 (lop1)
cogni_w4(cog1)
pssu_w4 (pss1)
psin_w4 (psi1)
cd14_w6 (cd1)
allo8_w6 (all1);
[bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];

Output:
  stand sampstat cinterval;

! The suffixes, _w1, _w2, _w4, and _w6 indicate that variables are measured at waves 1, 2, 4, and 6 respectively.
! id = identification number; age = age; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pffac = physical frailty factor;

! **Model 2**

! For stratification by low physical activity, depressive symptoms, poor social support, and poor social integration, the corresponding binary variables (using means as the cut-off values) are created and used in place of age group (as in Model 1).

! **Model 3**

```
Title: Latent growth curve model for prediction of physical frailty with multiple indicators and incorporating
indirect effects
Data: File is physical frailty1.dat;
Define:
    age_c65 = age_w2 - 65;
Variable:
  Names are
    id sex age_w2 sex slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6
    exhau_w6 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2
    loedu_w2 bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4
    cogni_w1 cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4
  Usevariables are
    slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6 exhau_w6
    cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2 loedu_w2
    bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 sex age_c65;
  Categorical are
    exhau_w2 exhau_w4 exhau_w6;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  pffac_w2 BY slow_w2 (s)
  weak_w2 (w)
  exhau_w2 (e);
  [slow_w2] (si);
  [weak_w2] (wi);
  [exhau_w2$1] (ei);
  pffac_w4 BY slow_w4 (s)
  weak_w4 (w)
  exhau_w4 (e);
  [slow_w4] (si);
  [weak_w4] (wi);
  [exhau_w4$1] (ei);
  pffac_w6 BY slow_w6 (s)
  weak_w6 (w)
  exhau_w6 (e);
  [slow_w6] (si);
  [weak_w6] (wi);
  [exhau_w6$1] (ei);

  slow_w2 WITH slow_w4;
  slow_w2 WITH slow_w6;
```

```
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_e_w2 h_alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_e_w2 h_alc_w2 loedu_w2 lowth_w2;
cd14_w2 ON
cesd6_w1 (cescd)
lowpa_w1 (lopcd)
cogni_w1(cogcd)
pssu_w1 (psscd)
psin_w1 (psicd);
allo8_w2 ON
cesd6_w1 (cesall)
lowpa_w1 (lopall)
cogni_w1(cogall)
pssu_w1 (pssall)
psin_w1 (psiall);
cd14_w4 ON
cesd6_w2 (cescd)
lowpa_w2 (lopcd)
cogni_w2(cogcd)
pssu_w2 (psscd)
psin_w2 (psicd);
allo8_w4 ON
cesd6_w2 (cesall)
lowpa_w2 (lopall)
cogni_w2(cogall)
pssu_w2 (pssall)
psin_w2 (psiall);
cd14_w6 ON
cesd6_w4 (cescd)
lowpa_w4 (lopcd)
cogni_w4(cogcd)
pssu_w4 (psscd)
psin_w4 (psicd);
allo8_w6 ON
cesd6_w4 (cesall)
lowpa_w4 (lopall)
cogni_w4(cogall)
pssu_w4 (pssall)
psin_w4 (psiall);
cd14_w2 WITH allo8_w2;
cd14_w4 WITH allo8_w4;
cd14_w6 WITH allo8_w6;
```

```
  pffac_w2 ON
  cesd6_w1 (ces)
  lowpa_w1 (lop)
  cogni_w1(cog)
  pssu_w1 (pss)
  psin_w1 (psi)
  cd14_w2 (cd)
  allo8_w2 (all);
  pffac_w4 ON
  cesd6_w2 (ces)
  lowpa_w2 (lop)
  cogni_w2(cog)
  pssu_w2 (pss)
  psin_w2 (psi)
  cd14_w4 (cd)
  allo8_w4 (all);
  pffac_w6 ON
  cesd6_w4 (ces)
  lowpa_w4 (lop)
  cogni_w4(cog)
  pssu_w4 (pss)
  psin_w4 (psi)
  cd14_w6 (cd)
  allo8_w6 (all);
  [bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2
  allo8_w4 allo8_w6 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1 cogni_w2
  cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
  Model constraint:
  new (ind22 ind23 ind24 ind25 ind26
  ind32 ind33 ind34 ind35 ind36);
  ind22 = cescd*cd;
  ind23 = lopcd*cd;
  ind24 = cogcd*cd;
  ind25 = psscd*cd;
  ind26 = psicd*cd;
  ind32 = cesall*all;
  ind33 = lopall*all;
  ind34 = cogall*all;
  ind35 = pssall*all;
  ind36 = psiall*all;
Output:
  stand sampstat cinterval;

! The suffixes, _w1, _w2, _w4, and _w6 indicate that variables are measured at waves 1, 2, 4, and 6
respectively.
! id = identification number; age = age; sex = gender; slow = slowness; weak = weakness; exhaust =
exhaustion; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake;
```

lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pffac = physical frailty factor;

! Stratification by gender and age group are as for Model 1.

! **Model 4**

! For stratification by poor social support, and poor social integration, the corresponding binary variables (using means as the cut-off values) are created and used in place of age group (as in Model 3).

! Sensitivity analysis for Model 1

```
Title: Latent growth curve model for prediction of physical frailty with multiple indicators incorporating the
Wu-Carroll shared parameter model to account for missing data being MNAR
Data: File is physical frailty1.dat;
Define:
    age_c65 = age_w2 - 65;
Variable:
  Names are
    id sex age_w2 sex slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6
    exhau_w6 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2
    loedu_w2 bmi_30 bmi_20 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 ind2 ind4 ind6;
  Usevariables are
    slow_w2 weak_w2 exhau_w2 slow_w4 weak_w4 exhau_w4 slow_w6 weak_w6 exhau_w6
    cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2 lowth_w2 loedu_w2
    bmi30_w2 bmi20_w2 lowpa_w1 lowpa_w2 lowpa_w4 cesd6_w1 cesd6_w2 cesd6_w4 cogni_w1
    cogni_w2 cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4 sex ind2 ind4 ind6
    age_c65 d4 d6;
  Categorical are
    exhau_w2 exhau_w4 exhau_w6 d4 d6;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Data Missing:
  Names are ind2 ind4 ind6;
  Type = sdropout;
  Binary = d4 d6;
Model:
  pffac_w2 BY slow_w2 (s)
  weak_w2 (w)
  exhau_w2 (e);
  [slow_w2] (si);
  [weak_w2] (wi);
  [exhau_w2$1] (ei);
  pffac_w4 BY slow_w4 (s)
  weak_w4 (w)
  exhau_w4 (e);
  [slow_w4] (si);
  [weak_w4] (wi);
  [exhau_w4$1] (ei);
  pffac_w6 BY slow_w6 (s)
  weak_w6 (w)
  exhau_w6 (e);
  [slow_w6] (si);
```

