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Exploring Frailty and Cognitive Functioning Trajectories in Later Life

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Declaration

I declare that I have composed this thesis and that the work has not been submitted for any other degree or professional qualification. I confirm that all work submitted is my own, except for sections which have included parts of co-authored publications. Contributions to co-authored work is indicated below. I confirm that I have acknowledged the work of others where this has been referenced within this thesis. The work in this thesis has not been submitted for any other degree or professional qualification.

The commentary referenced in Chapter 1 was previously published in *International Psychogeriatrics* as “A pragmatic tool to identify aspects of frailty”, by Tom Russ (supervisor) and Miles Welstead (student). Conception of the commentary: TR. Drafted the paper: TR, **MW**. Revised the paper: TR. Approved the final version of the paper: TR, **MW**

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During my PhD studies, I have also contributed to the following publications which are referenced throughout the thesis:

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psychosocial variables during COVID-19 lockdown: Evidence from the Lothian Birth Cohort 1936. *International journal of environmental research and public health*, 18(1), 210.

Corley, J., Okely, J. A., Taylor, A. M., Page, D., **Welstead**, M., Skarabela, B., ... & Russ, T. C. (2021). Home garden use during COVID-19: Associations with physical and mental wellbeing in older adults. *Journal of environmental psychology*, 73, 101545.

Taylor, A. M., Page, D., Okely, J. A., Corley, J., **Welstead**, M., Skarabela, B., ... & Cox, S. R. (2021). Impact of COVID-19 lockdown on psychosocial factors, health, and lifestyle in Scottish octogenarians: the Lothian Birth Cohort 1936 Study. *Plos one*, 16(6), e0253153.

Gregory, S., Killin, L., Pullen, H., Dolan, C., Hunter, M., **Welstead**, M., Ritchie, CW. (2021) Public attitudes to the use of routinely and non-routinely collected healthcare data in dementia and brain health research. *JMIR Preprints*. 03/06/2021:30918

Baranyi, G., **Welstead**, M., Corley, J., Deary, I., Muniz-Terrera, G., Redmond, P., . . Pearce, J. (2021). Is life-course neighbourhood deprivation associated with frailty and frailty progression from age 70 to 82 in the Lothian Birth Cohort 1936? *medRxiv*, 2021.2009.2003.21263087. doi:10.1101/2021.09.03.21263087

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Mullin, D. S., Cockburn, A., **Welstead**, M., Russ, T. C., Luciano, M., Muniz-Terrera, G. (2021) Motoric cognitive risk: A systematic prognostic review and meta-analysis of longitudinal cohort studies of older adults. *Accepted for publication in Alzheimer's and Dementia.*

Mendis, S., Tan, M., **Welstead**, M., Muniz-Terrera, G., Russ, T. C. Socioeconomic status and adult structural brain imaging: a systematic review of life course epidemiology studies. *Manuscript being finalised.*

Chapter 6.3 references an ongoing consortia project that I contributed to as part of the neuroCHARGE working group

Signed,

Miles Welstead

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Abstract

Understanding the ageing process in later life is a crucial step in identifying those at highest risk of health decline, and in implementing effective prevention and treatment strategies. However, measuring the ageing process is a complex and divisive issue. As chronological age does not necessarily capture the vast heterogeneity of older age, we require the development of quantifiable health states. This thesis explored two of these states: Frailty and mild cognitive impairment. A consensus on the concept of frailty and how it should be measured remains elusive; however, it is generally understood to describe a state of higher vulnerability to adverse events such as disease, disability, dementia, and death. Mild cognitive impairment (MCI) is a health state that describes a borderland between normal cognitive functioning and dementia, exhibited by mild subjective and objective cognitive impairments but a retained independency and ability to undertake activities of daily living. This thesis explored later life ageing trajectories using these health states and ultimately sought to provide a foundation for further research and clinical care to build upon.

The first study acts as an introduction to the concept of frailty by conducting a systematic review of publications that explore frailty trajectories. After screening 8,318 publications, 25 met the eligibility criteria. Findings showed that the field has a considerable degree of heterogeneity in how studies measure frailty, the statistics they use to interpret their results, and the types of populations they sample. Despite this, some valuable conclusions can be made: as expected, frailty increases with age, and these increases are consistently associated with certain factors such as socioeconomic factors, social support, physical activity, and brain pathologies. I conclude that more longitudinal research is required in the field, specifically research that compares and contrasts the ways in which frailty is quantified.

The second study investigated the association between chronic inflammation and frailty trajectories in the Lothian Birth Cohort 1936. Using two common measures (Frailty index and Fried phenotype) and two blood-based inflammatory biomarkers (Fibrinogen and C-reactive protein), frailty is tracked over approximately 12 years. Findings showed that Fibrinogen was significantly associated with higher baseline Frailty index score (β = 0.011, 95% CI [0.002, 0.020], $p < .05$). Additionally, over the 12-year follow-up, higher baseline C-reactive protein (β = 0.001, 95% CI [0.000, 0.002], $p < .05$) and Fibrinogen (β = 0.004, 95% CI [0.001, 0.007], $p < .05$) were both significantly associated with increased Frailty index change. For the Fried phenotype, higher baseline inflammation biomarkers were associated with higher baseline frailty status ($p < .001$), but there were no significant associations over the 12-year follow-up. Accordingly, inflammation appeared to be associated with higher rates of frailty over time but the way in which you measure frailty can affect this association.

The third study aimed to explore the heterogeneity of frailty trajectories and account for the probability that not all individuals follow the same path. Using a quadratic latent class mixed model, subpopulations of frailty trajectories were identified over approximately 12 years in the Lothian Birth Cohort 1936. Analyses revealed three classes of frailty trajectories which begin at different intercepts and follow different slopes: Low (61%, $n = 632$), Medium (36%, $n = 368$), or High (3%, $n = 28$). Those in the Low class were younger, had higher education, higher age 11 cognitive ability, and were from a higher social class when compared to those in either Medium or High classes. These findings help to demonstrate the heterogeneous nature of frailty progression and indicate that not all older adults will follow a similar path. This has clinical implications for identifying those on steeper trajectories and implementing effective prevention strategies.

The fourth study shifted focus to the cognitive aspects of later life decline by exploring the health state known as mild cognitive impairment or MCI. This study introduced the concept and detailed how it was coded and implemented in the Lothian Birth Cohort 1936. MCI is implemented at three

waves of the cohort at ages 76 (*n* = 567), 79 (*n* = 441), and 82 years (*n* = 341). In line with similar cohorts, rates of MCI showed an increase at each wave between 76 and 82 years from 15% to 18%. Additionally, two subtypes of MCI were derived: amnestic, which solely considered memory related cognitive decline, and non-amnestic, which considered non-memory related cognitive impairments (executive function, attention, language, and visuospatial skills). These subtypes also showed increases over time in the cohort, however, the non-amnestic subtype showed rates that were higher than expected compared to similar cohorts. This study highlighted the prevalence of MCI in the Lothian Birth Cohort 1936 and opened the door for further study of cognitive ageing trajectories.

The fifth and final study considered transitions in MCI status and the factors that may be associated with these changes in the Lothian Birth Cohort 1936. Progressions and reversions in MCI status between the ages of 76 and 82 years were assessed. At age 76, 14% of the sample had MCI, compared to 19% at age 82. Findings showed that over the six-year period, 74% remained cognitively healthy, 12% transitioned to MCI, 7% reverted to healthy cognition, and 7% maintained their baseline MCI status. Multinomial logistic regression analysis indicated that these transitions are affected by factors including age, cardiovascular disease, and number of depressive symptoms. This study illustrates the volatility of cognitive states in later life and highlights several factors, including depression, which may be associated with these changes.

This thesis provided an exploration of the ageing process by considering the trajectories of frailty and MCI in the Lothian Birth Cohort 1936. The findings contribute to an expanding field of longitudinal research, which hopes to understand how health statuses like frailty and MCI change over time, and the salient factors associated with these changes. Incremental advances like those seen in the studies in this thesis allow for a better understanding of how the ageing process affects us in later life, ultimately leading to better prevention strategies and interventions that allow every individual to follow their healthiest ageing trajectory.

Lay Summary

Understanding how and why we age is an important step in improving and maintaining quality of life for older people. Research into ageing can benefit greatly from studies of the health of individuals at multiple periods over time. By doing so, we are able to map out the health trajectories that people follow and assess why certain people are more at risk of decline than others. Accordingly, for this thesis I utilised the Lothian Birth Cohort 1936, which is a study made up of participants who were all given the same intelligence test at age 11 in 1947. Subsequently, they were re-contacted in the early 2000s and given a series of mental and physical tests. These tests were repeated every three years, bringing a current total of five data time points. This study of older adults provided a valuable dataset upon which the studies in this thesis are based.

Measuring health declines related to the ageing process can be difficult and therefore, in research and clinical care it is common to use concepts that can detect individuals with physical and mental health deterioration. Understanding how and why these concepts change over time gives us greater insight into how we can help prevent the health declines associated with ageing, and even help to reverse some of the declines that have taken effect. This thesis focussed on two of these concepts: frailty and mild cognitive impairment.

Frailty refers to a concept designed to capture someone's risk of adverse events; someone with a high level of frailty is more likely to be affected by disease, disability, or death. This thesis began by summarising what is currently known in the research literature about how and why frailty changes over time. Findings showed that frailty tends to increase as people age, and that these increases are associated with several factors such as how much social support a person has, their physical activity levels, financial status, and their social class. I conclude that further research is needed to better understand the paths of frailty in later life.

Next, two studies were conducted into frailty using the Lothian Birth Cohort 1936. The first of the studies used two different ways of measuring frailty and explored the relationship between frailty and inflammation in the body. Somewhat mixed results showed that the associations between frailty and inflammation differed according to the way in which frailty was measured. As a result, a more consistent way of measuring frailty is needed, until that time, researchers should use multiple ways of measuring frailty to allow for comparisons and ensure that not everything is dependent on one measure. The second frailty study explored individual differences in frailty change over time. Findings showed that in the Lothian Birth Cohort 1936 not all individuals follow the same rate of frailty change over time. Analyses showed that the cohort has three groups of individuals who tend to follow the same path of frailty over time. Further inspection of these three groups revealed that those on the steepest and most harmful trajectory of frailty were older, had lower education, lower age 11 cognitive ability, and were from a lower social class. Accordingly, frailty can affect different groups of individuals in different ways and it is important for healthcare plans to consider this when identifying those at highest risk of health decline.

The second section of this thesis explored a concept known as mild cognitive impairment - or MCI - that describes the middle ground between healthy brain function and dementia. Using previously published guidelines, I developed a measure in the Lothian Birth Cohort 1936 that allowed the identification of participants with MCI. As expected, rates of MCI increased as participants got older. I then looked at the changes in MCI over time and found that it was relatively common for participants to fluctuate between healthy brain functioning and an MCI state. These shifts were associated with various factors including age, cardiovascular disease, and depression. MCI could be a useful way of identifying people at high risk of further decline, but it is important to understand the factors that are associated with risk of fluctuations in brain function.

This thesis aimed to provide more detail into the health trajectories of later life, with a particular focus on exploring the factors that lead some people to decline faster than others. Thesis findings showed that the use of frailty and MCI can be fraught with uncertainty and inconsistency, but despite this, they can provide great insight into the ageing process. Future research will invariably continue to unearth more information about ageing and work towards the development of interventions that improve later life health trajectories.

Contents Table

List of Abbreviations

AIC	Akaike information criterion
aMCI	Amnestic mild cognitive impairment
APOE ε4	Apolipoprotein epsilon 4
BIC	Bayesian information criterion
BMI	Body mass index
CaMos	Canadian Multicentre Osteoporosis Study
CI	Confidence interval
CRP	C-reactive protein
ELSA	English Longitudinal Study of Ageing
FI	Frailty index
GEE	Generalized estimating equations
GLOW	Global Longitudinal Study of Osteoporosis in Women 3-Year Hamilton Cohort
GP	General practitioner
GWAS	Genome-wide association study
HADS-D	Hospital Anxiety and Depression Scale
HRS	Health and Retirement Study
IANA-IAGG	International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics
IL-6	Interleukin 6
LASA	Longitudinal Aging Study Amsterdam
LBC1936	Lothian Birth Cohort 1936
MAP	Memory and Aging Project
MCI	Mild cognitive impairment
MHT	Moray House Test
MMSE	Mini mental state examination
NaMCI	Non-amnestic mild cognitive impairment
NIA-AA	National Institute on Aging-Alzheimer's Association
NOS	Newcastle–Ottawa scale

OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROS	Religious Orders Study
SHARE	Survey of Health Aging and Retirement in Europe
SMS	Scottish Mental Survey
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

Chapter 1: Introduction

This doctoral thesis explored the trajectories of ageing in later life, with a particular focus on frailty and mild cognitive impairment. It investigated the disparities of ageing trajectories and aimed to home in on why certain individuals show steeper rates of decline compared to others. Moreover, it intended to assess whether there are factors associated with age-related decline that may be able to inform prevention measures and interventions.

The opening chapter outlines the aims of the thesis. First, a broad overview is given of the current issues faced within the field of ageing research and the importance of tackling the many hurdles that we continue to encounter. Frailty and cognitive impairment are introduced as major themes, and the role of longitudinal research is presented as a tool for addressing these issues.

The chapter introduces the complexities of how frailty is operationalised. More detail is then given as to how the various ways in which frailty can be quantified. Finally, focus is given to the two most widespread measures; the Frailty index and the Fried phenotype.

Mild cognitive impairment (MCI) is then introduced as a different way of quantifying age-related decline. The concept is described and there is discussion of some of the most recent research in this field.

Parts of our commentary on the use of frailty tools previously published in *International Psychogeriatrics* are incorporated into this chapter (Russ & Welstead, 2020).

1.1 Overview of ageing and the role of research

Compared to centuries past, humans have seen a substantial increase in life expectancy, largely attributable to the creation of vaccines, improved diets, more hygienic living conditions, and general advances in the field of medicine

(Vardell, 2020). Now, more than any time throughout history, humans are more likely to live for longer and experience a relatively healthy life. However, over the past century, the double-edged nature of these advancements has become increasingly evident.

Population ageing, which describes the increasing proportion of older people in a population, is existent in most countries around the world. The United Nations projects that over two billion people aged 60 and over will be alive in 2050 (Mba, 2010; United Nations, 1985). These dramatic demographic shifts have major ramifications, one of which is the increasing diagnosis rates of dementia. The global public health crisis of dementia poses a challenge that the scientific and medical field have grappled with for decades, with a frustrating lack of success (Schneider, 2020; Zeisel, Bennett, & Fleming, 2020). The physical and mental toll that dementia and other age-related brain diseases can take on an individual and their friends and relatives can be devastating (Epstein-Lubow, 2014). Equally, the economic cost for health care to accommodate an exponentially growing proportion of older adults affected by age-related disease is significant. In 2015, the worldwide cost of dementia was estimated to be approximately $818 billion US dollars (World Health Organization, 2019). Accordingly, the individual and global impact that an ageing population has had, and will continue to have in the future, is substantial.

Tackling these critical issues can be partially achieved with the implementation of high quality scientific research, which explores the complex processes of ageing and identifies the salient factors associated with age-related health deterioration. Considering the web of underlying processes affecting the health of older adults, extensive research is required to decipher the intricacies of ageing. This will subsequently provide insights into the most effective ways to combat decline, ultimately paving the way for healthier ageing. One way in which to quantify the process of ageing is through a health state known as frailty.