[weak_w6] (wi);
[exhau_w6$1] (ei);
slow_w2 WITH slow_w4;
slow_w2 WITH slow_w6;
slow_w4 WITH slow_w6;
weak_w2 WITH weak_w4;
weak_w2 WITH weak_w6;
weak_w4 WITH weak_w6;
i s | pffac_w2@0 pffac_w4@1 pffac_w6@2;
i WITH s;
i ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
s ON age_c65 sex bmi30_w2 bmi20_w2 smo_w2 alc_w2 loedu_w2 lowth_w2;
pffac_w2 ON cesd6_w1 (ces)
lowpa_w1 (lop)
cogni_w1(cog)
pssu_w1 (pss)
psin_w1 (psi)
cd14_w2 (cd)
allo8_w2 (all);
pffac_w4 ON cesd6_w2 (ces)
lowpa_w2 (lop)
cogni_w2(cog)
pssu_w2 (pss)
psin_w2 (psi)
cd14_w4 (cd)
allo8_w4 (all);
pffac_w6 ON cesd6_w4 (ces)
lowpa_w4 (lop)
cogni_w4(cog)
pssu_w4 (pss)
psin_w4 (psi)
cd14_w6 (cd)
allo8_w6 (all);
d4 ON i (1)
s (2)
age_c65 (3)
sex (4)
bmi30_w2 (5)
bmi20_w2 (6)
smo_w2 (7)
alc_w2 (8)
loedu_w2 (9)
lowth_w2 (10)
cesd6_w2 (11)
lowpa_w2 (12)
cogni_w2 (13)
pssu_w2 (14)

```
  psin_w2 (15)
  cd14_w4 (16)
  allo8_w4 (17);
  d6 ON i (1)
  s (2)
  age_c65 (3)
  sex (4)
  bmi30_w2 (5)
  bmi20_w2 (6)
  smo_w2 (7)
  alc_w2 (8)
  loedu_w2 (9)
  lowth_w2 (10)
  cesd6_w4 (11)
  lowpa_w4 (12)
  cogni_w4 (13)
  pssu_w4 (14)
  psin_w4 (15)
  cd14_w6 (16)
  allo8_w6 (17);
  [bmi30_w2 bmi20_w2 cd14_w2 cd14_w4 cd14_w6 allo8_w2 allo8_w4 allo8_w6 smo_w2 alc_w2
  loedu_w2 lowth_w2 cesd6_w1 cesd6_w2 cesd6_w4 lowpa_w1 lowpa_w2 lowpa_w4 cogni_w1 cogni_w2
  cogni_w4 pssu_w1 pssu_w2 pssu_w4 psin_w1 psin_w2 psin_w4];
Output:
  stand sampstat cinterval;
```

! The suffixes, _w1, _w2, _w4, and _w6 indicate that variables are measured at waves 1, 2, 4, and 6 respectively.
! id = identification number; age = age; sex = gender; slow = slowness; weak = weakness; exhaust = exhaustion; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pffac = physical frailty factor; ind2, ind4, ind6 = represents physical frailty factor at waves 2, 4, and 6 respectively where missing occurs when all three indicators have missing values; d4, d6 = physical frailty missing value indicators at waves 4 and 6 respectively;

Paper 4:

! **Model 1**

```
Title: Discrete time survival analysis for prediction of death by physical frailty
Data: File is physical frailty2.dat;
Define:
  Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
  cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
Variable:
  Names are
    id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Usevariables are
    dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Categorical are
    dea_w3 dea_w4 dea_w5;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
  Link = logit;
Model:
  death BY dea_w3@1 dea_w4@1 dea_w5@1;
  death@0;
  death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2
  smo_w2 alc_w2 cesd6_w2 cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2;
  [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
  lowth_w2 loedu_w2 psin_w2 pssu_w2];
Output:
  stand sampstat cinterval tech4;
```

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5 respectively.

! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score (standardized and centred on mean);

```
Title: Discrete time survival analysis for prediction of death by physical frailty including interaction with
gender
  Data: File is physical frailty2.dat;
  Define:
    Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
    pfxsex = pf_mean*sex;
  Variable:
    Names are
      id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
      alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
    Usevariables are
      dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
      alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
    Categorical are
      dea_w3 dea_w4 dea_w5;
    Missing are ALL (-9999);
  Analysis:
    Algorithm = integration;
    Integration = montecarlo;
    Estimator = mlr;
    Link = logit;
  Model:
    death BY dea_w3@1 dea_w4@1 dea_w5@1;
    death@0;
    death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2
    smo_w2 alc_w2 cesd6_w2 cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2
    pfxsex (pfxsex);
    [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
    lowth_w2 loedu_w2 psin_w2 pssu_w2 pfxsex];
    Model constraint:
    New (male female pf_ma pf_fe);
    male = 1;
    female = 2;
    pf_ma = pf + (pfxsex*male);
    pf_fe = pf + (pfxsex*female);
    Model test:
    0 = pf_ma - pf_fe;
  Output:
    stand sampstat cinterval tech4;

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5
respectively.
! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo
= smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 =
underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment;
```

pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score (standardized and centred on mean);

! For stratification by age, interaction of physical frailty with age (pfxage) is included instead of that with gender. In addition:

Model constraint:
New (loage meage hiage pf_loage pf_meage pf_hiage pflo_or pfme_or pfhi_or);
loage = 65;
meage = 75;
hiage = 85;
pf_loage = pf + (pfxage*loage);
pf_meage = pf + (pfxage*meage);
pf_hiage = pf + (pfxage*hiage);
Model test:
0 = pf_loage - pf_hiage;

! **Model 2**

! For stratification by obesity, smoking, and high alcohol intake, their binary variables are used in place of gender (as in Model 1).