1.2 What is frailty, and is it preventable?

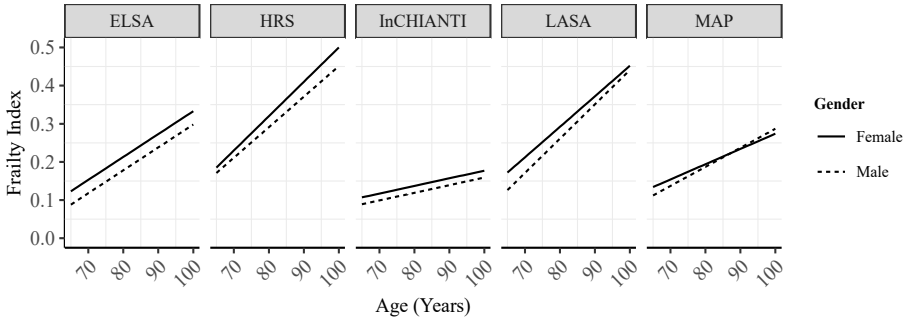
There are a plethora of health conditions that become increasingly prevalent in later life (Jaul & Barron, 2017). Due to population ageing there are more people reaching older age, and accordingly, there is an increase in discrepancy between lifespan, which describes the number of years an individual lives, and healthspan, the number of years an individual lives free from disability and disease (Sathyan & Verghese, 2020). Without research and novel solutions, this discrepancy and the prevalence of these age-related health conditions will continue to increase exponentially in the future. The health issues affecting older adults are complex, with myriad risk and causal factors that are difficult to disentangle, and whilst the process of ageing is universal, the factors affecting individuals are not uniform. However, in general, older adults are at risk of increases in physical and mental decline (Jaul & Barron, 2017).

One way to define such increased vulnerability to health deterioration is through the concept of frailty. The presence of the word frailty in the English language has a long history dating back to the 14th century as a description of entities or concepts that exhibit weakness and vulnerability (Collins English Dictionary, 2021). Use of the word was particularly common throughout English literature, such as the infamous and distinctly politically incorrect soliloquy from Hamlet, ‘Frailty, thy name is woman!’ (Shakespeare, 2007). In more recent times, the word frailty has become increasingly linked to a way of describing the human condition, and for more than two decades it has been recognised in the clinical and research field as a geriatric syndrome (Mekli et al., 2018).

Frailty is a distinct entity which can lead to an increased vulnerability to disease, disability, and death (Lang, Michel, & Zekry, 2009). Furthermore, it is widely accepted that frailty is not defined by one single symptom, rather it is a syndrome (Lang et al., 2009). However, there remains considerable divergence of opinion as to how frailty should be measured. The core issue of these debates stems from whether frailty should be measured using solely

physical attributes, or whether it in fact should encompass a range of health domains including mental and physical healthiness, and cognitive impairment. This has led there to be two main schools of thoughts, that of a physical frailty which is solely concerned with physical health deficits, and a multidimensional frailty that takes a more holistic approach by seeing frailty as an accumulation of deficits covering a range of health domains (Fried et al., 2001; Mitnitski, Mogilner, & Rockwood, 2001). Whilst some argue that frailty is a singular condition, others contend that a physical frailty and an accumulation of deficits frailty are distinct entities (Cesari, Gambassi, Abellan van Kan, & Vellas, 2013). However, frailty is typically treated as a singular concept, which has caused concern due to the potential for conflating distinct conditions under the same frailty banner. Future research is required to address this by comparing and contrasting the different ways of quantifying frailty to work towards a more refined operational definition. Chapter 4 of this thesis contributes to this process by contrasting a physical and multidimensional frailty measure in the same study.

Another way of establishing a better understanding of what frailty entails is to measure it over time to identify the factors that may influence frailty change. It has been well established that frailty changes over time, and that these changes are not consistent across different groups of individuals. For example, a forthcoming study which I contributed to the research design of, analyses five independent cohorts using a coordinated analytical approach to evaluate longitudinal frailty changes as assessed by a accumulation of deficits frailty measurement tool (Jenkins, Hoogendijk, et al., 2021). As shown in Figure 1.1, frailty progresses over time but each cohort has a different trajectory, indicating that there are factors such as sex, age, and education affecting this progression.



ELSA: English Longitudinal Study of Ageing; **InCHIANTI**: Invecchiare in Chianti; **HRS**: Health and Retirement Study; **LASA**: Longitudinal Aging Study Amsterdam; **MAP**: Memory and Aging Project

Figure 1.1: Graphical representation of the estimated model trajectory across several different cohorts by gender (Jenkins, Hoogendijk, et al., 2021)

Understanding the factors that may affect frailty change is imperative to develop targeted prevention strategies. One major factor which this thesis took into consideration is that of cognitive impairment, which has been connected as a risk factor and as an outcome of frailty within a cycle of decline (Robertson, Savva, & Kenny, 2013; Searle & Rockwood, 2015). Accordingly, this thesis explored the role of cognitive impairment both as part of the frailty definition, and as a distinct entity in the form of mild cognitive impairment.

1.3 How can frailty be measured?

With an ageing population, an improved understanding of how frailty develops and changes over time, and its impact on various outcomes, is crucial to optimise health trajectories in later life (Hoogendijk et al., 2017). Exploring these changes over time requires a frailty measurement tool. However, an issue with conducting any frailty research is choosing and justifying the way in which you measure frailty. Whilst many frailty measurement tools exist and are used frequently in clinical and research settings according to the subjective preference of the clinician or researcher, there remains divergence in opinion as to what frailty actually entails, and

subsequently how it should be quantified (Aguayo et al., 2017). There has been consensus in some areas, particularly when it comes to the notion of a solely physical frailty. In 2013, a paper was published with delegates from six major international frailty groups, which, despite differences in opinion in some areas, came to four major consensus points on the phenomenon of physical frailty (Morley et al., 2013). Firstly, it was agreed that physical frailty should be considered a medical syndrome, one which has various causes and which is characterised by a reduction in strength, endurance, and physiological function, which all contribute to a higher risk of increased dependency and/or death. Secondly, consensus was met on the notion that physical frailty is preventable and treatable with certain prevention strategies or interventions. Thirdly, there are existing ways in which physical frailty can be measured, subsequently allowing clinicians to identify those who are deemed frail. Fourthly, the group concluded that to help reduce prevalence of frailty all those over the age of 70 years old, and all those with a significant degree of weight loss as a result of a chronic disease should be screened for physical frailty.

Accordingly, it has been possible to reach some agreement in the field, albeit, only in regard to the notion of physical frailty, rather than a frailty which encompasses other factors. Major differences in opinion remain between those who regard frailty as a uniquely physical syndrome and those who consider frailty to be multidimensional, incorporating not only physical vulnerability, but also other domains such as psychological functioning and social conditions (Dolenc & Rotar-Pavlič, 2019). Despite these operational differences, attempts to quantify frailty are common, with numerous scales and measures being created and implemented as research and clinical tools (Russ & Welstead, 2020). As noted by Wallace, McGarrigle, Rockwood, Andrew, and Theou (2020), over 65 frailty measurement tools have been identified that are currently in use, a surplus which only goes to illustrate the divergence in the field. Furthermore, studies investigating the results of eight common frailty scales found that frailty prevalence in a particular population

varied from 6.1% to 43.9%, depending on the instrument used (Theou, Brothers, Mitnitski, & Rockwood, 2013).

Due to the lack of a definitive definition of frailty, there is not currently no ‘gold standard’ measurement tool. Accordingly, clinicians in primary care tend to use tools according to personal preference and practicality. Reports find that just under 65% of physicians use more than one frailty measurement tool in their practice (Bruyère et al., 2017). In terms of the differences between research and clinical settings, clinicians may give preference to frailty measurement tools that incorporate an element of social vulnerability. Being able to identify those in a vulnerable care situation can be incredibly valuable to a clinician but perhaps less so to a researcher. This lack of consistency makes the standardisation of frailty measurement particularly difficult.

This lack of consistency makes the standardisation of frailty measurement particularly difficult. Ultimately, the goal of research is to reach a consensus on how best to operationalise frailty in different settings. However, realistically a universally accepted gold standard frailty tool is unlikely, and it may be that future research is best placed to standardise frailty tools for different types of use (eg. clinical vs research). A key step in this endeavour is to assess what we know about the current ways of measuring frailty and how they compare to each other. This will allow for clear information on the practicality of the major frailty tools to make it easier for researchers and clinicians to make an informed choice. There are so many examples of frailty scales used around the world that detailing them all in this thesis would be impractical. Accordingly, here I highlight the two most widely used measures: the Frailty index (Mitnitski et al., 2001; Rockwood & Mitnitski, 2007) and the Fried phenotype (Fried et al., 2001). These two instruments differ both in theory and in practice and illustrate the major differences in the field. Both measures are detailed below.

Frailty Index

The Frailty index (FI) was developed as a proxy for frailty by measuring the accumulation of age-related conditions, disorders, and disabilities (Mitnitski et

al., 2001; Rockwood & Mitnitski, 2007). The accumulation of deficits FI approach can be used to quantify individual variation in frailty related deficits sensitively (Chamberlain, Sauver, et al., 2016). It is recommended that 30 to 40 variables are chosen from several organ systems (physical capabilities, cognitive status, psychological functioning, and chronic health conditions) to optimise the validity of the index (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). Variables are chosen which reflect deficits that generally increase in older age and a FI score between 0 and 1 is calculated. This is achieved by calculating the number of deficits in a particular individual divided by the total number of deficits measured. For example, if 30 deficits were measured and an individual has 15 of those deficits present, then their FI score would be 15 ÷ 30 = 0.5. Typically studies have found that an upper limit to the FI exists whereby no individuals score higher than 0.65 - 0.7 at which point death occurs (Armstrong, Mitnitski, Launer, White, & Rockwood; Rockwood & Mitnitski, 2007). The use of a FI is somewhat divisive due to the subjectivity involved whereby users are able to choose which deficits are included in its composition. FI scores are created according to detailed instructions and rules which dictate the type and approximate number of deficits to include (Searle et al., 2008). Accordingly, researchers are able to choose available variables from their dataset and, if they meet the inclusion criteria, can include them in their index. Because of the subjectivity and potential bias involved in this creation, FIs can differ from dataset to dataset. However, despite the heterogeneity between numbers and types of deficits included, studies have found consistency between different FIs in different studies. There has been reliability found between their predictive value of adverse outcomes, trajectory slopes, and their maximal limit before death occurs (Searle et al., 2008). For example, Hoogendijk et al. (2017) created a FI in the Longitudinal Aging Study Amsterdam (LASA) and validated this by showing its predictive validity for mortality which was consistent with previously reported FI findings in other datasets. The value of a FI was illustrated and shown to be an effective measure in exploring how frailty develops over time and how it can affect various outcomes. Additionally,

Stolz, Mayerl, Rásky, and Freidl (2018) investigated the effect of sample attrition on FI trajectories and found that previously used models in frailty research are valid and provide good estimates in older age despite high rates of dropout. Hoogendijk et al. (2017) also emphasised the importance of continuing to apply FIs in different cohorts to compare its characteristics in various settings.

Fried Phenotype

Developed by Fried and colleagues, the Fried Phenotype measure takes a solely physiological approach by measuring several markers which have been found to predict the emergence of frailty. The Fried Phenotype criteria measures frailty according to five dimensions thought to reflect the affected systems of frailty: weight loss; exhaustion; weakness; slowness whilst walking; and low levels of physical activity (Fried et al., 2001). This method typically measures frailty as a categorical variable meaning that individuals are deemed either Non-Frail, Pre-Frail, or Frail. Accordingly, the Fried Phenotype is arguably more practical and easier to implement than the FI. However, it also has its own limitations. Most notably, due to the categorical approach, the measure is arguably less sensitive to subtle changes than the FI.

The operational differences are apparent yet a strong correlation is found between them (R = 0.65) (Aguayo et al., 2017; Rockwood, Andrew, & Mitnitski, 2007). Table 1.1 compares the main differences between the FI and the Fried phenotype.

Frailty Index	Fried Phenotype
Comprised of 30 – 40 health deficits covering a range of domains including cognitive, physical, and mental health	Comprised of five pre-defined physical dimensions: weight loss, exhaustion, weakness, slowness, and low physical activity

Measured continuously on a scale from 0 to 1: comprised of number of health deficits present in individual divided by total number of health deficits included in the index.	Typically measured categorically: Non-frail, Pre frail, Frail. Although some studies are known to use continuously modified versions e.g. (Liu, Han, Gahbauer, Allore, & Gill, 2018)
User chooses their own items to include in the measure according to set of rules established by Searle et al. (2008).	Dimensions are pre-defined and cannot be changed, however the way in which each dimension is measured may differ (Bandeen-Roche et al., 2006).
Can detect subtle fluctuations in frailty between or within individuals	Due to categorization, less able to detect minor frailty changes.

Table 1.1: Comparing the characteristics of the Frailty index and the Fried phenotype

Whilst these different approaches to the quantification of frailty have been the subject of much dispute (Gordon, Masud, & Gladman, 2013), it has also been suggested that frailty measures such as the Fried phenotype and the FI are distinct instruments which should be used to complement rather than oppose each other (Cesari et al., 2013). Although this suggestion is primarily directed at clinical care, research has recently shown the benefit of using both instruments in unison. Gale, Westbury, and Cooper (2018) used both the Fried phenotype and FI in the English Longitudinal Study of Ageing (ELSA) to measure the effect of loneliness and social isolation on frailty change, irrespective of the way it is measured. Findings differed according to the measure used, highlighting the discrepancies between the two most utilised measures of frailty. An advantage of both measures is that they can be retrospectively created for any dataset that meet the conditions set out, i.e. as long as there are enough appropriate variables that satisfy certain criteria. In light of this, establishing these measurements in longitudinal cohorts allows for further exploration of frailty trajectories, and subsequently, better

health outcomes for older adults. The empirical studies of this thesis utilised the Lothian Birth Cohort 1936, which is introduced in Chapter 3.

1.4 Mild cognitive impairment

Another way in which to quantify the process of age-related decline is to identify those deemed to have mild cognitive impairment (MCI). MCI has been used to describe the status of individuals who do not meet the severity threshold for dementia diagnosis, but nevertheless exhibit a state of cognitive function that is impaired to a greater level than expected for their age and years of education (Albert et al., 2011). This is an important transitional zone to cover, because the differences between normal age-related decline and the early stages of dementia can be difficult to differentiate (Artero, Petersen, Touchon, & Ritchie, 2006). Whilst much remains unclear, previous studies estimate that between 8% and 15% of those with MCI progress to dementia each year (Petersen, 2016). In recent years, dementia research has seen a larger focus on prevention strategies aiming to establish those who are at high risk of MCI and dementia in midlife and therefore be able to implement prevention strategies at an earlier stage (Albert et al., 2011; Petersen et al., 2018).

A crucial step in providing the groundwork for prevention strategies is conducting longitudinal research that explores changes in cognitive status changes over time. As discussed by Overton, Pihlsgård, and Elmståhl (2019), research which focusses on the stability of MCI over time is only beginning to emerge (Pandya, Lacritz, Weiner, Deschner, & Woon, 2017; Petersen et al., 2018). The phenomena of ‘yo-yoing’ between a cognitively healthy state and an MCI state are well documented (Zonderman & Dore, 2014), however, research is required that assesses how and why these shifts occur. Accordingly, Chapters 6 and 7 explored the longitudinal trajectories of MCI, and the factors associated with cognitive changes over time. This adds to a body of research, which questions the stability of MCI and identifies the salient factors associated with reversion to a cognitively healthy state.

1.5 Thesis overview

As summarised in this introduction, research has an important role in tracking the trajectories of ageing in later life and providing a foothold for clinical intervention and prevention strategy. This thesis aimed to summarise our understanding of ageing trajectories using frailty and cognitive impairment as ways of quantifying late life decline. The opening chapters focus solely on frailty as the primary outcome, whilst the subsequent chapters shift focus to cognitive impairment.

Frailty is a dynamic condition, which is likely to change over time. For over a decade prominent frailty researchers have been highlighting the importance of longitudinal studies that aim to identify risk factors for frailty change (Espinoza & Fried, 2007). These calls have only grown louder and many frailty researchers are proponents of the need for further longitudinal research which explores frailty change over time and the physical, social, and psychological factors that may contribute to this change (Ntanasi et al., 2020). In order to understand the current state of longitudinal frailty research, this thesis begins in Chapter 2 with an in-depth account of frailty, specifically by systematically reviewing the current literature on how frailty trajectories change over time. This chapter also highlights areas that the rest of the thesis explores further. Chapter 3 begins by introducing the Lothian Birth Cohort 1936, upon which this thesis' empirical studies are based. The chapter then provides a methodological insight into how frailty measurement tools are derived in the cohort, and lays the foundations for the frailty empirical studies to come. Chapter 4 describes the first empirical study of the thesis, exploring the associations between inflammation and frailty. Chapter 5 assesses the latent frailty trajectories in the cohort. Chapters 6 and 7 shift to focus on the prevalence of mild cognitive impairment in the cohort, and how certain predictors may affect changes in this prevalence over time. Chapter 8 closes out the thesis with discussions of the findings, recommendations for future research, and conclusions.