! For stratification by low physical activity, allostatic load, depressive symptoms, cognitive impairment, low wealth, poor social support, and poor social integration, their continuous variables are used in place of age (as in Model 1). However, the model constraint command estimates the effect of physical frailty factor score at the mean, as well as one standard deviation above and below the mean of these variables.

```
! Model 3
 Title: Discrete time survival analysis for prediction of death by physical frailty with indiect effects through
 low physical activity, depressive symptoms, and cognitive impairment
 Data: File is physical frailty2.dat;
 Define:
  Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
  cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
 Variable:
  Names are
    id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Usevariables are
    dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Categorical are
    dea_w3 dea_w4 dea_w5;
  Missing are ALL (-9999);
 Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
  Link = logit;
 Model:
  death BY dea_w3@1 dea_w4@1 dea_w5@1;
  death@0;
  death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 cd14_w2 allo_w2 smo_w2 alc_w2
  lowpa_w2 (loptodea)
  cesd6_w2 (cestodea)
  cogni_w2 (cogtodea)
  lowth_w2 loedu_w2 psin_w2 pssu_w2;
  lowpa_w2 ON pf_mean (pftolop)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  cesd6_w2 ON pf_mean (pftoces)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  cogni_w2 ON pf_mean (pftocog)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  lowpa_w2 WITH cesd6_w2 cogni_w2;
  cesd6_w2 WITH cogni_w2;
  [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
  lowth_w2 loedu_w2 psin_w2 pssu_w2];
  Model constraint:
  new (indlop indces indcog);
  indlop = pftolop*loptodea;
  indces = pftoces*cestodea;
```

```
    indcog = pftocog*cogtodea;
  Output:
    stand sampstat cinterval tech4;

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5
respectively.
! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo
= smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 =
underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment;
pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score
(standardized and centred on mean);
```

```
Title: Discrete time survival analysis for prediction of death by physical frailty with indiect effects through
low physical activity, depressive symptoms, and cognitive impairment, and including interaction of
physical frailty with gender
Data: File is physical frailty2.dat;
Define:
  Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
  cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
  pfxlop = pf_mean*lowpa_w2;
  pfxces = pf_mean *cesd6_w2;
  pfxcog = pf_mean *cogni_w2;
  pfxsex = pf_mean *sex;
Variable:
  Names are
    id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Usevariables are
    dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean pfxlop pfxces pfxcog
    pfxsex;
  Categorical are
    dea_w3 dea_w4 dea_w5;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
  Link = logit;
  Bootstrap = 1000;
Model:
  death BY dea_w3@1 dea_w4@1 dea_w5@1;
  death@0;
  death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 cd14_w2 allo_w2 smo_w2 alc_w2
  lowpa_w2 (loptodea)
  cesd6_w2 (cestodea)
  cogni_w2 (cogtodea)
  lowth_w2 loedu_w2 psin_w2 pssu_w2
  pfxlop pfxces pfxcog;
  lowpa_w2 ON pf_mean (pftolop)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2 pfxsex (pfsexlop);
  cesd6_w2 ON pf_mean (pftoces)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2 pfxsex (pfsexces);
  cogni_w2 ON pf_mean (pftocog)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2 pfxsex (pfsexcog);
  lowpa_w2 WITH cesd6_w2 cogni_w2;
```

```
    cesd6_w2 WITH cogni_w2;
    [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
    lowth_w2 loedu_w2 psin_w2 pssu_w2 pfxlop pfxces pfxcog pfxsex];
    Model constraint:
    new (m f indlop_m indlop_f indces_m indces_f indcog_m indcog_f);
    m = 1;
    f = 2;
    indlop_m = (pftolop + pfsexlop*m)*(loptodea);
    indlop_f = (pftolop + pfsexlop*f)*(loptodea);
    indces_m = (pftoces + pfsexces*m)*(cestodea);
    indces_f = (pftoces + pfsexces*f)*(cestodea);
    indcog_m = (pftocog + pfsexcog*m)*(cogtodea);
    indcog_f = (pftocog + pfsexcog*f)*(cogtodea);
    Model test:
    0 = indlop_m – indlop_f;
  Output:
    stand sampstat cinterval (bcbootstrap) tech4;
```

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5 respectively.
! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment; pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score (standardized and centred on mean);
! The Model test command is implemented to test significance for differences in indirect effects through low physical activity, depressive symptoms, and cognitive impairment in turn across gender.

! For stratification by age, interaction of physical frailty with age (pfxage) is included instead of that with gender. In addition:

```
Model constraint:
    new (indlop65 indlop75 indlop85 indces65 indces75 indces85
    indcog65 indcog75 indcog85);
    indlop65 = (pftolop + pfagelop*65)*(loptodea);
    indlop75 = (pftolop + pfagelop*75)*(loptodea);
    indlop85 = (pftolop + pfagelop*85)*(loptodea);
    indces65 = (pftoces + pfageces*65)*(cestodea);
    indces75 = (pftoces + pfageces*75)*(cestodea);
    indces85 = (pftoces + pfageces*85)*(cestodea);
    indcog65 = (pftocog + pfagecog*65)*(cogtodea);
    indcog75 = (pftocog + pfagecog*75)*(cogtodea);
    indcog85 = (pftocog + pfagecog*85)*(cogtodea);
```

where pfagelop, pfageces, and pfagecog are coefficients for the effect of interactions of physical frailty factor score with age, on low physical activity, depressive symptoms, and cognitive impairment respectively.

! **Model 4**

! For stratification by poor social support and poor social integration, their continuous variables are used in place of age (as in Model 3). However, the model constraint command estimates the effect of physical frailty factor score at the mean, as well as one standard deviation above and below the mean of these variables.

! Sensitivity analyses using phantom variables

```
 Title: Discrete time survival analysis for prediction of death by physical frailty, while implementing
 sensitivity analyses using phantom variables
 Data: File is physical frailty2.dat;
 Define:
  Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
  cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
 Variable:
  Names are
    id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Usevariables are
    dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Categorical are
    dea_w3 dea_w4 dea_w5;
  Missing are ALL (-9999);
 Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
  Link = logit;
 Model:
  death BY dea_w3@1 dea_w4@1 dea_w5@1;
  death@0;
  death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2
  smo_w2 alc_w2 cesd6_w2 cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2
  u@x;
  u BY;
  u@1;
  u WITH pf_mean@y
  sex@0 age_w2@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 bmi30_w2@0 bmi20_w2@0
  lowpa_w2@0 cesd6_w2@0 cogni_w2@0 pssu_w2@0 psin_w2@0 loedu_w2@0 lowth_w2@0;
  [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
  lowth_w2 loedu_w2 psin_w2 pssu_w2];
 Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5
respectively.
! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo
= smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 =
underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment;
pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score
(standardized and centred on mean); u = phantom variable;
! x = equivalent to multiples of the effect of physical frailty on death; y = correlation between u and
physical frailty;
```

```
Title: Discrete time survival analysis for prediction of death by physical frailty with indiect effects through
low physical activity, depressive symptoms, and cognitive impairment, while implementing sensitivity
analyses using phantom variables
Data: File is physical frailty2.dat;
Define:
  Center age_w2 sex bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2
  cogni_w2 lowth_w2 loedu_w2 psin_w2 pssu_w2 (grandmean);
Variable:
  Names are
    id dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Usevariables are
    dea_w3 dea_w4 dea_w5 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 lowpa_w2 smo_w2
    alc_w2 cesd6_w2 cogni_w2 psin_w2 pssu_w2 loweq_w2 loebi_w2 pf_mean;
  Categorical are
    dea_w3 dea_w4 dea_w5;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
  Link = logit;
Model:
  death BY dea_w3@1 dea_w4@1 dea_w5@1;
  death@0;
  death ON pf_mean age_w2 sex bmi30_w2 bmi20_w2 cd14_w2 allo_w2 smo_w2 alc_w2
  lowpa_w2 (loptodea)
  cesd6_w2 (cestodea)
  cogni_w2 (cogtodea)
  lowth_w2 loedu_w2 psin_w2 pssu_w2
  u@x;
  lowpa_w2 ON pf_mean (pftolop)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  cesd6_w2 ON pf_mean (pftoces)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  cogni_w2 ON pf_mean (pftocog)
  sex age_w2 cd14_w2 allo_w2 smo_w2 alc_w2 bmi30_w2 bmi20_w2 pssu_w2 psin_w2 loedu_w2
  lowth_w2;
  lowpa_w2 WITH cesd6_w2 cogni_w2;
  cesd6_w2 WITH cogni_w2;
  u BY;
  u@1;
  u WITH pf_mean@y lowpa_w2@z1 cesd6_w2@z2 cogni_w2@z3
  sex@0 age_w2@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 bmi30_w2@0 bmi20_w2@0
  pssu_w2@0 psin_w2@0 loedu_w2@0 lowth_w2@0;
```

```
  [pf_mean bmi30_w2 bmi20_w2 lowpa_w2 cd14_w2 allo_w2 smo_w2 alc_w2 cesd6_w2 cogni_w2
  lowth_w2 loedu_w2 psin_w2 pssu_w2];
  Model constraint:
  new (indlop indces indcog);
  indlop = pftolop*loptodea;
  indces = pftoces*cestodea;
  indcog = pftocog*cogtodea;
 Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w3, _w4, and _w5 indicate that variables are measured at waves 2, 3, 4, and 5
respectively.
! id = identification number; age = age; sex = gender; cd14 = chronic disease; allo8 = allostatic load; smo
= smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 =
underweight; lowpa = low physical activity; cesd6 = depressive symptoms; cogni = cognitive impairment;
pssu = poor social support; psin = poor social integration; pf_mean = physical frailty factor score
(standardized and centred on mean); u = phantom variable;
! x = equivalent to multiples of the effect of physical frailty on death; y = correlation between u and
physical frailty; z1 = correlation between u and low physical activity; z2 = correlation between u and
depressive symptoms; z3 = correlation between u and cognitive impairment;
```

Paper 5:

```
! Model 1
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  sex (sexadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  sex (sexadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
```

```
  pf_w4 ON pf_w2 (pfpf)
  badl6_w2 (adlpf)
  sex (sexpf)
  age_w2 (agepf)
  cd14 (cdpf)
  allo (allpf)
  bmi30_w2 (b30pf)
  bmi20_w2 (b20pf)
  smo_w2 (smopf)
  alc_w2 (alcpf)
  lowth_w2 (lowpf)
  loedu_w2 (loepf)
  pssu_w2 (psspf)
  psin_w2 (psipf);
  pf_w6 ON pf_w4 (pfpf)
  badl6_w4 (adlpf)
  sex (sexpf)
  age_w2 (agepf)
  cd14 (cdpf)
  allo (allpf)
  bmi30_w2 (b30pf)
  bmi20_w2 (b20pf)
  smo_w2 (smopf)
  alc_w2 (alcpf)
  lowth_w2 (lowpf)
  loedu_w2 (loepf)
  pssu_w2 (psspf)
  psin_w2 (psipf);
  badl6_w4 WITH badl6_w6 pf_w4;
  pf_w6 WITH pf_w4 badl6_w6;
  [cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w4, and _w6 indicate that variables are measured at waves 2, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease
(standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low
wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support
(standardized); psin = poor social integration (standardized); pf = physical frailty factor score
(standardized); badl6 = number of basic activities of daily living items performed with difficulty;
```