The aims of this thesis were ambitious yet realistic. In parallel with the concept of “marginal gains not a magic bullet” (Corley, Cox, & Deary, 2018), the thesis aimed to provide incremental insights in the global effort to understand how health status in later life changes over time, and the factors which may affect this change. By providing a better understanding of the way in which frailty and mild cognitive impairment change over time, I hoped to provide better insight into the process of ageing, and subsequently ways in which to reduce the risk of age-related health declines. Finally, the thesis aimed to supplement the empirical studies of this thesis with commentary on the state of the field of ageing trajectory research and areas in which future research is necessary.

Chapter 2: A Systematic Review of Frailty Trajectories

2.1 Introduction

This chapter acts as a preliminary step in assembling a better understanding of how and why frailty changes over time. As discussed in Chapter 1, whilst many aspects of frailty remain contested, one widely accepted outlook is that, irrespective of the measurement tool employed, frailty is not always stable over time. Indeed this has been illustrated in numerous studies, such as Gill, Gahbauer, Allore, and Han (2006) who conducted a prospective study finding that frailty states change over time in the majority of older adults. Furthermore, in a systematic review of transitions in frailty states, Kojima, Taniguchi, Iliffe, Jivraj, and Walters (2019) concluded that current research indicates that elderly individuals can make dynamic transitions across frailty categories (Non-frail, Pre-frail, Frail), both improving or worsening over time. However, it was also emphasised that relatively little is known about these changes. Due to the dynamic nature of frailty, a singular measurement in time may not accurately represent the within person fluctuations that can occur. Accordingly, longitudinal research has particular value as it allows researchers to examine how frailty changes over time in certain populations.

Despite this value, longitudinal frailty research also has the potential limitation of sample attrition in older populations that could invalidate results. Stolz et al. (2018) examined the significance of this in existing studies and found that the validity of longitudinal frailty trajectory studies was not threatened by sample attrition. Therefore, the current dearth of longitudinal frailty trajectory research needs resolving as it provides valuable information on how frailty changes over time according to various factors. Understanding these changes and pooling together current longitudinal findings enables future research to focus on the most pertinent areas. This is important as it enables us to identify the most harmful frailty trajectories and potentially allows for intervention to put individuals on a path which is less detrimental to their overall health (Chamberlain, Sauver, et al., 2016).

Systematic reviews are regarded as the gold standard in identifying, scrutinising, and summarising the best evidence available in a research field (Munn, Stern, Aromataris, Lockwood, & Jordan, 2018). For that reason, a systematic review provides a fitting foundation to instigate this thesis. This chapter details a systematic review of frailty trajectories which was published in *The Gerontologist* (Miles Welstead, Jenkins, Russ, Luciano, & Muniz-Terrera, 2021). This review allows us to understand where the field of longitudinal frailty research currently lies, and what important themes require attention. Accordingly, this chapter acts as a reference point and assists in defining the parameters for the rest of the thesis.

2.2 A Systematic Review of Frailty Trajectories: Their Shape and Influencing Factors

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Review Article

A Systematic Review of Frailty Trajectories: Their Shape and Influencing Factors

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Abstract

Background and Objectives: Frailty describes an increased vulnerability to adverse events such as disease or injury. Combating this state remains a major challenge for geriatric research. By exploring how and why frailty changes throughout later life we will be better positioned to improve ways of identifying and treating those at high risk.

Research Design and Methods: We systematically reviewed publications that captured rate of frailty progression over time and established any associated risk or protective factors that affected this progression. We included longitudinal observational studies which quantified frailty trajectories in adults aged 50+ using any validated continuous frailty measurement tool.

Results: After screening 8,318 publications, 25 met our criteria. Findings show that despite a great degree of heterogeneity in the literature, progression of frailty is unquestionably affected by numerous risk and protective factors, with particular influence exhibited by social demographics, brain pathology, and physical comorbidities.

Discussion and Implications: Findings that the gradient of frailty progression is affected by various influencing factors are valuable to clinicians and policymakers as they will help identify those at highest frailty risk and inform prevention strategies. However, the heterogeneous methodological approaches of the publications included in this review highlight the need for consensus within the field to promote more coordinated research. Improved consistency of methods will enable further data synthesis and facilitate a greater understanding of the shape of frailty over time and the influencing factors contributing to change, the results of which could have crucial implications for frailty risk reduction.

Keywords: Frail, Trajectory, Rate of change, Risk factors

Defining frailty proves highly challenging and while a universally accepted definition remains elusive, it is generally accepted to describe an age-related vulnerability which increases an individual's susceptibility to injury, disability, hospitalization, and mortality (Iwasaki et al., 2018). Although this syndrome is greatly associated with the aging process, it is not an inevitable part of it (Ahmed, Mandel, & Fain, 2007). Hence, the study of frailty *change* becomes imperative to understand why certain individuals become increasingly frail at a quicker rate than others do. With an improved understanding of this process comes the enhanced ability to identify and treat those at greatest risk of decline.

Currently, there is no gold standard frailty measurement tool (Aguayo et al., 2017); however, several measures have been devised and widely utilized in the field. The

frailty index (FI) conceptualizes frailty as an accumulation of deficits across multiple body systems (e.g., physical, social, cognitive) and calculates an individual's total number of deficits to quantify frailty on a continuous scale from 0 to 1 (Marshall, Nazroo, Tampubolon, & Vanhoutte, 2015; Mitnitski, Mogilner, & Rockwood, 2001; Rockwood & Mitnitski, 2007; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). Importantly, the researcher chooses the deficits included in the FI and accordingly the composition of each FI differs between different studies. Provided the deficits included in the composition of an FI follow the established criteria proposed by Searle et al. (2008), FI scores have been shown to be reliable across studies (Mitnitski et al., 2001; Rockwood & Mitnitski, 2007). Other frailty measures have taken a different approach by focusing on markers that predict the emergence of physical frailty. By far the most utilized of this method is the Fried Phenotype, which measures frailty according to five criteria thought to reflect the affected systems of frailty: weight loss; exhaustion; weakness; slowness while walking; and low levels of physical activity (Fried et al., 2001). This method typically measures frailty as a categorical variable meaning that individuals are deemed either Non-Frail, Pre-Frail, or Frail. However, variations of this method allow scores to be used on a continuous scale of affected dimensions from 1 to 5. A further development of this yields a continuous composite score by standardizing raw dimension scores into *z*-scores and averaging these to create a composite measure of frailty (Buchman, Wilson, Bienias, & Bennett, 2009).

Previous research has largely focused on categorizing individuals into discrete frailty states rather than considering frailty as a continuum (Kojima, Taniguchi, Iliffe, Jivraj, & Walters, 2019). Research has also primarily been confined to cross-sectional studies (Stenholm et al., 2018). While these studies can be informative, they make the examination of frailty changes over time much more difficult as they are restricted to one time point and they only reveal an individual's overall status (Non-Frail, Pre-Frail, or Frail), rather than a more precise measurement (Buchman et al., 2009). Understanding how frailty changes over time by synthesizing current longitudinal findings is a crucial step in identifying the most harmful and most promising frailty trajectories. Improved understanding of these trajectories will help to inform future interventions that aim to put individuals on a frailty path which is less detrimental to their overall health (Chamberlain et al., 2016). Furthermore, identifying the factors that can affect the nature of frailty trajectories is paramount, as these will inform clinical care strategies. For instance, particular lifestyle factors may influence the progression of frailty over time and subsequently represent potentially modifiable areas for prevention and treatment strategies to focus on.

A previous review considered continuously measured frailty trajectories: O'Caoimh et al. (2018) conducted a systematic review on frailty trajectories and transitions exclusively sourced from publications released by the European Joint Action Member States. Three publications were identified, among which a high level of heterogeneity was found in the type of frailty change reported, follow-up length, and their choice of sampling approach. O'Caoimh et al. (2018) suggested that widening the search to publications from countries across the world would allow better insight into the topic. Accordingly, this systematic review considers observational longitudinal publications published around the world, which have measured frailty as a continuous variable over time and subsequently explored frailty trajectories. In this systematic review, we aim to highlight the field's current limitations and summarize our understanding of how frailty progresses over time and how the rate of frailty change can be influenced by certain factors. By doing so we aim to inform future researchers and policymakers about the way in which frailty can manifest in certain groups, information which will be useful for creating effective intervention strategies.

Research Design and Methods

This systematic review followed standard guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). A protocol was created and published on the International Prospective Register of Systematic Review, reference; CRD42019126334 (accessible at https://edin.ac/2zeie9a).

Rationale for Eligibility Criteria

Inclusion/exclusion criteria were defined by following the PICOS format, a framework used to develop a structured response to a health care question (Higgins & Green, 2008). Due to higher prevalence of frailty in older age we focused on adults 50 years and older (Ahmed et al., 2007). Frailty measures were only included if they had been widely used and validated. Only measures that quantified frailty as a continuous variable were included as this allowed rate of change to be assessed. Some scales, although categorical by design, are used in a continuous fashion. In these cases, it was decided that these publications should be included. Additionally, intervention studies were excluded because this review was not focused on the effect of an intervention on frailty trajectories, simply the effect of aging. Full eligibility criteria were as follows: *Publications were included if:* (a) they contained any validated tool which measured frailty as a continuous variable, (b) frailty trajectories were quantified over more than two time points, (c) they contained human participants aged 50 years old or older at baseline, and (d) it was an observational study. *Publications were excluded if:* (a) the publication was any of the following: intervention studies, letters, editorials, systematic reviews, meta-analyses, viewpoints, comments, books, abstracts, dissertations, and (b) the full text was not written in English.

Identification of Publications

The scientific literature was systematically searched using the databases MEDLINE, EMBASE, and CINAHL. Each database was searched using headings and free text. The searches were not limited by publication date and included all publications up to March 30, 2020. For a link to the search strategy, see Supplementary Text S1. Reference lists of included studies were also hand-searched and screened for any further publications.

Publication Selection

M. Welstead and N. D. Jenkins independently screened titles and abstracts of the publications retrieved in the searches. At each stage of screening and quality assessment, disputes were discussed and resolved by a third independent reviewer (G. Muniz-Terrera) with expertise in frailty trajectories. For publications which potentially met the eligibility criteria, full texts were reviewed by M. Welstead and N. D. Jenkins and for those included, the quality and risk of bias of the publications were assessed using the Newcastle–Ottawa scale (NOS) for cohort studies (Wells et al., 2011). Consistent with previous literature (Kojima et al., 2019), publications scoring 5 or less were excluded.

Data Extraction

Data were extracted from all included publications including: author, journal, year of publication, title, contact details, country, study type, cohort, population, baseline age, baseline and end of follow-up sample size, time points/follow-up time, study objectives, frailty measure, statistical methodology, covariates, findings, and conclusions. Data were extracted by M. Welstead, with N. D. Jenkins undertaking a 20% sample extraction to verify similar findings.

Results

A total 12,484 publications were initially identified. After removing duplicates, 8,318 publications remained, the titles and abstracts of which were read and screened. Subsequently, the full text of 190 publications was screened. Of these, 25 were selected that met the eligibility criteria. No further publications were found from hand-searching reference lists. Figure 1 shows a PRISMA flow diagram illustrating this process and detailing the reasons for exclusion. Of the publications included, data were collected in the United States (n = 9) (Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Buchman et al., 2009, 2014; Buchman, Yu, Wilson, Schneider, & Bennett, 2013; Chen, Mair, Bao, & Yang, 2015; Liu, Han, Gahbauer, Allore, & Gill, 2018; Lohman, Mezuk, & Dumenci, 2017; Peek, Howrey, Ternent, Ray, & Ottenbacher, 2012; Yang & Lee, 2010), United Kingdom (n = 3) (Marshall et al., 2015; Rogers et al., 2017; Stow, Matthews, & Hanratty, 2018), Canada (n = 3)

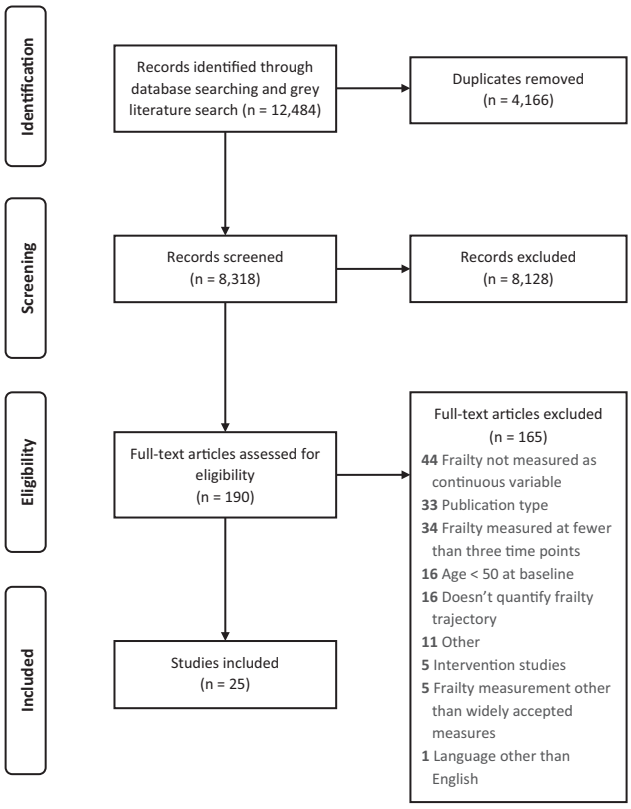

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the pathway of systematically reviewing frailty trajectories.

(Gajic-Veljanoski et al., 2018; Li, Papaioannou, Thabane, Cheng, & Adachi, 2016; Mitnitski, Song, & Rockwood, 2012), the Netherlands (n = 1) (Hoogendijk et al., 2018), and across Europe (n = 3) (Stolz, Mayerl, Rásky, & Freidl, 2018; Stolz, Mayerl, Waxenegger, Rásky, & Freidl, 2017; Walkden et al., 2018). Data quality was assessed by the NOS (Wells et al., 2011) found that publications ranged in their scores from 7 to 9 (mean [SD] = 8.2 [0.6]). Table 1 provides a summary of all included publications.

Studies Using a Method Based on the FI

The vast majority of publications exploring continuously measured frailty change over time used the FI (n = 13). However, within this selection of publications, choice of statistical analytic method varied. Publications either employed generalized estimating equations (GEEs), variations of random effects models, or mixture modeling methodologies to estimate frailty trajectories. GEE is a methodology that extends generalized linear models to correlated measures over time and estimates the population change over time (Muthén & Shedden, 1999). Random effects models (and latent growth curve models) estimate the average change over time and the heterogeneity of individual trajectories about this average (Laird & Ware, 1982). Mixture models can be understood

as extensions of these models to identify subgroups of individuals with similar developmental trajectories (Liang & Zeger, 1986).