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty with
stratification by gender
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Classes = c(2);
  Knownclass = c(sex = 1-2);
  Missing are ALL (-9999);
Analysis:
  Type = mixture;
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  %overall%
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  pf_w4 ON pf_w2 (pfpf)
```

badl6_w2 (adlpf)
age_w2 (agepf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
pf_w6 ON pf_w4 (pfpf)
badl6_w4 (adlpf)
age_w2 (agepf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
%c#1%
badl6_w4 ON badl6_w2 (adladl1)
pf_w2 (pfadl1)
age_w2 (agead1l)
cd14 (cdadl1)
allo (alladl)
bmi30_w2 (b30adl1)
bmi20_w2 (b20adl1)
smo_w2 (smoadl1)
alc_w2 (alcadl1)
lowth_w2 (lowadl1)
loedu_w2 (loeadl1)
pssu_w2 (pssadl1)
psin_w2 (psiadl1);
badl6_w6 ON badl6_w4 (adladl1)
pf_w4 (pfadl1)
age_w2 (ageadl1)
cd14 (cdadl1)
allo (alladl1)

bmi30_w2 (b30adl1)
bmi20_w2 (b20adl1)
smo_w2 (smoadl1)
alc_w2 (alcadl)1
lowth_w2 (lowadl1)
loedu_w2 (loeadl1)
pssu_w2 (pssadl1)
psin_w2 (psiadl1);
pf_w4 ON pf_w2 (pfpf1)
badl6_w2 (adlpf1)
age_w2 (agepf1)
cd14 (cdpf1)
allo (allpf1)
bmi30_w2 (b30pf1)
bmi20_w2 (b20pf1)
smo_w2 (smopf1)
alc_w2 (alcpf1)
lowth_w2 (lowpf1)
loedu_w2 (loepf1)
pssu_w2 (psspf1)
psin_w2 (psipf1);
pf_w6 ON pf_w4 (pfpf1)
badl6_w4 (adlpf1)
age_w2 (agepf1)
cd14 (cdpf1)
allo (allpf1)
bmi30_w2 (b30pf1)
bmi20_w2 (b20pf1)
smo_w2 (smopf1)
alc_w2 (alcpf1)
lowth_w2 (lowpf1)
loedu_w2 (loepf1)
pssu_w2 (psspf1)
psin_w2 (psipf1);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
%c#2%
badl6_w4 ON badl6_w2 (adladl2)
pf_w2 (pfadl2)
age_w2 (ageadl2)
cd14 (cdadl2)
allo (alladl2)
bmi30_w2 (b30adl2)
bmi20_w2 (b20adl2)
smo_w2 (smoadl2)
alc_w2 (alcadl2)

lowth_w2 (lowadl2)
loedu_w2 (loeadl2)
pssu_w2 (pssadl2)
psin_w2 (psiadl2);
badl6_w6 ON badl6_w4 (adladl2)
pf_w4 (pfadl2)
age_w2 (ageadl2)
cd14 (cdadl2)
allo (alladl2)
bmi30_w2 (b30adl2)
bmi20_w2 (b20adl2)
smo_w2 (smoadl2)
alc_w2 (alcadl2)
lowth_w2 (lowadl2)
loedu_w2 (loeadl2)
pssu_w2 (pssadl2)
psin_w2 (psiadl2);
pf_w4 ON pf_w2 (pfpf2)
badl6_w2 (adlpf2)
age_w2 (agepf2)
cd14 (cdpf2)
allo (allpf2)
bmi30_w2 (b30pf2)
bmi20_w2 (b20pf2)
smo_w2 (smopf2)
alc_w2 (alcpf2)
lowth_w2 (lowpf2)
loedu_w2 (loepf2)
pssu_w2 (psspf2)
psin_w2 (psipf2);
pf_w6 ON pf_w4 (pfpf2)
badl6_w4 (adlpf2)
age_w2 (agepf2)
cd14 (cdpf2)
allo (allpf2)
bmi30_w2 (b30pf2)
bmi20_w2 (b20pf2)
smo_w2 (smopf2)
alc_w2 (alcpf2)
lowth_w2 (lowpf2)
loedu_w2 (loepf2)
pssu_w2 (psspf2)
psin_w2 (psipf2);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
Model test:

```
  0 = pfadl1 - pfadl2;
Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w4, and _w6 indicate that variables are measured at waves 2, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease
(standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low
wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support
(standardized); psin = poor social integration (standardized); pf = physical frailty factor score
(standardized); badl6 = number of basic activities of daily living items performed with difficulty;
```

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty with
stratification by age group
Data: File is physical frailty3.dat;
Define:
  IF age_w2 GE 75 THEN age75_w2 = 2;
  IF age_w2 LT 75 THEN age75_w2 = 1;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Classes = c(2);
  Knownclass = c(age75_w2 = 1-2);
  Missing are ALL (-9999);
Analysis:
  Type = mixture;
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  %overall%
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
```

lowth_w2 (lowadl)
loedu_w2 (loeadl)
pssu_w2 (pssadl)
psin_w2 (psiadl);
pf_w4 ON pf_w2 (pfpf)
badl6_w2 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
pf_w6 ON pf_w4 (pfpf)
badl6_w4 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
%c#1%
badl6_w4 ON badl6_w2 (adladl1)
pf_w2 (pfadl1)
age_w2 (agead1l)
sex (sexadl1)
cd14 (cdadl1)
allo (alladl)
bmi30_w2 (b30adl1)
bmi20_w2 (b20adl1)
smo_w2 (smoadl1)
alc_w2 (alcadl1)
lowth_w2 (lowadl1)

loedu_w2 (loeadl1)
pssu_w2 (pssadl1)
psin_w2 (psiadl1);
badl6_w6 ON badl6_w4 (adladl1)
pf_w4 (pfadl1)
age_w2 (ageadl1)
sex (sexadl1)
cd14 (cdadl1)
allo (alladl1)
bmi30_w2 (b30adl1)
bmi20_w2 (b20adl1)
smo_w2 (smoadl1)
alc_w2 (alcadl)1
lowth_w2 (lowadl1)
loedu_w2 (loeadl1)
pssu_w2 (pssadl1)
psin_w2 (psiadl1);
pf_w4 ON pf_w2 (pfpf1)
badl6_w2 (adlpf1)
age_w2 (agepf1)
sex (sexpf1)
cd14 (cdpf1)
allo (allpf1)
bmi30_w2 (b30pf1)
bmi20_w2 (b20pf1)
smo_w2 (smopf1)
alc_w2 (alcpf1)
lowth_w2 (lowpf1)
loedu_w2 (loepf1)
pssu_w2 (psspf1)
psin_w2 (psipf1);
pf_w6 ON pf_w4 (pfpf1)
badl6_w4 (adlpf1)
age_w2 (agepf1)
sex (sexpf1)
cd14 (cdpf1)
allo (allpf1)
bmi30_w2 (b30pf1)
bmi20_w2 (b20pf1)
smo_w2 (smopf1)
alc_w2 (alcpf1)
lowth_w2 (lowpf1)
loedu_w2 (loepf1)
pssu_w2 (psspf1)
psin_w2 (psipf1);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;