Generalized Estimating Equations

Four publications utilized GEE as a model for exploring the average trajectories of frailty over time. Hoogendijk et al. (2018) tracked FI change in the Longitudinal Aging Study Amsterdam (LASA) over a 17-year period with follow-ups every 3 years. Overall mean FI increased from baseline to end of follow-up (mean FI 0.17–0.39), showing a statistically significant increase in FI over time (0.05, $p < .001$) when adjusted for sex and baseline age. A quadratic term was added to the model to test for nonlinearity; however, this was not statistically significant. Machado-Fragua et al. (2019) also explored frailty trajectories of 644 participants of the LASA study, finding that FI increased linearly (mean FI 0.13–0.17) after 13 years' follow-up. Li et al. (2016) studied 3,985 women aged 55 and older from the Global Longitudinal Study of Osteoporosis in Women 3-Year Hamilton Cohort (GLOW) to explore changes in FI after a major osteoporotic fracture. It was found that average change in FI progressed linearly over 3 years post-baseline (scores at each respective yearly follow-up = 0.24, 0.29, 0.31, 0.34). Lastly, Gajic-Veljanoski et al. (2018) followed community-dwelling adults aged 50 and older from the Canadian Multicentre Osteoporosis Study (CaMos) with follow-up at 5 and 10 years. Overall frailty as assessed by an FI was found to increase over the 5-year follow-up (mean increase of 0.03), but subsequently decrease the following 5 years (mean decrease of 0.02), thus exhibiting an unexpected nonlinear trajectory.

Random Effect Approaches

Ten publications used random-effect approaches that considered within-participant rate of frailty change. Yang and Lee (2010) collated various birth cohorts from the Health and Retirement Survey (HRS). Using growth curve models to estimate age trajectories of an FI, linear and quadratic age coefficients showed statistical significance ($p < .001$), indicating an increase in average FI (average increase 0.05) with further increases for every additional 10 years of age (0.01 with every 10 years). Using the same HRS cohort, Lohman et al. (2017) followed 13,495 participants over five waves between 2004 and 2012. Latent growth models estimated the number of average increases in deficits for each wave. A model adjusted for age, race, gender, marital status, household income, and smoking found a positive slope of frailty deficit accumulation over time by showing that on average 0.56 deficits (95% confidence interval [CI]: 0.49–0.63) were accumulated at each wave. Due to their FI consisting of 30 items, this equates to an average FI increase of 0.02 (0.56 ÷ 30) at each time point, building upon the baseline average FI of 0.18 (5.26 ÷ 30). Chen et al. (2015) also used the HRS in the United States to examine frailty trajectories stratifying the sample by race. Overall, growth curve analysis showed linear FI increases in the three race groups over a 12-year follow-up, although not significantly so for the Hispanic group. A quadratic effect was also statistically significant for all groups.

Stolz et al. (2017) used the Survey of Health Aging and Retirement in Europe (SHARE) data set to assess the impact of occupational class and wealth on the FI trajectories of 24,383 participants over a period of 9 years. By utilizing a quadratic growth model, it was revealed that FI trajectories increased nonlinearly (0.01, $p < .001$). Walkden et al. (2018) also used the SHARE data set with random effects multilevel models to determine FI trajectories, finding linear but not quadratic increases in frailty over 9 years in both a migrant and nonmigrant group. Thibeau, McDermott, McFall, Rockwood, and Dixon (2019) used a latent growth model to explore the frailty trajectory of 632 participants in the Victoria Longitudinal Study. Findings showed a significant increase in frailty scores over 8 years' follow-up ($p < .01$), and significant variability in the patterns of decline ($p < .01$). Various publications used the English Longitudinal Study of Aging (ELSA) to explore frailty trajectories. Marshall et al. (2015) used growth curve modeling across five waves of ELSA, finding an acceleration in frailty over time ($p < .001$). Rogers and Fancourt (2020) calculated the trajectory of frailty progression over 10 years in the ELSA study, finding a linear rate of progression in FI. Rogers et al. (2017) also analyzed frailty trajectories using the same cohort, and reported a significant quadratic term of the estimated mean trajectory ($p < .001$). Finally, using linear mixed-effects models, Aguayo et al. (2019) found that among 5,377 ELSA participants, frailty had a significant linear increase (0.002 in FI with each year of age) and they also found a small quadratic effect.

Mixture Models

Mixture models were employed by two of the publications to identify latent subpopulations of FI trajectories. Stow et al. (2018) found that in an English cohort of individuals attending their general practitioner (GP), a quadratic mixed model was the best fit. Using electronic GP records to create an FI, over 1 year with monthly intervals, FI progressed significantly over the year (mean of 0.25 at baseline with a linear increase of 0.002 per month). An added quadratic term improved the model but only showed a small additive effect per month. Latent growth mixture models allowed the identification of three distinct frailty trajectories: rapidly rising (0.02 FI increase per month, 2.2% of sample), moderately increasing (0.01 FI increase per month, 21.2% of sample), and stable (0.001 FI increase per month, 76.6% of sample).

Stephan et al. (2020) explored frailty trajectories of five adjacent birth cohorts from the Cooperative Health Research in the Region of Augsburg cohort

study. Using generalized linear mixed models, findings showed that although frailty levels were higher in more recent cohorts (>1933), FI showed a consistent increase with age in all cohorts. Stolz et al. (2018) used SHARE over a 12-year period with five waves of FI data. Despite a high attrition rate whereby more than half of the participants dropped out of the study, linear mixed models, which assumed missing data at random, were able to provide good estimates of frailty trajectories. Findings showed a great deal of heterogeneity within individual-level trajectories but an overall nonlinear increase in FI scores with particularly heightened increases from 70 years and older. It was noted that trajectories of the participants who dropped out (n = 12,381) were steeper than those who completed the final wave of follow-up (n = 8,663). Consequently, the effect of higher attrition at each follow-up wave meant that subsequent waves became increasingly selective toward those with a more gradual incline in FI and accordingly may have underestimated the trend of frailty change. Stolz, Mayerl, and Freidl (2019) followed their 2018 study by using mixed location-scale models to model frailty trajectories of 4,514 participants in the SHARE data set. This approach is an extension of a mixed effects model that permits the explicit modeling of the variance terms and showed linear frailty growth increased over a 10-year period. However, findings also showed that within-person deviations from the trajectories increased with age, meaning that over time, the rates of up and down fluctuations from an individual's frailty trajectory also increased.

Other Models

Finally, of those publications using the FI, Mitnitski et al. (2012) used the Canadian National Population Health Survey, with Poisson distributions which can calculate the number of accumulations in FI over time. Analyses found that on average FI rates increased linearly at each of the waves of data collection; however, individual rates of change were subject to much heterogeneity in their level of decline, with some even showing improvements over time.

Publications Using a Measurement Based on the Fried Phenotype

Publications measuring rate of change with a continuous (n = 2) or composite modification (n = 4) of the Fried Phenotype (Fried et al., 2001) were less common but still provided a valuable insight into rate of frailty change. As

Table 1. Summary of Included Publications Which Assess Rate of Frailty Change Over Time

Author (year), country	Frailty measurement tool	Baseline n	Years follow-up	Time points
Aguayo et al. (2019), United Kingdom	Frailty index (36 items)	5,377	10	6
Buchman et al. (2014), United States	Composite Fried criteria	2,167	15	Up to 15
Buchman et al. (2013), United States	Composite Fried criteria	791	Until death	Up to 14
Buchman et al. (2007), United States	Composite Fried criteria	823	8	Up to 8
Buchman et al. (2009), United States	Composite Fried criteria	832	8	Up to 8
Chen aet al. (2015), United States	Frailty index (30 items)	10,312	12	Up to 7
Gajic-Veljanoski et al. (2018), Canada	Frailty index (30 items)	7,753	10	3
Hoogendijk et al. (2018), The Netherlands	Frailty index (32 items)	1,659	17	6
Li et al. (2016), Canada	Frailty index (34 items)	3,985	3	4
Liu et al. (2018), United States	Continuous Fried criteria (0–5)	690	9	Up to 6
Lohman et al. (2017), United States	Frailty index (30 items)	13,495	8	5
Machado-Fragua et al. (2019), The Netherlands	Frailty index (32 items)	644	13	5
Marshall et al. (2015), United Kingdom	Frailty index (60 items)	11,220	12	5
Mitnitski et al. (2012), Canada	Frailty index (31 items)	4,330	6	7
Peek et al. (2012), United States	Continuous Fried criteria (0–4)	2,061	11	5
Rogers et al. (2017), United Kingdom	Frailty index (56 items)	8,649	Mean of 10	Up to 6
Rogers and Fancourt (2020), United Kingdom	Frailty index (56 items)	4,575	10	6
Stephan et al. (2020), Germany	Frailty index (50 items)	632	9	3
Stolz et al. (2017), Europe	Frailty index (40 items)	20,965	9	4
Stolz et al. (2018), Europe	Frailty index (40 items)	21,044	12	5
Stolz et al. (2019), Europe	Frailty index (50 items)	4,514	12	6
Stow et al. (2018), United Kingdom	Frailty index (36 items)	13,149	1	Up to 12
Thibeau et al. (2019), Canada	Frailty index (33 items)	2,512	8	3
Walkden et al. (2018), Europe	Frailty index (60 items)	95,635	9	5
Yang and Lee (2010), United States	Frailty index (30 items)	84,878	Various	5

with the FI, differences in statistical analyses existed between publications.

GEEs and Random Effects Models

Buchman and colleagues used data from the Religious Orders Study (ROS) and the Memory and Aging Project (MAP) in several publications where a frailty measure similar to Fried's criteria was employed. This included grip strength, timed walk, body composition, and fatigue. A composite score was calculated from these factors by converting them into *z*-scores using the means and standard deviations of scores at baseline. Similar trends showing gradual increases in frailty were found; however, these varied slightly depending on the cohorts and statistical analyses used. Buchman et al. (2007) followed 823 participants of the MAP study every year for up to 8 years. Using ordinary least squares regression, the rate of frailty change on the composite scale over the follow-up period was calculated for each participant. Initial scores ranged from –1.73 to 1.92, and average rate of change was found to increase at 0.09 (±0.30) units per year. This publication was followed up by Buchman et al. (2009), who used the same participants and used GEE to show similar findings that frailty composite scores were found to significantly increase with each annual time point (0.08, $p < .001$). Importantly, this publication also compared the difference in rate of change estimations when looked at cross-sectionally versus longitudinally. Findings showed that the cross-sectional effect of frailty across age substantially underestimated the actual rate of change, with the effect in the longitudinal models two and a half times higher. Buchman et al. (2013) followed 791 participants of the MAP and ROS studies every year for up to 14 years (mean = 6.4, $SD = 2.8$) to explore frailty rate of change. Using a linear mixed-effect model, this time frailty was found to increase each year (mean of 0.12 units per year). A follow-up from this group reinforced these findings with Buchman et al. (2014) using a sample of 2,167 participants in the same cohorts. Using bivariate random coefficient models to estimate the rate of change across multiple observations, frailty was shown to increase each year (0.09 units per year).

Mixture Models

Peek et al. (2012) used a sample of 2,061 Mexican Americans aged 65 and older within five waves of the Hispanic Established Populations for the Epidemiologic Study of the Elderly. Over the course of 12 years, rate of frailty change was assessed using a continuously measured modification of the Fried Phenotype (Fried et al., 2001). Using trajectory mixture modeling, three distinct frailty trajectories were identified: a consistently low group, a progressive moderate group, and a progressive high group. Despite the lack of reported coefficients for each slope, the three trajectories were reported to differ, significantly so between the progressive moderate and progressive high group ($p = .01$). Liu et al. (2018) also explored distinct trajectories of frailty, this time in relation to overlap between cognition and frailty. Using the Yale Precipitating Events Project, a continuous modification of the Fried Phenotype was used to quantify frailty every 18 months for 9 years. In this instance, a mixed modeling approach allowed for the identification of four distinct joint trajectories into which individuals fell: those with no cognitive or frailty decline (27.8%); a slow cognitive decline with a progressive frailty (45.5%); a quick cognitive decline with a progressive frailty (20.2%); and an accelerated cognitive and frailty decline (6.5%).

Handling of Missing Data

The majority of publications either did not report a method of handling missing data, or used a method involving the exclusion of participants who had a certain level of missing data throughout the follow-up period. Other publications dealt with missing data with a variety of statistical analysis methods including multiple and mean imputation and dummy variable adjustment that made the assumption that data were missing at random. See Tables 2 and 3 for details.

Risk and Protective Factors

All of the included publications discussed rate of change and factors associated with it. However, the risk and protective factors associated with rate of change varied across publications. Significant factors are summarized in Figure 2.

Age

Age is a factor which was frequently found to be associated with frailty level and change, although the direction of the association varied by publication. Whereas Rogers et al. (2017) showed that the gradient of frailty trajectory was found to differ by age group in older adults, others reported either the opposite or null effects. Mitnitski et al. (2012) reported that slopes of frailty change did not differ according to age and Hoogendijk et al. (2018) found that despite absolute change in FI being higher for those who were older at baseline, the rate of increase across the follow-up was similar between a 65–75 and 75+ group, indicating that rate of change is relatively stable across age groups. Peek et al. (2012), who used mixture models to find three distinct frailty trajectories, found that age was a significant factor in determining membership in a moderate and high progressive trajectory, suggesting that older age not only increases risk of frailty progression but also follows a separate trajectory to younger age groups. By comparing different birth cohorts, Stephan et al. (2020) showed that frailty levels can differ depending on when you were born; however, the actual rate of frailty change over time is not significantly affected.

Table 2. Summary of the Statistical Models Used in Included Publications Using the Frailty Index (FI)

Type of analysis	Publication	Statistical method as reported in publication	Time metric	Covariates explored	Results (rate of change)	Treatment of missing data
Generalized estimating equations	Gajic-Veljanoski et al. (2018)	Multivariate generalized estimating equations	Time	Osteoporotic fractures, obesity, physical activity	Linear then nonlinear	Multiple imputation and scenario analyses
	Hoogendijk et al. (2018)	Generalized estimating equations	Time	Age	Linear	Excluded those with >20% missing data
	Li et al. (2016)	Generalized estimating equations	Time	Osteoporotic fractures	Linear	Multiple imputation
	Machado-Fragua et al. (2019)	Multivariable generalized estimating equations	Time	Vitamin K	Linear	Excluded those with missing values
Random effect approaches	Aguayo et al. (2019)	Linear mixed-effects models	Age	Diabetes, hemoglobin A1C, fasting plasma glucose	Linear and nonlinear	Multiple imputation
	Chen et al. (2015)	Growth curve analysis	Time	Hours of caregiving undertaken, race	Linear	Mean imputation
	Lohman et al. (2017)	Latent growth curve modeling	Time	Depression, falls, nursing home admissions	Linear	Secondary missing data analysis
	Marshall et al. (2015)	Multilevel growth curve models	Age	Gender, wealth	Linear and nonlinear	Excluded those with <30 FI items
	Rogers et al. (2017)	Multilevel growth curve models	Age	Age, physical activity	Nonlinear	Excluded those with <30 FI items
	Rogers and Fancourt (2020)	Multilevel growth curve models	Age	Cultural engagement	Linear	Excluded those with missing values
	Stolz et al. (2017)	Growth curve models	Time	Country	Nonlinear	Excluded those with >5% missing data
	Thibeau et al. (2019)	Latent growth modeling	Age	Sex, executive function, processing speed	Linear	Excluded participants without enough data
	Walkden et al. (2018)	Random effects multilevel models	Age	Migrant status	Linear	Coded as missing at random where >20% missing data
	Yang and Lee (2010)	Growth curve models	Age	Age	Linear and nonlinear	Excluded those with <25 FI items
Mixed models	Stephan et al. (2020)	Generalized linear mixed models	Age	Birth cohort membership	Linear	Excluded those with >20% missing data
	Stolz et al. (2018)	Linear mixed model	Age	Education, effect of dropping out of study	Nonlinear	Compared data missing at random and not at random
	Stolz et al. (2019)	Mixed-effects regression models	Age	Location, education, sex	Linear	Not reported
	Stow et al. (2018)	Latent growth mixture models	Time to death	Age, mortality	Nonlinear	Not reported
Other models	Mitnitski et al. (2012)	Poisson approximation model	Time	Age	Linear	Not reported

Table 3. Summary of the Statistical Models Used in Included Publications Using the Fried Criteria

Type of analysis	Publication	Statistical method as reported in publication	Time metric	Covariates explored	Results (rate of change)	Treatment of missing data
Generalized estimating equations	Buchman et al. (2009)	Generalized estimating equations	Time	Mortality	Linear	Excluded those without valid follow-up data
Random effects models	Buchman et al. (2007)	Linear fixed-effects model	Time	Brain pathology	Linear	Excluded those without valid follow-up data
	Buchman et al. (2013)	Linear fixed-effects model	Time	Brain pathology	Linear	Excluded those without valid follow-up data
	Buchman et al. (2014)	Bivariate random coefficient models	Time	Brain pathology	Linear	Excluded those without valid follow-up data
Mixed models	Liu et al. (2018)	Group-based mixed modeling approach	Time	Mini-Mental State Examination scores	Linear	Not reported, low rate of attrition
	Peek et al. (2012)	Trajectory mixed models	Time	Age, education, wealth, social support	Linear	Not reported

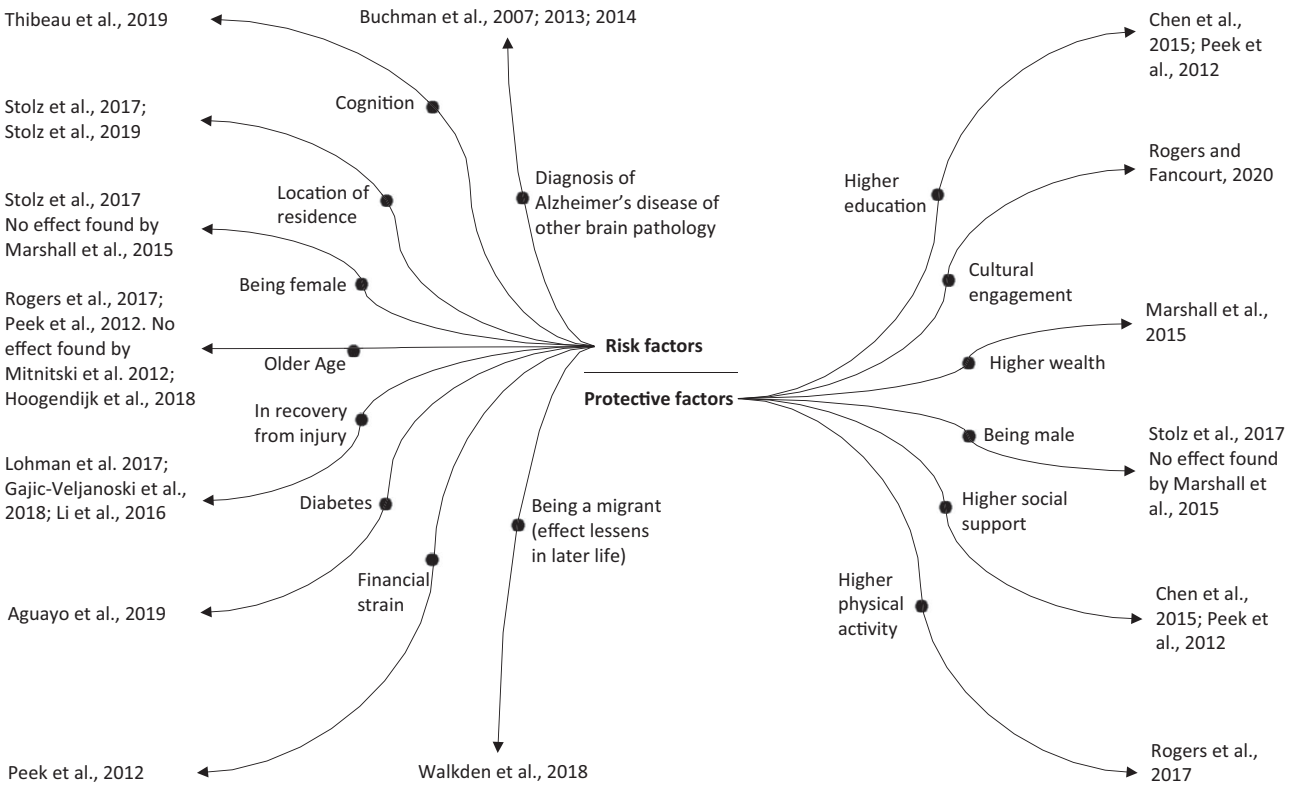

Figure 2. Diagram summarizing the risk and protective factors associated with rate of frailty change.

Gender

A further example of the disparities in findings is shown in the effect gender can have on rate of frailty change. While Stolz et al. (2017) found that women accumulated health deficits at a quicker rate than men, Marshall et al. (2015) found that although women had higher frailty scores than men at each time point, their slopes were consistent across the follow-up period, indicating that these gender disparities did not widen over time.

Brain Pathology

Three publications from the same research group explored the rate of frailty change in relation to brain pathology. Buchman et al. (2007) found that rate of frailty change was associated with incident Alzheimer's disease, showing that every 0.1 increase per year in frailty score equated to a 12% increased risk of developing Alzheimer's disease. Furthermore, Buchman et al. (2013) showed that more than 8% of the variance of a steeper decline in frailty was explained by several brain pathologies including microinfarcts, Alzheimer's disease, Lewy body disease, and nigral neuronal loss, indicating that brain pathologies are associated with steeper declines of frailty in older age. Finally, Buchman et al. (2014) showed that brain pathology showed independent associations with frailty change and also with cognitive change over their follow-up period.

Comorbidities and Injury

Surprisingly, few longitudinal publications have focused on the associations between frailty rate of change and disease, illness, or injury. Aguayo et al. (2019) showed that in a fully adjusted model, the presence of baseline diabetes was associated with significantly higher FI levels over time and that this difference stayed consistent over time. Risk of injury was also associated with rate of frailty change. Lohman et al. (2017) found that per-unit increase in frailty deficit accumulation at each wave the likelihood of suffering from a serious fall increased by 52% (odds ratio [OR] = 1.52, CI: 1.12–2.08). Related to these findings were two publications suggesting that rate of frailty change is particularly high for those recovering from osteoporotic fractures (Gajic-Veljanoski et al., 2018; Li et al., 2016).

Socioeconomic Factors

Two studies found a protective effect of education on rate of frailty change (Chen et al., 2015; Peek et al., 2012). Peek et al. (2012) identified three distinct frailty trajectories and found that higher education related to a lower chance of membership to the high frailty trajectory group (–0.19, $p < .01$). Similarly, financial factors were found to affect trajectories, with the same publication showing that financial strain was significantly related to frailty increase in the low and moderate groups, but not in the high group (low; 0.24, $p < .05$, moderate; 0.06, $p < .01$). Marshall et al. (2015) reinforced these findings with results showing that poorer individuals have steeper slopes than those in a wealthier category. Finally, social support networks were suggested to affect frailty change. Findings by Chen et al. (2015) suggested that caring for grandchildren is associated with less of a decline in frailty even after accounting for a healthy older adult effect, although reverse causality cannot be ruled out. Peek et al. (2012), however, only found that social support influenced one out of their three distinct trajectories of frailty progression (a progressive moderate trajectory).

Location

Country of residence also seemed to have some influence on frailty change, possibly due to differences in socioeconomics between countries. Stolz et al. (2017) showed that when quadratic growth curve models were stratified by country, FI trajectories were steeper for those living in Southern European countries than countries further north. Stolz et al. (2019) reinforced these findings using mixed-effects location-scale regression models to show that frailty levels in Europe were lowest in Switzerland and highest in Spain. While no other studies explored these geographical differences, Walkden et al. (2018) explored differences in migrants versus nonmigrants and found that at 50 years old, migrants have higher levels on the FI compared with nonmigrants (0.15 vs 0.14, $p < .001$). However, over time migrants accumulate deficits at a slower rate than nonmigrants, until there is no significant difference between groups in those 80–90 years old. This convergence effect remained even after adjustment for numerous confounders.

Physical Activity

Rogers et al. (2017) found that for those who engaged in vigorous physical activity, frailty progression was significantly slowed in all age groups, indicating that lifestyle factors such as physical activity may be able to improve frailty trajectories, but that these changes must be substantial. However, discussion within this publication points out that they cannot prove causality, so it may be that increases in frailty decrease the level of physical activity. It is noted that future research should aim to address this issue of reverse causality.

Cognition

Although the study of "cognitive frailty" has been gaining traction in the frailty literature, we only found one publication which explored the association between cognitive ability and frailty trajectories. Thibeau et al. (2019) used latent growth models to show that a steeper increase in FI was associated with a more rapid decline in executive functions. A similar effect was found for processing speed in females but not in males. The direction of this relationship remains unclear.

Cultural Engagement

Rogers and Fancourt (2020) investigated the association between frailty and the engagement in cultural activities such as attending the theater, cinema, or a museum on a regular basis. A fully adjusted multilevel growth model showed FI trajectories for those with varying degrees of cultural engagement. Findings showed a dose–response relationship between older adults who had higher levels of cultural engagement (every few months or more) and lower risks of developing frailty and a slower progression of frailty over a 10-year follow-up.

Diet

Diet is a factor somewhat underrepresented in the longitudinal frailty literature. Only one publication addressed the effect that an element of diet can have on frailty rate of change. Machado-Fragua et al. (2019) investigated the association between frailty and vitamin K, a group of vitamins obtained from animal foods to aid the body in several essential processes. Findings showed that although higher baseline vitamin K was associated with a higher level of frailty, it was not associated with rate of change over time as FI levels increased consistently across all groups.

Discussion and Implications

Overall, our findings show a heterogeneous field of research with frailty trajectories measured in diverse ways, statistical analyses differing, and inconsistency in the reporting of findings. Despite this lack of consistency, in general, trajectories show a gradual worsening in frailty over time. Most publications reported linear trajectories; however, several also found quadratic changes which suggest a variation in rate of change over time, while some publications (Gajic-Veljanoski et al., 2018; Mitnitski et al., 2012; Rogers et al., 2017) did report small improvements in frailty over time for some participants. These improvements could be explained by the different rates of attrition of frailer individuals at follow-up visits across publications, potentially resulting in a healthy survivor effect.

Numerous risk factors were investigated in the publications, showing somewhat inconsistent findings. In particular the effect of age and gender on frailty trajectories remains unclear and warrants further study as current findings show conflicting results. Inconsistent findings regarding the effect of age could be attributed to the differential impact of a healthy survivor effect across samples; gender differences across publications might be explained by the combination of a longer life expectancy of women and differences in sample compositions. A common theme of the publications was that of socioeconomic status and its relationship to frailty. In general it was found that those who are less affluent, with lower education, and lower levels of social support, tend to follow a steeper frailty trajectory (Marshall et al., 2015; Stolz et al., 2017; Walkden et al., 2018). In particular, the effect of social support on frailty change was reported as a significant factor, with the potential to provide protective effects against a rapid decline trajectory (Chen et al., 2015; Peek et al., 2012). This highlights a major public health priority that should be explored further; if those with low socioeconomic status are at greater risk of a steep frailty decline, then interventions can potentially target these populations with greater effect. Injury (Gajic-Veljanoski et al., 2018) and brain pathology (Buchman et al., 2007, 2009, 2013, 2014) also seem to contribute to the gradient of frailty slope. Again, these findings have important implications by showing the potential for targeted interventions, such as lifestyle changes or earlier screening for brain health abnormalities, to mitigate harmful frailty trajectories in those at highest risk. Several publications were able to identify latent subpopulations with differing frailty trajectories. These findings indicate that frailty progression affects individuals differently according to a number of factors. This area of research is crucial as it allows us to explore why certain individuals have similar trajectories and potentially allows for interventions to be tailored to those at highest risk of membership to a steep decline trajectory. Accordingly, further longitudinal research should continue to explore why trajectories differ across individuals. For instance, future studies could investigate the differences in frailty trajectories according to certain hormones, inflammatory biomarkers, genetics, or even personality traits. Additionally, it will be important to understand how these risk factors interact with one another; for instance, future research may focus on uncovering mediating effects of particular factors on the rate of frailty change. There is significant potential for this line of research as it could help inform future intervention strategies and guide policy for those at highest risk of frailty. With a robust research base in frailty risk and prevention there will be the potential to improve our ability to accurately identify individuals who are at greatest risk of frailty. This paves the way for intervention strategies to be designed and tested to ultimately prevent or even reverse frailty progression. For instance, the research included in this review suggests several potential modifiable protective factors such as increased physical activity (Rogers et al., 2017), social support (Chen et al., 2015; Peek et al., 2012), and cultural engagement (Rogers & Fancourt, 2020). Accordingly, clinical care may adapt to target those with a high risk of rapid frailty progression, and provide increased support and education related to physical activity.

There were several limitations which make the results less generalizable. While the types of populations included were varied, developing countries with lower income, education, and health care were somewhat underrepresented. Also, our search only found publications that considered community-based populations with no publications looking at frailty in care homes or in clinical care. The lack of inclusion of these populations makes overall conclusions less generalizable as these individuals are likely to be the most frail (Gajic-Veljanoski et al., 2018). Our collective knowledge of frailty progression will be enhanced if future research improves the generalizability of study populations by including less-represented populations. Additionally, we did not search gray literature, ongoing/unpublished studies, or publications written in a language other than English, all of which may have provided additional information. Due to time restraints, primarily one researcher undertook data extraction with the second researcher undertaking a 20% sample extraction; however, ideally both researchers should complete the entire extraction independently to ensure validity. A further limitation, which affects most longitudinal

research, is the high incidence of sample attrition. The publications included in this review were no exception; for instance, Hoogendijk et al. (2018) saw a reduction in participants from 1,659 at baseline to 297 at 17-year follow-up. Several publications discussed their sample attrition rates and their method of dealing with missing data through the use of imputation or techniques which account for missing data such as maximum likelihood estimation (Lohman et al., 2017). These methods require assumptions to be made about the reasons for which data were missing. However, these assumptions were rarely explained or justified. Although longitudinal models have been shown to remain effective even with high sample attrition (Stolz et al., 2018), handling missing data in a justifiable manner should be prioritized in future research to reduce bias toward those who remain in the study and likely have lower levels of frailty. Without dealing with this issue and considering the condition of those who drop out of the study, we may be underestimating the levels of frailty in the general population.

An additional limitation that hampered our ability to synthesize published research is the diversity of factors investigated in relation to frailty trajectories. To enhance opportunities to evaluate consistency and reproducibility of results and perform evidence synthesis, future research should aim to estimate within-person frailty changes in a coordinated manner with higher consistency in choice of analytical models and variable coding. This will generate knowledge that will permit the comparison of trajectories of reference persons with identical age at baseline, gender, and education.

In the context of frailty trajectories, the use of continuous frailty measures rather than categorical comes with the distinct advantage of being able to assess minor but significant changes. This was demonstrated in many of the included publications whereby the changes recorded from baseline to follow-up would not have been considered significant had they been measured by a categorical measure. The identification of these subtle temporal changes and examination of factors associated with these changes is essential to enhance our knowledge of how frailty can be prevented or slowed down. However, the inclusion of any continuously quantified frailty measurement also has limitations due to the discrepancies between how frailty is conceptualized and the lack of a gold standard definition (Levers, Estabrooks, & Ross Kerr, 2006). The different methods are assumed to be measuring the same construct when they may in fact be tapping into different domains. Following a template set by Gale, Westbury, and Cooper (2018), utilizing both categorical and continuous measures of frailty may be useful in the future to compare these differing methods. It has been suggested that these measures should be used to complement rather than oppose each other to build a better picture of frailty (Cesari, Gambassi, van Kan, & Vellas, 2013). By comparing these methods it may help to bridge the gap and work toward establishing a gold standard of frailty measurement which allows results to be compared in an accurate and replicable fashion (Aguayo et al., 2017). However, as it stands, without a defined framework of frailty measurement and analysis, research will continue to be inconsistent and incomparable.

Given the high rates of frailty in older adults and the detrimental effects it can have on overall health and mortality, studying the way frailty progresses is crucial. Overall, our findings show a heterogeneous field of research with vastly different methods for measuring, analyzing, and reporting data, hampering our ability to undertake a meta-analysis. Much of our discussion emphasizes the necessity for a more consistent approach to longitudinal research. While progress has been made on the definition of frailty with senior researchers reaching a consensus on some aspects of a frailty definition (Morley et al., 2013), it may be necessary to undertake a coordinated methodological approach to longitudinal frailty research. By using similar approaches and statistical methods, it will be more likely that a meta-analysis can be undertaken, and a more precise understanding of our current research can be obtained.