[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
%c#2%
badl6_w4 ON badl6_w2 (adladl2)
pf_w2 (pfadl2)
age_w2 (ageadl2)
sex (sexadl2)
cd14 (cdadl2)
allo (alladl2)
bmi30_w2 (b30adl2)
bmi20_w2 (b20adl2)
smo_w2 (smoadl2)
alc_w2 (alcadl2)
lowth_w2 (lowadl2)
loedu_w2 (loeadl2)
pssu_w2 (pssadl2)
psin_w2 (psiadl2);
badl6_w6 ON badl6_w4 (adladl2)
pf_w4 (pfadl2)
age_w2 (ageadl2)
sex (sexadl2)
cd14 (cdadl2)
allo (alladl2)
bmi30_w2 (b30adl2)
bmi20_w2 (b20adl2)
smo_w2 (smoadl2)
alc_w2 (alcadl2)
lowth_w2 (lowadl2)
loedu_w2 (loeadl2)
pssu_w2 (pssadl2)
psin_w2 (psiadl2);
pf_w4 ON pf_w2 (pfpf2)
badl6_w2 (adlpf2)
age_w2 (agepf2)
sex (sexpf2)
cd14 (cdpf2)
allo (allpf2)
bmi30_w2 (b30pf2)
bmi20_w2 (b20pf2)
smo_w2 (smopf2)
alc_w2 (alcpf2)
lowth_w2 (lowpf2)
loedu_w2 (loepf2)
pssu_w2 (psspf2)
psin_w2 (psipf2);
pf_w6 ON pf_w4 (pfpf2)
badl6_w4 (adlpf2)
age_w2 (agepf2)

```
  sex (sexpf2)
  cd14 (cdpf2)
  allo (allpf2)
  bmi30_w2 (b30pf2)
  bmi20_w2 (b20pf2)
  smo_w2 (smopf2)
  alc_w2 (alcpf2)
  lowth_w2 (lowpf2)
  loedu_w2 (loepf2)
  pssu_w2 (psspf2)
  psin_w2 (psipf2);
  badl6_w4 WITH badl6_w6 pf_w4;
  pf_w6 WITH pf_w4 badl6_w6;
  [cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
  Model test:
  0 = pfadl1 - pfadl2;
Output:
  stand sampstat cinterval tech4;
```

! The suffixes, _w2, _w4, and _w6 indicate that variables are measured at waves 2, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease (standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support (standardized); psin = poor social integration (standardized); pf = physical frailty factor score (standardized); badl6 = number of basic activities of daily living items performed with difficulty;

! **Model 2**

! For stratification by poor social support and poor social integration, the corresponding binary variables (using means as the cut-off values) are created and used in place of age group (as in Model 1).

! **Model 3**

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty with indiect
effects through low physical activity, depressive symptoms, and cognitive impairment
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6 lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2
    cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6 lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2
    cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
```

pf_w4 ON pf_w2 (pfpf)
badl6_w2 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
pf_w6 ON pf_w4 (pfpf)
badl6_w4 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
lowpa_w4 ON lowpa_w2 (loplop)
pf_w2 (pflop)
sex (sexlop)
age_w2 (agelop)
cd14_w2 (cdlop)
allo_w2 (alllop)
smo_w2 (smolop)
alc_w2 (alclop)
pssu_w2 (psslop)
psin_w2 (psilop)
lowth_w2 (lowlop)
loedu_w2 (loelop)
bmi30_w2 (b30lop)
bmi20_w2 (b20lop);
lowpa_w6 ON lowpa_w4 (loplop)
pf_w4 (pflop)
sex (sexlop)

age_w2 (agelop)
cd14_w2 (cdlop)
allo_w2 (alllop)
smo_w2 (smolop)
alc_w2 (alclop)
pssu_w2 (psslop)
psin_w2 (psilop)
lowth_w2 (lowlop)
loedu_w2 (loelop)
bmi30_w2 (b30lop)
bmi20_w2 (b20lop);
cesd6_w4 ON cesd6_w2 (cesces)
pf_w2 (pfces)
sex (sexces)
age_w2 (ageces)
cd14_w2 (cdces)
allo_w2 (allces)
smo_w2 (smoces)
alc_w2 (alcces)
pssu_w2 (pssces)
psin_w2 (psices)
lowth_w2 (lowces)
loedu_w2 (loeces)
bmi30_w2 (b30ces)
bmi20_w2 (b20ces);
cesd6_w6 ON cesd6_w4 (cesces)
pf_w4 (pfces)
sex (sexces)
age_w2 (ageces)
cd14_w2 (cdces)
allo_w2 (allces)
smo_w2 (smoces)
alc_w2 (alcces)
pssu_w2 (pssces)
psin_w2 (psices)
lowth_w2 (lowces)
loedu_w2 (loeces)
bmi30_w2 (b30ces)
bmi20_w2 (b20ces);
cogni_w3 ON cogni_w2 (cogcog)
pf_w2 (pfcog)
sex (sexcog)
age_w2 (agecog)
cd14_w2 (cdcog)
allo_w2 (allcog)
smo_w2 (smocog)
alc_w2 (alccog)