Despite these mixed results, our overall findings help to elucidate the progressive nature of frailty and highlight the disparity in how it affects separate groups of individuals in different ways. In particular socioeconomic factors, social support, physical activity, and brain pathologies seem to provide some determination of how an individual's frailty will progress over time, a finding which has important implications for public health policy as well as individuals and their caregivers. A major issue with drawing firm conclusions is the differences in how frailty is conceptualized and measured. Consequently, future research needs to provide a more consistent method to frailty measurement, a first step in establishing this consistency may be by incorporating multiple frailty measures within the same studies in order to contrast findings. Researchers should also focus on longitudinal studies which explore the risk factors associated with frailty trajectories as these are likely to have implications for how frailty can be prevented and treated in the future.

Supplementary Material

Supplementary data are available at *The Gerontologist* online.

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Conflict of Interest

None reported.

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2.3 Concluding remarks

From the information gleaned in this systematic review, a foundation has been set for the rest of the thesis to build upon. As noted, longitudinal frailty research is inconsistent, and will continue to be this way as long as researchers use differing frailty measures and differing statistical measures. In the following chapters of the thesis, some of these issues are discussed further and potential measures are taken to avoid some of the inconsistencies commonly seen. For example, Chapter 5 explored the trajectories of frailty by comparing and contrasting two of the most prominent frailty measurement tools, the FI and the Fried phenotype.

Whilst the aim of this review was to provide a foothold for the thesis, it has also been referenced numerous times in various longitudinal frailty studies [e.g. (Bai et al., 2021; Takatori & Matsumoto, 2021; Verghese et al., 2021)], demonstrating the need for a coordinated approach in summarising the plethora of frailty research. Additionally, as part of the Lothian Birth Cohort research team we have begun exploring other factors which, as far as we are aware, have not been covered before in the longitudinal literature. For instance, I contributed to the research design of an imminent research paper which explores the association between late life frailty progression and neighbourhood deprivation status across the lifespan (Baranyi et al., 2021). By undertaking more research like this, it will be possible to build a holistic picture of how and why frailty progresses over time. It is the hope that the review will continue to help future researchers understand the current state of the literature in years to come and encourage more longitudinal frailty research like this.

Since the publication of the review, I have published several papers that would now be included in the search (M. Welstead, Luciano, Russ, & Muniz-Terrera, 2021; Miles Welstead et al., 2020), as well as two others which I contributed to that are currently under consideration for publication (Jenkins, Hoogendijk, et al., 2021; Jenkins, Welstead, et al., 2021). If longitudinal frailty

research continues to be produced, it may be necessary to update this review to take into account new findings.

Chapter 3: Deriving and implementing frailty measures in the Lothian Birth Cohort 1936

3.1 Introduction

This chapter introduces the Lothian Birth Cohort 1936, which is used for all the empirical studies in this thesis. To illustrate the value of this cohort several examples are given of published work that I contributed to as part of the Lothian Birth Cohort team during the COVID-19 lockdowns. I then propose that this cohort provides an ideal dataset with which to implement frailty measures such as the Frailty index (FI) and the Fried phenotype. Details are given on how these two measures are derived in the LBC1936 along with a brief description of prevalence rates over the five waves. More in-depth analysis of these measures is provided in Chapter 4. It is important to detail the derivation of these measures as both measurement tools, particularly the FI, require the researcher to incorporate a degree of decision-making. Accordingly, it is imperative to make clear how each measure is constructed and which variables are used. I conclude with a summary of the chosen frailty measurement tools, and remark on their subsequent uses in the following chapters and in the future. This chapter details several co-authored studies for which I contributed to the design, data collection, and write-up (Corley et al., 2020; Okely et al., 2021; Taylor et al., 2020).

3.2 The Lothian Birth Cohort 1936

Longitudinal cohorts are a key instrument for healthy ageing researchers. By repeatedly assessing the same individuals over time, it is possible to

examine the ageing process, homing in on how and why humans change over time. Longitudinal cohorts are utilised around the world to track changes and answer important questions. The Lothian Birth Cohort 1936 (LBC1936) is a follow-up study of the Scottish Mental Survey in 1947, which was conducted throughout Scottish schools with children born in 1936. Almost every child attending school on 4th June 1947 was asked to complete the Moray House Test of general intelligence (*n* = 70,805) (Scottish Council for Research in Education, 1949). The LBC1936 was formed in 2004 with the recruitment of 1,091 older adults from the Lothian area, most of whom had taken part in the Scottish Mental Survey in 1947 (Deary et al., 2007). Wave 1 was conducted between 2004 and 2007 when participants were approximately 70 years old. Participants were given a range of cognitive assessments, including the Moray House Test (MHT) first taken when they were 11 years old. This inclusion makes the Lothian Birth Cohorts unique as it gives the potential to explore the associations between early life cognitive ability and factors in later life. These factors include psychosocial, lifestyle, medical, biomarker, genetic, brain imaging, and other data collected (Taylor, Pattie, & Deary, 2018). Since then, participants have been followed every three years for repeat assessments, most recently for wave five containing 431 participants at age 82 (Taylor et al., 2018). Data collection for a sixth wave began in October 2021 with the aim to finish at the end of 2022. Data are collected by a multidisciplinary team of psychologists, medical staff, and radiographers across Edinburgh, Scotland. Sample attrition across the four waves of LBC1936 is significant, with less than half of the participants at wave 1 remaining at wave 5. Figure 3.1 illustrates the waves of data and number of participants.

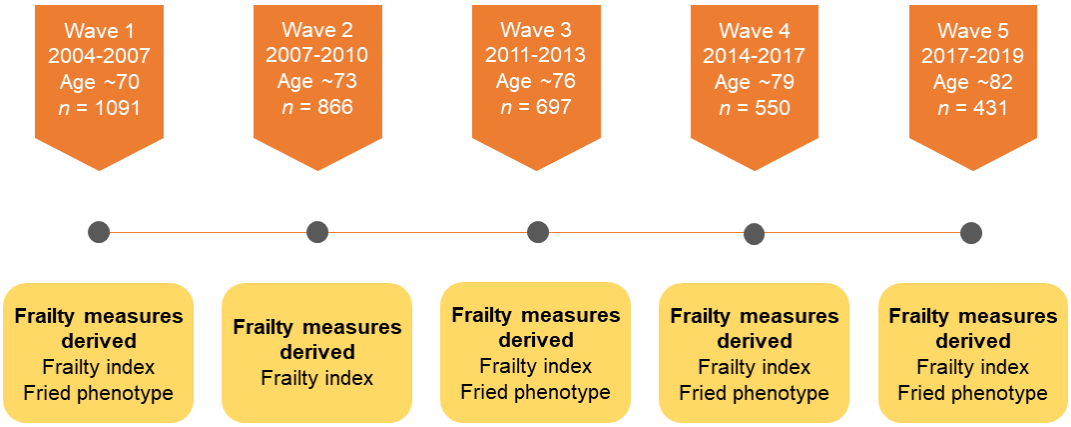

Figure 3.1 A timeline illustrating the frailty measurement tools derived at each wave of the Lothian Birth Cohort 1936

Since its inception, the LBC1936 has become widely recognised, and due to its novelty and wealth of information gathered it has contributed to a variety of high impact research (Taylor et al., 2018). The plethora of research produced from the LBC1936, ranging from epigenetics to childhood intelligence research, illustrates the extent to which longitudinal research can be useful in examining changes over time. Research utilising these types of cohorts can provide great insight into how we age, and subsequently, how we can optimise quality of life for older adults by identifying the factors associated with age-related physical and mental deterioration.

A recent example of the utility of such studies was demonstrated during the COVID-19 pandemic. Findings around the world indicated that older adults carry the highest risk of mortality related to COVID-19 (Shahid et al., 2020). Furthermore, the sudden worldwide lockdowns, which were imposed to help prevent the spread of the virus, had particularly strict rules for those over the age of 75. This meant that older adults were potentially at greater risk of mental and physical decline. As part of the Lothian Birth Cohorts team, we created an online survey asking LBC1936 participants about their experiences during the March 2020 lockdown in the United Kingdom. The initial study took a cross-sectional approach and explored the effect of the lockdown on participants'

psychosocial health and lifestyle finding small declines in physical and mental health (Taylor et al., 2020). Findings also showed that factors including cognitive function, occupational class, self-rated health, anxiety, and emotional stability were associated with the risk of psychosocial and physical decline.

Importantly, in the online survey we sent to participants we included self-report questions that had been assessed at previous waves of the LBC1936. This allowed us to also assess the longitudinal changes in physical activity, sleep quality, and psychosocial variables (Okely et al., 2021). Findings showed that, on average, physical activity levels decreased and perceived social support increased during the March 2020 lockdown. Additionally, certain personality traits including greater intellect, emotional stability, and extraversion were associated with more positive changes in our psychosocial and behavioural measures. Conversely, negative changes were associated more so with those with cardiovascular disease history, symptoms of anxiety, and those who lived alone. Findings like these highlight the disproportionate effect experiences like lockdown can have on certain individuals. This was further illustrated in our follow-up study using the same survey which found that those who had access to, and spent more time in, a home garden during lockdown were more likely to experience higher subjective wellbeing, including better physical and mental health, and sleep quality (Corley et al., 2020).

These studies demonstrate the important insights that longitudinal studies like the LBC1936 can bring. In this case, we hoped that our findings could be used specifically to inform pandemic related policies both now and in the future; however, research stemming from the LBC1936 is typically used more holistically to help understand the best ways in which to improve quality of life for those in later life. Accordingly, the LBC1936 provided an excellent cohort for this thesis to examine trajectories of ageing. Specifically, it was possible to explore whether participants tend to follow similar trajectories of frailty or cognitive impairment, assessing the factors that may be associated with this.

3.3 Deriving the measures in the Lothian Birth Cohort 1936

The first step of examining frailty trajectories was to implement the FI and Fried phenotype into the LBC1936. Five waves of the LBC1936 were used. As illustrated in Figure 3.1, waves 1-5 were used to derive the FI, whilst waves 1, 3, 4, and 5 were used to derive the Fried phenotype due to missing variables at wave 2.

Procedure for creating a Frailty index

The standard procedure for creating a FI detailed by Searle et al. (2008) is followed closely to ensure a consistent measure is developed. These guidelines state that 30 – 40 deficits must be chosen to make up the FI to optimise accuracy in predicting adverse outcomes (Mitnitski et al., 2001). For a deficit to be included in the index, it must meet five criteria as illustrated in Figure 3.2. Additionally, variables are screened to ensure that each are present in at least 1% of the LBC1936 and with no more than 5% missing data.

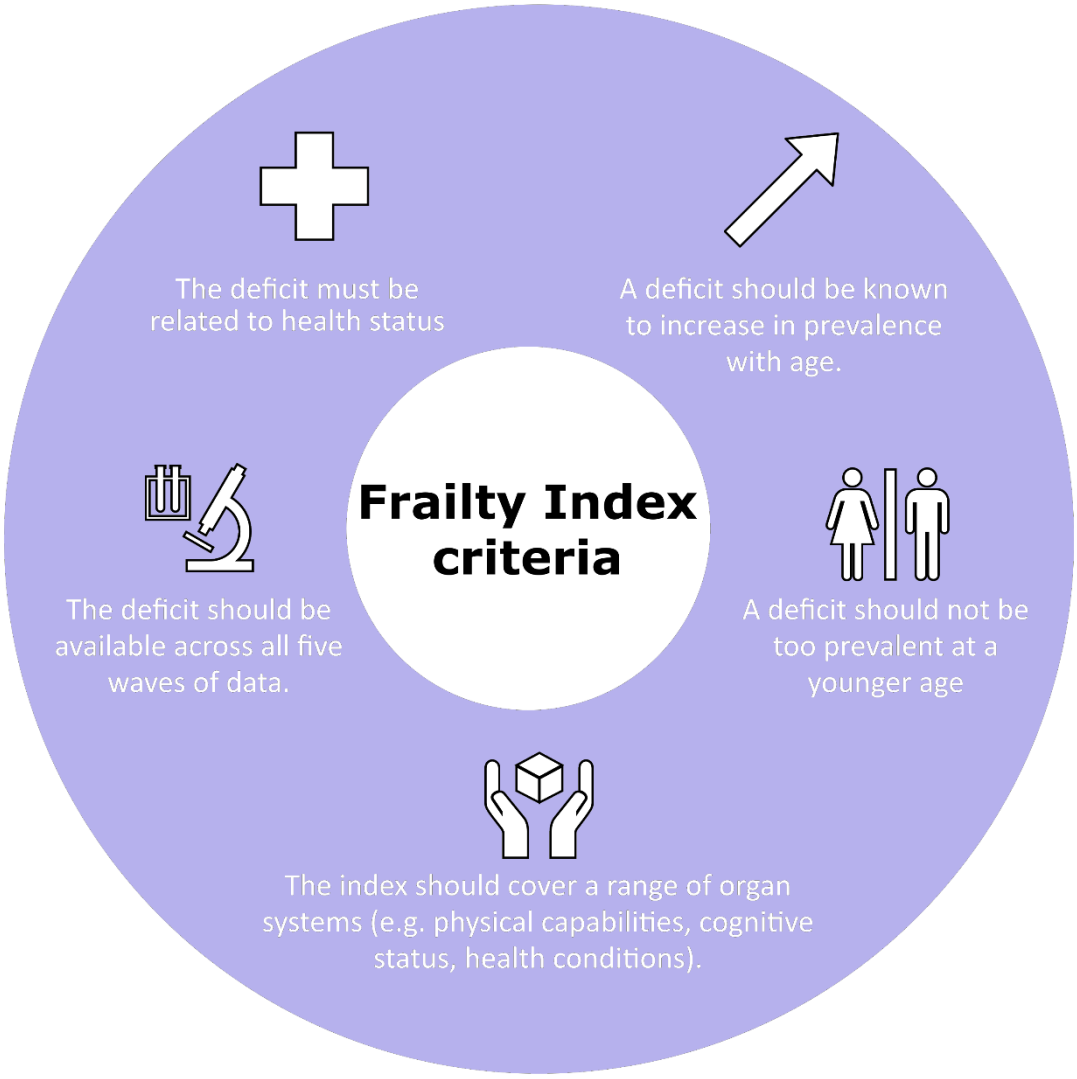

Figure 3.2: The five criteria a deficit must meet to be included in the Frailty index

Despite the LBC1936 containing a wealth of information that is suitable for a FI, identifying deficits that are consistently present across all waves proves challenging. The final selection of 30 deficits which met the criteria were consistent with those included in previous FI research. In accordance with guidance by Searle et al. (2008), each of these deficits were dichotomised as either 1 (present) or 0 (absent). Consistent with previous research, in some cases additional levels between 0 and 1 were coded, for instance, a further distinction of 0.5 was used to represent partially present deficits (e.g. BMI) (Chamberlain, Sauver, et al., 2016). Whilst this was simple for many binary

deficits such as the presence of cancer (Yes or No), for some deficits that were measured as a continuous variable (e.g. 6m walk time), established cut off points from previous literature were used. Where recognised or self-evident cut offs were not available, these were calculated in the recommended way by using percentiles (Theou et al., 2015). Participants in the lowest 5th percentile were coded as 1 and participants in-between the 5th and 20th percentile were coded as 0.5 indicating a half deficit, all others were coded as 0. As explored by Theou, Brothers, Peña, Mitnitski, and Rockwood (2014), FI can be coded as either dichotomous or ordinal with minimal impact on the performance of the index. Accordingly, consistent with previous FI literature (Godin, Armstrong, Wallace, Rockwood, & Andrew), for items with ordered response categories, scores were mapped to the 0–1 interval (e.g. for Likert questionnaires: 0- excellent, 0.25– very good, 0.5–good, 0.75–fair, 1–poor).

Once all variables were coded, a frailty score was computed for each participant at each of the four waves. This was achieved by dividing the participant's present deficits by the total amount of measured deficits (n = 30); for instance a participant with 11 present deficits at wave 1 would be given a score of 11 ÷ 30 = 0.36. Each participant was then given a score on a continuous scale between 0 (no deficits present) to 1 (all deficits present). A score above 0.7 was highly unlikely given that death is almost certain beyond this point (Rockwood & Mitnitski, 2007). All deficits and their cut off points are detailed in Table 3.1. Coding of the FI was undertaken within R (R Core Team, 2013).

Items	Coding	Cut offs based on
Systolic Blood Pressure	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Diabetes	Yes (1) or No (0)	Already binary variable
High Cholesterol	Yes (1) or No (0)	Already binary variable
Heart problem	Yes (1) or No (0)	Already binary variable
Stroke or mini stroke	Yes (1) or No (0)	Already binary variable
Crampy pains in calves	Yes (1) or No (0)	Already binary variable
Problems with blood circulation	Yes (1) or No (0)	Already binary variable
Thyroid Disorder	Yes (1) or No (0)	Already binary variable
Cancer	Yes (1) or No (0)	Already binary variable
Parkinson's disease	Yes (1) or No (0)	Already binary variable
Dementia	Yes (1) or No (0)	Already binary variable
Arthritis	Yes (1) or No (0)	Already binary variable
Any other chronic disease	Yes (1) or No (0)	Already binary variable
Polypharmacy	>4 medications (1), ≤4 medications (0)	Recommended technique (Theou et al., 2013)
Body Mass Index	18.5 to <25 (0), 25 to <30 (0.5), <18.5 or >equal to 30 (1)	Recommended technique (Chamberlain, Sauver, et al., 2016)
6m walk time (gait speed)	>10 seconds or physically unable (1), <10 seconds (0)	Recommended technique (Hoogendijk et al., 2017)

Items	Coding	Cut offs based on
Able to stand up from a chair	Yes (1) or No (0)	Already binary variable
Grip strength (strongest hand and stratified by sex and BMI)	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Townsend Disability Scale	11 – 18 (1), 0 -10 (0)	Recommended technique (Fiona Elaine Matthews et al., 2016)
Peak Expiratory Flow rate (stratified by sex)	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Forced expiratory volume (stratified by sex)	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Depression	11 -21 (1), 8 – 10 (0.5), 0 – 7 (0)	Recommended technique (Zigmond & Snaith, 1983)
Anxiety	11 -21 (1), 8 – 10 (0.5), 0 – 7 (0)	Recommended technique (Zigmond & Snaith, 1983)
MMSE	<10 (1), 11-17 (0.75), 18 – 20 (0.5), 20 – 24 (0.25), >24 (0)	Recommended technique (Searle et al., 2008)
Digit Symbol	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Block Design	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)

Items	Coding	Cut offs based on
Verbal Fluency	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Matrix Reasoning	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Reaction time test	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)
Delayed recall	<5th percentile (1), 5th-20th percentile (0.5), >20th percentile (0)	Recommended technique (Theou et al., 2015)

Table 3.1: Items constituting the Lothian Birth Cohort 1936 Frailty index and their coding/cut off points

Procedure for creating the Fried Phenotype

Frailty status in LBC1936 was calculated using the Fried phenotype in waves where adequate information was available: waves 1, 3, 4, and 5. Consistent with previous usage of the Fried criteria in the LBC1936 (Gale, Ritchie, Cooper, Starr, & Deary, 2017), five dimensions were measured as reported in Table 3.2. Coding of the Fried Phenotype was undertaken within R (R Core Team, 2013).

Dimension	Measurement method
Weight loss	Body Mass Index (BMI) calculated as weight ÷ height. The criteria was fulfilled if the result was less than 18.5kg/ m^2 at first visit, or ≥10% loss since previous visit at wave 3 or 4.
Exhaustion	Assessed by a question in the Hospital Anxiety and Depression Scale (HADS-D), 'I feel as if I'm slowed down' (Zigmond & Snaith, 1983). Presence of exhaustion was indicated by a response of 'Very often' or 'Nearly all the time'.

Weakness	Handgrip strength, three measurements taken on each hand with a dynamometer, strongest of these was taken. Accounting for sex and BMI, those in the bottom 20% of the distribution were considered to fulfil the weakness criteria.
Slowness	Maximum gait speed at which a participant can walk 6 metres. Once adjusted for sex and height, those in the lowest 20% were considered to fulfil the slowness criteria.
Lower physical activity	As assessed by a Likert scale ranging from one to six indicating degree of physical activity. Adjusting for sex, those in the bottom 20% fulfilled the low physical activity criteria.

Table 3.2: Dimensions of the Fried Phenotype and how they were measured

Overall the measure categorised those fulfilling none of the criteria as Non-frail, Pre-frailty was defined as the presence of one to two of the criteria, and more than two criteria was defined as Frail (Fried et al., 2001).

3.4 Prevalence of frailty in the Lothian Birth Cohort 1936

Here I provide a brief overview of the prevalence of frailty in the LBC1936, however, in-depth analysis is provided in Chapter 4. For both frailty measures, the prevalence was in line with expectations based on previous findings (Fried et al., 2001; Searle et al., 2008; Miles Welstead, Natalie D Jenkins, et al., 2021; Williams, Jylhävä, Pedersen, & Hägg, 2019). Frailty levels increased in both measures and correlations between the FI and Fried Phenotype were moderate, ranging from 0.36 to 0.47.

The FI showed a steady increase from mean (SD) = 0.16 (0.1) at wave 1 to mean (SD) = 0.22 (0.1) at wave 5 as illustrated in Figure 3.3 which was plotted using a linear mixed effects model in R with the GGplot function (R Core Team, 2013).

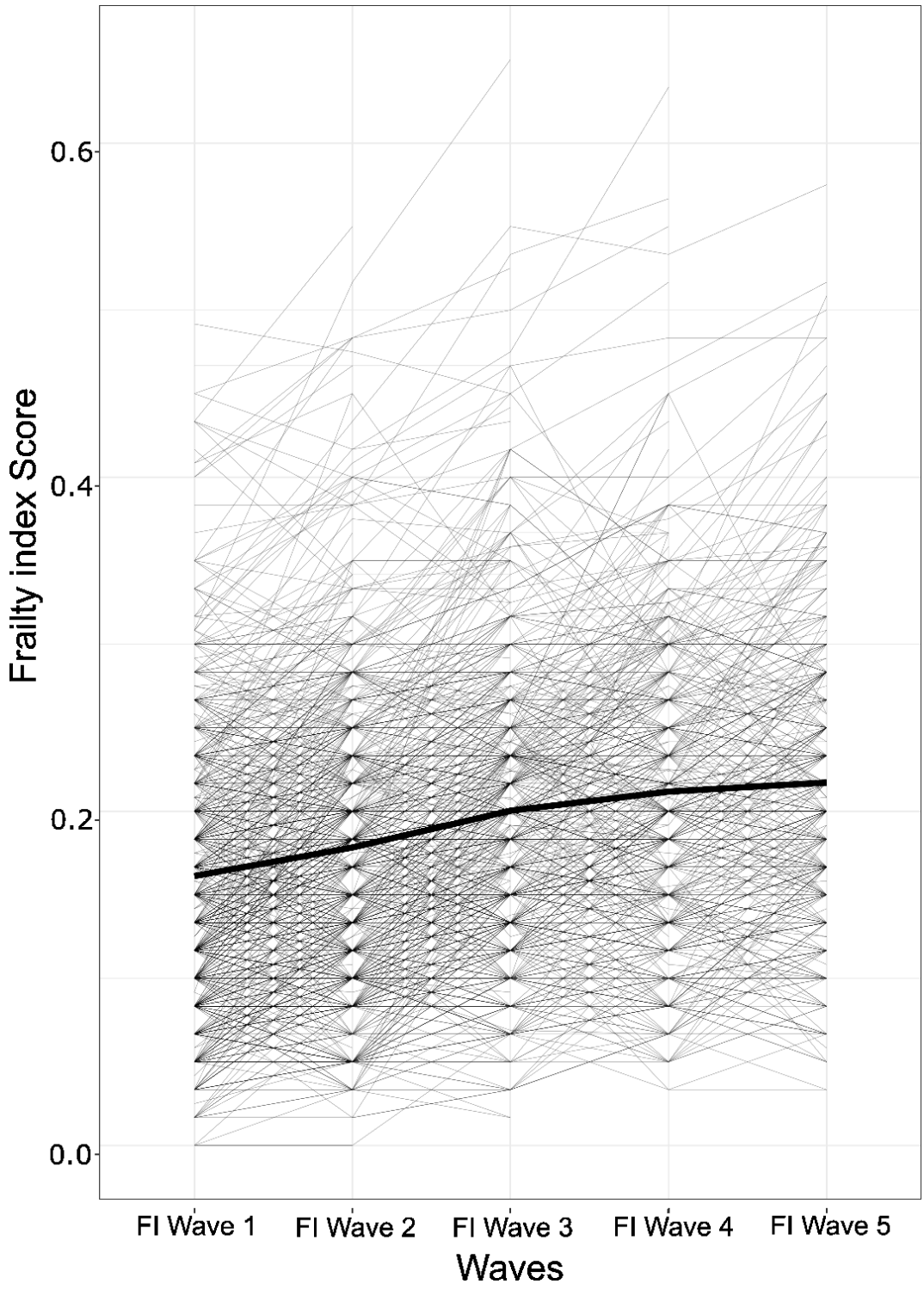

Figure 3.3: A plot of Frailty index trajectories for each individual over the course of follow-up.

As shown in Table 3.3, there do not appear to be gender differences in FI at any wave.

	Male	Female	*p* value
Wave 1 FI (*n* = 1091)			0.210
Mean (SD)	0.159 (0.085)	0.166 (0.086)	
Wave 2 FI (*n* = 866)			0.772
Mean (SD)	0.178 (0.089)	0.179 (0.086)	
Wave 3 FI (*n* = 697)			0.938
Mean (SD)	0.201 (0.092)	0.201 (0.090)	
Wave 4 FI (*n* = 550)			0.755
Mean (SD)	0.214 (0.093)	0.211 (0.092)	
Wave 5 FI (*n* = 431)			0.469
Mean (SD)	0.214 (0.087)	0.220 (0.097)	

Table 3.3: Characteristics of the FI at each wave

Results for the Fried Phenotype showed that proportions of those who were frail increased from 9% at wave 1 to 14% at wave 5. No significant gender differences were found at any wave. Attrition rates over the course of the follow-up showed a similar proportionate withdrawal rate between those who had pre-frailty or frailty at baseline that persisted or improved over time (25% attrition) compared to those healthy at baseline who became pre-frail or frail (24% attrition). As illustrated in Figure 3.4 there was instability in frailty status over time, with many individuals showing improvements and deteriorations. I explore this fluidity more in Chapter 4 in relation to markers of inflammation.

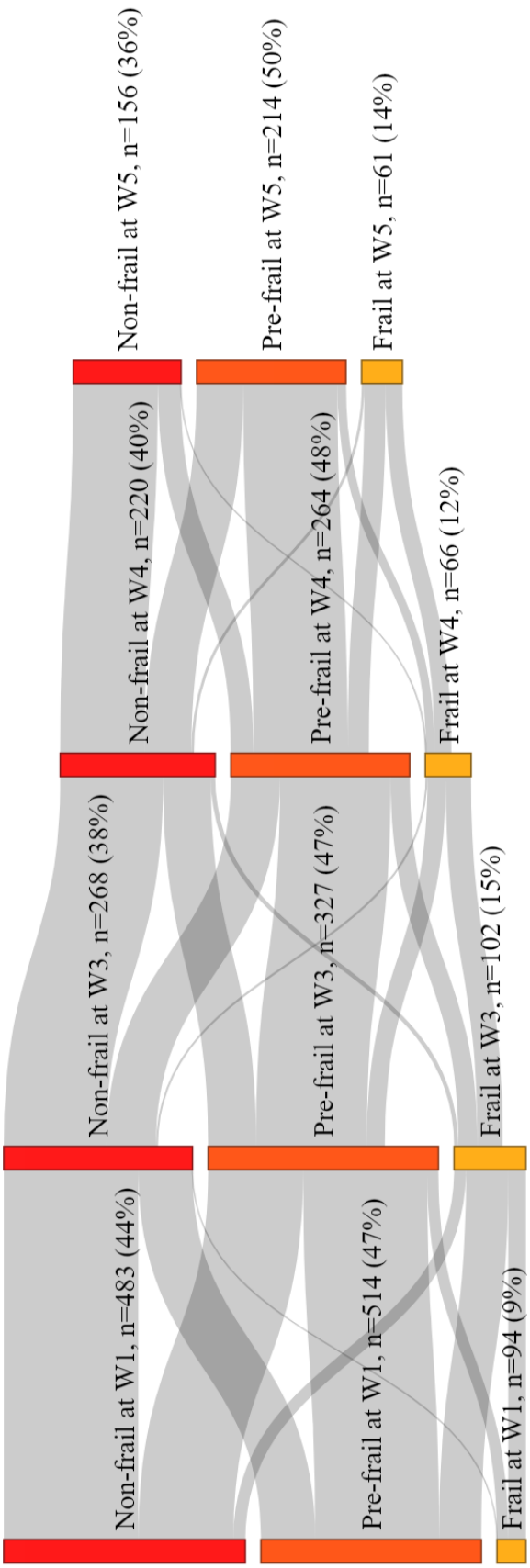

Figure 3.4: Characteristics of the Fried phenotype at each wave

3.5 Concluding remarks on the implemented frailty measures

A critical step in priming the empirical studies of this thesis was to derive measures that would enable the exploration of frailty over time in the LBC1936. I chose the two most widely used measures of frailty, partly to allow the comparison of the measures against each other, and partly to enable the research to be more harmonious with the wider frailty research field. By deriving these measures, it is possible for new inferences about frailty to be made. Both measures of frailty displayed the expected distributions and increases with age (Fried et al., 2001; Searle et al., 2008). Rates of frailty in this cohort were less prevalent than the general population (Gale et al., 2017). This was anticipated given that participants of the LBC1936 tend to rate higher than the general population on variables such as socio-economic status (Taylor et al., 2018), which has been linked to frailty rates (Szanton, Seplaki, Thorpe, Allen, & Fried, 2010).

With the measures implemented, it was possible to utilise the frailty measures in a longitudinal study that assessed the progression of frailty in relation to potential influential factors such as inflammation. R script for deriving this tool has been shared upon request to facilitate future studies on frailty using the LBC1936.

Chapter 4: Exploring frailty progression and its associated factors in the Lothian Birth Cohort 1936

4.1 Introduction

This chapter contains the first empirical study of the thesis and utilises the two frailty measures derived in the LBC1936. There are two main aims for this research paper. First, to explore the association between frailty and inflammation. Much like frailty, chronic inflammation is seen as a significant risk factor for morbidity and mortality (Sanada et al., 2018). These parallels make the association between frailty and inflammation of particular interest, with some biological measures of frailty even including inflammation as a marker for frailty (Blodgett, Theou, Howlett, & Rockwood, 2017; Ritt, Jäger, Ritt, Sieber, & Gaßmann, 2017). The association between frailty and inflammation is well documented in cross-sectional research, however, less research has been conducted longitudinally. Accordingly, these associations were explored longitudinally over a 12-year period in the LBC1936. Establishing a better understanding of how frailty and inflammation are associated over time is an important step in developing risk reduction interventions. It also provides insight into whether inflammation should be included in future frailty measures.

A second main aim for this research paper was to compare and contrast the two frailty measures to assess whether the same conclusions can be drawn from each, despite the differences in their composition. As touched upon in Chapters 1 and 2, one of the main limiting factors of the frailty literature is the variation in frailty measures used. Most studies choose a single measure to define frailty, which makes comparisons to other literature using different measurement tools problematic as it may not take into account that different measurement tools may not be measuring the same thing (Malmstrom, Miller, & Morley, 2014). Accordingly, by using the two most popular frailty measures it is possible to assess their differences and similarities.