```
  pssu_w2 (psscog)
  psin_w2 (psicog)
  lowth_w2 (lowcog)
  loedu_w2 (loecog)
  bmi30_w2 (b30cog)
  bmi20_w2 (b20cog);
  cogni_w4 ON cogni_w3 (cogcog)
  pf_w4 (pfcog)
  sex (sexcog)
  age_w2 (agecog)
  cd14_w2 (cdcog)
  allo_w2 (allcog)
  smo_w2 (smocog)
  alc_w2 (alccog)
  pssu_w2 (psscog)
  psin_w2 (psicog)
  lowth_w2 (lowcog)
  loedu_w2 (loecog)
  bmi30_w2 (b30cog)
  bmi20_w2 (b20cog);
  lowpa_w2 WITH cesd6_w2 cogni_w2;
  cesd6_w2 WITH cogni_w2;
  lowpa_w4 WITH cesd6_w4 cogni_w3;
  cesd6_w4 WITH cogni_w3;
  lowpa_w6 WITH cesd6_w6 cogni_w4;
  cesd6_w6 WITH cogni_w4;
  [cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2
  lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2 cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4];
  Model constraint:
  new (IND1 IND2 IND3);
  IND1 = (pflop*lopadl);
  IND2 = (pfces*cesadl);
  IND3 = (pfcog*cogadl);
Output:
  stand sampstat cinterval tech4;
```

! The suffixes, _w2, _w3, _w4, and _w6 indicate that variables are measured at waves 2, 3, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease (standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support (standardized); psin = poor social integration (standardized); lowpa = low physical activity (standardized); cesd6 = depressive symptoms (standardized); cogni = cognitive impairment (standardized); pf = physical frailty factor score (standardized); badl6 = number of basic activities of daily living items performed with difficulty;

! Stratification by gender and age group are as for Model 1.

! **Model 4**

! For stratification by poor social support, and poor social integration, the corresponding binary variables (using means as the cut-off values) are created and used in place of age group (as in Model 3).

! Sensitivity analyses including exposure-mediator interaction

! Additional variables for interaction of physical frailty with mediators (low physical activity, depressive symptoms, and cognitive impairment) are created and included in the prediction of activity limitation.

! Sensitivity analyses using phantom variables

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty, while
implementing sensitivity analyses using phantom variables
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  sex (sexadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl)
  u1@x;
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  sex (sexadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl)
```

```
  u2@x;
  pf_w4 ON pf_w2 (pfpf)
  badl6_w2 (adlpf)
  sex (sexpf)
  age_w2 (agepf)
  cd14 (cdpf)
  allo (allpf)
  bmi30_w2 (b30pf)
  bmi20_w2 (b20pf)
  smo_w2 (smopf)
  alc_w2 (alcpf)
  lowth_w2 (lowpf)
  loedu_w2 (loepf)
  pssu_w2 (psspf)
  psin_w2 (psipf)
  u1@y;
  pf_w6 ON pf_w4 (pfpf)
  badl6_w4 (adlpf)
  sex (sexpf)
  age_w2 (agepf)
  cd14 (cdpf)
  allo (allpf)
  bmi30_w2 (b30pf)
  bmi20_w2 (b20pf)
  smo_w2 (smopf)
  alc_w2 (alcpf)
  lowth_w2 (lowpf)
  loedu_w2 (loepf)
  pssu_w2 (psspf)
  psin_w2 (psipf)
  u2@y;
  badl6_w4 WITH badl6_w6 pf_w4;
  pf_w6 WITH pf_w4 badl6_w6;
  u1 BY;
  u1@1;
  u2 BY;
  u2@1;
  u2 ON u1;
  u1 WITH age_w2@0 sex@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 pssu_w2@0 psin_w2@0
  lowth_w2@0 loedu_w2@0 bmi30_w2@0 bmi20_w2@0;
  u2 WITH age_w2@0 sex@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 pssu_w2@0 psin_w2@0
  lowth_w2@0 loedu_w2@0 bmi30_w2@0 bmi20_w2@0;
  [cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w4, and _w6 indicate that variables are measured at waves 2, 4, and 6 respectively.
```

! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease (standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support (standardized); psin = poor social integration (standardized); pf = physical frailty factor score (standardized); badl6 = number of basic activities of daily living items performed with difficulty; u1, u2 = phantom variables;

! x = equivalent to multiples of the effect of the strongest predictor (other than physical frailty) on activity limitation; y = correlation between u and physical frailty;

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty with indiect
effects through low physical activity, depressive symptoms, and cognitive impairment, while implementing
sensitivity analyses using phantom variables
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6 lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2
    cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6 lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2
    cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4;
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl)
  u1@x;
  badl6_w6 ON badl6_w4 (adladl)
  pf_w4 (pfadl)
  age_w2 (ageadl)
  sex (sexadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
```

psin_w2 (psiadl);
u2@x;
pf_w4 ON pf_w2 (pfpf)
badl6_w2 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf)
u1@y;
pf_w6 ON pf_w4 (pfpf)
badl6_w4 (adlpf)
age_w2 (agepf)
sex (sexpf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf)
u2@y;
badl6_w4 WITH badl6_w6 pf_w4;
pf_w6 WITH pf_w4 badl6_w6;
lowpa_w4 ON lowpa_w2 (loplop)
pf_w2 (pflop)
sex (sexlop)
age_w2 (agelop)
cd14_w2 (cdlop)
allo_w2 (alllop)
smo_w2 (smolop)
alc_w2 (alclop)
pssu_w2 (psslop)
psin_w2 (psilop)
lowth_w2 (lowlop)
loedu_w2 (loelop)
bmi30_w2 (b30lop)

bmi20_w2 (b20lop)
u1@z1;
lowpa_w6 ON lowpa_w4 (loplop)
pf_w4 (pflop)
sex (sexlop)
age_w2 (agelop)
cd14_w2 (cdlop)
allo_w2 (alllop)
smo_w2 (smolop)
alc_w2 (alclop)
pssu_w2 (psslop)
psin_w2 (psilop)
lowth_w2 (lowlop)
loedu_w2 (loelop)
bmi30_w2 (b30lop)
bmi20_w2 (b20lop)
u2@z1;
cesd6_w4 ON cesd6_w2 (cesces)
pf_w2 (pfces)
sex (sexces)
age_w2 (ageces)
cd14_w2 (cdces)
allo_w2 (allces)
smo_w2 (smoces)
alc_w2 (alcces)
pssu_w2 (pssces)
psin_w2 (psices)
lowth_w2 (lowces)
loedu_w2 (loeces)
bmi30_w2 (b30ces)
bmi20_w2 (b20ces)
u1@z2;
cesd6_w6 ON cesd6_w4 (cesces)
pf_w4 (pfces)
sex (sexces)
age_w2 (ageces)
cd14_w2 (cdces)
allo_w2 (allces)
smo_w2 (smoces)
alc_w2 (alcces)
pssu_w2 (pssces)
psin_w2 (psices)
lowth_w2 (lowces)
loedu_w2 (loeces)
bmi30_w2 (b30ces)
bmi20_w2 (b20ces)
u2@z2;

cogni_w3 ON cogni_w2 (cogcog)
pf_w2 (pfcog)
sex (sexcog)
age_w2 (agecog)
cd14_w2 (cdcog)
allo_w2 (allcog)
smo_w2 (smocog)
alc_w2 (alccog)
pssu_w2 (psscog)
psin_w2 (psicog)
lowth_w2 (lowcog)
loedu_w2 (loecog)
bmi30_w2 (b30cog)
bmi20_w2 (b20cog)
u1@z3;
cogni_w4 ON cogni_w3 (cogcog)
pf_w4 (pfcog)
sex (sexcog)
age_w2 (agecog)
cd14_w2 (cdcog)
allo_w2 (allcog)
smo_w2 (smocog)
alc_w2 (alccog)
pssu_w2 (psscog)
psin_w2 (psicog)
lowth_w2 (lowcog)
loedu_w2 (loecog)
bmi30_w2 (b30cog)
bmi20_w2 (b20cog)
u2@z3;
lowpa_w2 WITH cesd6_w2 cogni_w2;
cesd6_w2 WITH cogni_w2;
lowpa_w4 WITH cesd6_w4 cogni_w3;
cesd6_w4 WITH cogni_w3;
lowpa_w6 WITH cesd6_w6 cogni_w4;
cesd6_w6 WITH cogni_w4;
u1 BY;
u1@1;
u2 BY;
u2@1;
u1 WITH age_w2@0 sex@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 pssu_w2@0 psin_w2@0
lowth_w2@0 loedu_w2@0 bmi30_w2@0 bmi20_w2@0;
u2 WITH age_w2@0 sex@0 cd14_w2@0 allo_w2@0 smo_w2@0 alc_w2@0 pssu_w2@0 psin_w2@0
lowth_w2@0 loedu_w2@0 bmi30_w2@0 bmi20_w2@0;
u2 ON u1;
[cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2
lowpa_w2 lowpa_w4 lowpa_w6 cesd6_w2 cesd6_w4 cesd6_w6 cogni_w2 cogni_w3 cogni_w4];

```
  Model constraint:
  new (IND1 IND2 IND3);
  IND1 = (pflop*lopadl);
  IND2 = (pfces*cesadl);
  IND3 = (pfcog*cogadl);
Output:
  stand sampstat cinterval tech4;
```

! The suffixes, _w2, _w3, _w4, and _w6 indicate that variables are measured at waves 2, 3, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease (standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support (standardized); psin = poor social integration (standardized); lowpa = low physical activity (standardized); cesd6 = depressive symptoms (standardized); cogni = cognitive impairment (standardized); pf = physical frailty factor score (standardized); badl6 = number of basic activities of daily living items performed with difficulty; u1, u2 = phantom variables;

! x = equivalent to multiples of the effect of the strongest predictor (other than physical frailty) on activity limitation; y = correlation between u and physical frailty; z1 = equivalent to multiples of the effect of the strongest predictor (other than physical frailty) on low physical activity; z2 = equivalent to multiples of the effect of the strongest predictor (other than physical frailty) on depressive symptoms; z3 = equivalent to multiples of the effect of the strongest predictor (other than physical frailty) cognitive impairment;

! Sensitivity analyses using negative binomial regression

```
Title: Autoregressive cross-lagged model for prediction of activity limitation by physical frailty using
negative binomial regression
Data: File is physical frailty3.dat;
Variable:
  Names are
    id badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Usevariables are
    badl6_w2 badl6_w4 badl6_w6 age_w2 sex cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2
    lowth_w2 loedu_w2 pssu_w2 psin_w2 pf_w2 pf_w4 pf_w6;
  Count are
    badl6_w2 (nbi) badl6_w4 (nbi) badl6_w6 (nbi);
  Missing are ALL (-9999);
Analysis:
  Algorithm = integration;
  Integration = montecarlo;
  Estimator = mlr;
Model:
  badl6_w4 ON badl6_w2 (adladl)
  pf_w2 (pfadl)
  sex (sexadl)
  age_w2 (ageadl)
  cd14 (cdadl)
  allo (alladl)
  bmi30_w2 (b30adl)
  bmi20_w2 (b20adl)
  smo_w2 (smoadl)
  alc_w2 (alcadl)
  lowth_w2 (lowadl)
  loedu_w2 (loeadl)
  pssu_w2 (pssadl)
  psin_w2 (psiadl);
  badl6_w4#1 ON badl6_w2 (adladl1)
  pf_w2 (pfadl1)
  sex (sexadl1)
  age_w2 (ageadl1)
  cd14 (cdadl1)
  allo (alladl1)
  bmi30_w2 (b30adl1)
  bmi20_w2 (b20adl1)
  smo_w2 (smoadl1)
  alc_w2 (alcadl1)
  lowth_w2 (lowadl1)
  loedu_w2 (loeadl1)
  pssu_w2 (pssadl1)
  psin_w2 (psiadl1);
```

badl6_w6 ON badl6_w4 (adladl)
pf_w4 (pfadl)
sex (sexadl)
age_w2 (ageadl)
cd14 (cdadl)
allo (alladl)
bmi30_w2 (b30adl)
bmi20_w2 (b20adl)
smo_w2 (smoadl)
alc_w2 (alcadl)
lowth_w2 (lowadl)
loedu_w2 (loeadl)
pssu_w2 (pssadl)
psin_w2 (psiadl);
badl6_w6#1 ON badl6_w4 (adladl1)
pf_w4 (pfadl1)
sex (sexadl1)
age_w2 (ageadl1)
cd14 (cdadl1)
allo (alladl1)
bmi30_w2 (b30adl1)
bmi20_w2 (b20adl1)
smo_w2 (smoadl1)
alc_w2 (alcadl1)
lowth_w2 (lowadl1)
loedu_w2 (loeadl1)
pssu_w2 (pssadl1)
psin_w2 (psiadl1);
pf_w4 ON pf_w2 (pfpf)
badl6_w2 (adlpf)
sex (sexpf)
age_w2 (agepf)
cd14 (cdpf)
allo (allpf)
bmi30_w2 (b30pf)
bmi20_w2 (b20pf)
smo_w2 (smopf)
alc_w2 (alcpf)
lowth_w2 (lowpf)
loedu_w2 (loepf)
pssu_w2 (psspf)
psin_w2 (psipf);
pf_w6 ON pf_w4 (pfpf)
badl6_w4 (adlpf)
sex (sexpf)
age_w2 (agepf)
cd14 (cdpf)

```
  allo (allpf)
  bmi30_w2 (b30pf)
  bmi20_w2 (b20pf)
  smo_w2 (smopf)
  alc_w2 (alcpf)
  lowth_w2 (lowpf)
  loedu_w2 (loepf)
  pssu_w2 (psspf)
  psin_w2 (psipf);
  badl6_w4 WITH badl6_w6 pf_w4;
  pf_w6 WITH pf_w4 badl6_w6;
  [cd14_w2 allo_w2 bmi30_w2 bmi20_w2 smo_w2 alc_w2 lowth_w2 loedu_w2 pssu_w2 psin_w2];
Output:
  stand sampstat cinterval tech4;

! The suffixes, _w2, _w4, and _w6 indicate that variables are measured at waves 2, 4, and 6 respectively.
! id = identification number; age = age (standardized); sex = gender; cd14 = chronic disease
(standardized); allo = allostatic load (standardized); smo = smoking; alc = high alcohol intake; lowth = low
wealth; loedu = low education; bmi30 = obesity; bmi20 = underweight; pssu = poor social support
(standardized); psin = poor social integration(standardized); pf = physical frailty factor score
(standardized); badl6 = number of basic activities of daily living items performed with difficulty;
```