The treatment of time in longitudinal analyses is important factor to consider as a decision is required on how to define change over the study period. Typically, researchers either use chronological age or the time since study baseline as the metric (MacDonald & Stawski, 2016). The choice here has been shown to influence the results so it is an important consideration (Morrell, Brant, & Ferrucci, 2009). The use of chronological ageing in this capacity has several limitations. Firstly, it is argued that rather than it representing a casual mechanism, it instead acts as a proxy upon which causal factors accumulate over time (MacDonald & Stawski, 2016). Therefore, it is not an accurate representation of the underlying mechanisms that affect health decline. Secondly, it is necessary to consider age heterogeneity at baseline when choosing chronological age as the time metric. Some studies choose to explore age trajectories looking at both cross sectional age differences and longitudinal age changes, modelling them over time to assess age related health trajectories (Sliwinski, Hoffman, & Hofer, 2010). However, this relies on the unsubstantiated assumption that cross sectional and longitudinal data converges into a common trajectory. Due to the limitations of using chronological ageing, time since study baseline is often used as a time metric in longitudinal modelling (MacDonald & Stawski, 2016). The studies within this thesis utilised this approach as it has consistently been shown to be more parsimonious, with a better fit, and the most accurate results of within individual change (Morrell et al., 2009). Furthermore, because participants of the LBC1936 are all born in the same year there is less of a requirement to account for between person differences in age (Sliwinski et al., 2010). Although, due to a three year data collection window for each data wave, age was controlled for in our analyses in line with previous LBC1936 publications (Taylor et al., 2018).

A further consideration in conducting longitudinal analyses is which covariates to include. The LBC1936 has a wealth of data from which to draw upon and several covariates are included in this study including Childhood cognitive ability. Lothian Birth Cohort publications typically control for childhood cognitive function even if the outcome variable includes a cognitive

component. This is because various studies have shown that early life cognitive ability is linked to later life health outcomes (Deary & Batty, 2007). In particular, findings have shown links between lower childhood cognitive function and an increased risk of frailty (Gale et al. 2016), later life cognitive impairment (Deary, Whiteman, Starr, Whalley, & Fox, 2004), and other factors such as inflammation (Luciano, Marioni, Gow, Starr, & Deary, 2009). With this in mind, it is possible that previous cross sectional ageing research is confounded by cognitive function in early life. Accordingly, I felt it necessary to control for such an effect and exclude reverse causation as an explanation. Additionally, including childhood cognitive function as a control variable provides insight into whether higher childhood cognitive function translates to a cognitive reserve that protects against frailty.

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4.2 Inflammation as a risk factor for the development of frailty in the Lothian Birth Cohort 1936

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Inflammation as a risk factor for the development of frailty in the Lothian Birth Cohort 1936

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ABSTRACT

Background: Research suggests that frailty is associated with higher inflammation levels. We investigated the longitudinal association between chronic inflammation and frailty progression.

Methods: Participants of the Lothian Birth Cohort 1936, aged 70 at baseline were tested four times over 12 years (wave 1: $n = 1091$, wave 4: $n = 550$). Frailty was assessed by; the Frailty Index at waves 1–4 and Fried phenotype at waves 1, 3 and 4. Two blood-based inflammatory biomarkers were measured at wave 1: Fibrinogen and C-reactive protein (CRP).

Results: Fully-adjusted, linear mixed effects models showed higher Fibrinogen was significantly associated with higher wave 1 Frailty Index score ($\beta = 0.011$, 95% CI[0.002,0.020], $p < .05$). Over 12 year follow-up, higher wave 1 CRP ($\beta = 0.001$, 95% CI[0.000,0.002], $p < .05$) and Fibrinogen ($\beta = 0.004$, 95% CI[0.001,0.007], $p < .05$) were significantly associated with increased Frailty Index change. For the Fried phenotype, wave 1 Pre-frail and Frail participants had higher CRP and Fibrinogen than Non-frail participants ($p < .001$). Logistic regression models calculated risk of worsening frailty over follow-up and we observed no significant association of CRP or Fibrinogen in minimally-adjusted nor fully-adjusted models.

Conclusions: Findings showed a longitudinal association of higher wave 1 CRP and Fibrinogen on worsening frailty in the Frailty Index, but not Fried Phenotype. A possible explanation for this disparity may lie in the conceptual differences between frailty measures (a biopsychosocial vs physical approach). Future research, which further explores different domains of frailty, as well the associations between improving frailty and inflammation levels, may elucidate the pathway through which inflammation influences frailty progression. This may improve earlier identification of those at high frailty risk.

1. Introduction

Although a definitive definition of frailty has yet to be established, it is generally accepted to refer to a clinical syndrome associated with an increased state of vulnerability in older adults (Iwasaki et al., 2018). This vulnerability increases an individual's risk of injury, disability, hospitalisation, and mortality (Fried et al., 2001). However, our understanding of frailty's aetiology remains poor (Hubbard and Woodhouse, 2010). Inflammation is a defence response undertaken by the immune system to combat harmful factors affecting the body (Pawelec et al., 2014). However, particularly in later life, chronic inflammation at low levels (inflamm-ageing) may develop even in the absence of infection (Samson et al., 2019). In order to measure inflammation, markers obtained from blood samples are often used. For instance, Fibrinogen, a plasma protein synthesised in the liver increases in the blood in response to systemic inflammation (Davalos and Akassoglou, 2012). Similarly, C-reactive protein (CRP), an acute phase protein found in blood plasma increases in concentration in response to inflammatory cytokines like Interleukin 6 (IL-6), and thus acts as a reliable indicator of inflammation in the body (Sproston and Ashworth, 2018). Elevated levels of inflammatory markers like Fibrinogen and CRP are consistently found amongst older people (Singh and Newman, 2011) and could potentially contribute to an increased risk of various diseases in later life (Pawelec et al., 2014; Sanada et al., 2018). Much

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like frailty, inflamm-ageing is seen as a significant risk factor for morbidity and mortality (Sanada et al., 2018) and is more pronounced in women (Samson et al., 2019). A recent systematic review and meta-analysis of 31 cross-sectional studies showed that frail and pre-frail individuals had significantly higher levels of inflammatory markers, including Fibrinogen and CRP (Soysal et al., 2016, 2017). These findings make the interaction between frailty and inflammation of particular interest.

A salient issue in frailty research is the surplus of measurement tools available. Frailty is measured differently both in conception and operationalisation. Two of the main measurement tools illustrate this disparity: the Fried phenotype measures frailty according to five physical measurements (weight loss, exhaustion, level of physical activity, walking speed, and weakness) and categorises individuals as Non-frail, Pre-frail, or Frail (Fried et al., 2001); the Frailty Index (FI) measures frailty as a continuous variable according to at least 30 physical, psychological, and social deficits across an individual's life (Mitnitski et al., 2001; Rockwood and Mitnitski, 2007). As far as we are aware, only four publications have examined the longitudinal association between inflammation and frailty, three of which used the Fried phenotype (Reiner et al., 2009; Baylis et al., 2013; Gale et al., 2013), and one (Puts et al., 2005) which used a self-created but unvalidated measure based on nine physical and psychological frailty indicators. In a meta-analysis of the four studies, no overall association was observed between inflammatory markers and incidence of frailty over time (Soysal et al., 2016, 2017). In a 2005 frailty and inflammation paper, the lack of longitudinal research exploring this association was discussed (Puts et al., 2005). Over a decade later a 2016 review paper highlighted that there remains a need for more of this research (Soysal et al., 2016, 2017).

Here we test the association between frailty and inflammation in the Lothian Birth Cohort 1936 (LBC1936). By exploring the association of inflammation and frailty over time, it may be possible to determine markers which are able to predict frailty risk. This could have important implications for public health intervention strategies for the care of elderly people. A recent systematic review (Welstead et al., 2020), concluded that, in lieu of a gold standard frailty measurement tool, it may be beneficial to utilise multiple measures. Subsequently, we used both the FI and the Fried phenotype to assess associations with inflammation and evaluate any potential differences in findings according to the measure used. To our knowledge, no previous longitudinal studies have explored frailty and inflammation in this manner. Our goal was to test the association between baseline inflammation levels and progression of frailty by end of follow-up, 12 years later. We hypothesised that those with higher baseline inflammation levels would also have an increased level of baseline frailty in both frailty measures. Over the follow-up, we predicted that higher baseline inflammation would be associated with a steeper trajectory of FI change during follow-up and a higher risk of Fried phenotype transition from Non-Frail to Pre-Frail or Frail.

2. Methods

2.1. Study sample

From 2004 to 2007, 1091 participants from the Lothian Birth Cohort 1936 (LBC1936) with a mean (SD) age of 69 (0.83) years, 49.8% female, were recruited and tested at baseline. Follow-up waves were conducted every three years spanning 12 years in total (wave 2 $n = 866$, wave 3 $n = 697$, wave 4 $n = 550$). Sample attrition across follow-up left 550 participants at wave 4. Table 1 reports summary information at each wave. For more details on the cohort, see the LBC1936 profile papers (Deary et al., 2011; Taylor et al., 2018; Deary et al., 2007). LBC1936 was conducted according to the Declaration of Helsinki guidelines with ethical permission obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56), Lothian Research Ethics Committee (LREC/2003/2/29), and Scotland A Research Ethics Committee (07/MRE00/58). Written consent was obtained from all participants.

2.2. Inflammation measures

At baseline, blood samples were drawn, and of interest to this study, analysed for two commonly used biomarkers of inflammation: CRP (mg/l) and Fibrinogen (g/L) (Del Giudice and Gangestad, 2018). CRP assays were undertaken with a dry slide immune-rate method with an OrthoFusion 5.1 FS analyser. Consistent with previous research (Corley et al., 2015), CRP values over 10 mg/l were excluded from analysis due to the likelihood that they represent acute illness. CRP distributions were positively skewed, however none of the transformations tried improved this distribution, and for the sake of interpretability, measures were left untransformed. Furthermore, inspection of residuals did not identify departure from distributional assumptions. Fibrinogen samples were obtained with a Clauss assay (Luciano et al., 2009), and measures were normally distributed and no values were excluded.

2.3. Frailty measures

The FI was constructed at each wave according to pre-established guidelines (Searle et al., 2008). We included 30 deficits covering different body systems (psychological, cognitive, and physical). Whilst some cut-off values were clear (e.g. a disease is present or absent), others were not (e.g. grip strength), in these cases previously established methods were used (Searle et al., 2008). Deficits and cut-off values are reported in Table A1. For each participant the number of present deficits was summed and divided by the total number of deficits ($n = 30$). Computed scores ranged from 0 to 1, with higher scores representing a higher degree of frailty.

The Fried phenotype is based on five pre-specified dimensions: weight loss, exhaustion, physical health, walking speed, and grip strength. The presence of one or two of these dimensions indicated that an individual is Pre-frail, whilst three or more indicated Frailty. Fried phenotype was calculated at all waves other than wave 2 due to insufficient data. Full details are reported in Appendix A.

2.4. Covariates

For FI and Fried phenotype analyses we included covariates: age, sex, smoking status (current/ex/never), alcohol intake (units per week), years of formal full-time education, occupational social class (professional/managerial/skilled, non-manual/skilled manual or semiskilled/unskilled), and childhood IQ (measured with the Moray House Test in the LBC1936 at age 11) (Penrose, 1949). Childhood IQ was included as a covariate due to previous findings in the LBC1936 indicating that lower intelligence in childhood is associated with increased inflammation (Luciano et al., 2009) and an increased risk of frailty in older age (Gale et al., 2016). For details on how social class and Childhood IQ was derived, see Appendix B. Additionally, for Fried phenotype analyses we added covariates that were not included for FI analyses due to their inclusion in the composition of the measure. These included: self-reported history of various chronic diseases, depressive symptoms from the Hospital Anxiety and Depression scale (HADS) (Zigmond and Snaith, 1983) and Body Mass Index (BMI). As one of the HADS questions was included in the composition of the Fried Phenotype, this question was removed when deriving the depressive symptoms covariate.

2.5. Missing data

Over the four waves, there were a small number of instances where it was not possible to take certain measures for some participants. In these instances we used multiple imputation with the MICE package in

Table 1
Summary characteristics of participants at each LBC1936 wave.

Variables	Wave 1 (Baseline)	Wave 2	Wave 3	Wave 4
Participants (*n*)	1091	866	697	550
Age in years, mean (SD)	69.6 (0.8)	72.5 (0.7)	76.3 (0.7)	79.4 (0.6)
Female, *n* (%)	543 (49.8%)	418 (48.3%)	337 (48.4%)	275 (50%)
FI, mean (SD)	0.16 (0.1)	0.18 (0.1)	0.20 (0.1)	0.21 (0.1)
Fried phenotype, *n* (%)				
Non-frail	478 (44%)	Insufficient data to construct phenotype	269 (39%)	222 (40%)
Pre-frail	520 (48%)		326 (47%)	259 (47%)
Frail	93 (8%)		102 (14%)	69 (13%)
CRP (mg/l), mean (SD)	3.5 (2.4)	3.3 (2.4)	2.5 (2.3)	2.4 (2.2)
Fibrinogen (g/L), mean (SD)	3.3 (0.6)	3.3 (0.6)	3.0 (0.6)	3.1 (0.5)

Note. CRP: C - reactive protein; FI: Frailty Index.

R version 3.5.3 (Buuren and Groothuis-Oudshoorn, 2010; R Core Team, 2018). Five imputations were used to estimate missing data needed for the creation of our frailty measures, and a total of 49 missing values were replaced with substituted values.

2.6. Statistical analyses

Due to the differences in how frailty is quantified in the Fried phenotype (categorical) and the FI (continuous), we used different statistical techniques for each measure. Linear mixed effects models using the LME4 package in R (R Core Team, 2018) were used to estimate change in FI scores from baseline to wave 4 and evaluate the association between baseline CRP and Fibrinogen and frailty trajectories. Models describing linear and accelerating change were fitted and adjusted for covariates, and then the best fitting model was chosen according to BIC fit indices. Fig. 1 illustrating the progression of FI over time was created using the GGPlot2 function in R (R Core Team, 2018).

Logistic regression was undertaken with the GLM function in R (R Core Team, 2018) to calculate the association between baseline CRP and Fibrinogen on the odds of frailty transition in the Fried phenotype between baseline and wave 4 (transition/no transition). Transitions were considered present if there was a worsening in frailty status i.e. from Non-Frail to Pre-Frail or Frail, or Pre-frail to Frail. Improvements in frailty status were also seen over the follow-up period with approximately 12% of participants showing an improvement in frailty status. Due to the focus of our study on frailty decline, these cases were not included in our analyses. Pearson's correlation coefficients were used to assess the inter-relationships between the inflammatory markers. An initial baseline model was calculated which controlled for age and sex, before computing a final model adjusting for other covariates. *t*-tests were used to describe sex group differences and assess baseline associations between inflammation and baseline frailty. Due to the use of two separate outcomes, there was no requirement for multiple testing corrections.

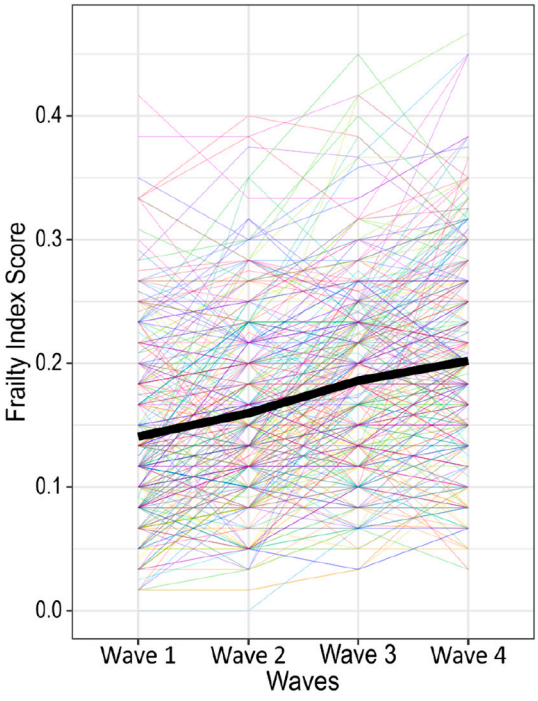

Fig. 1. A plot of Frailty Index trajectories and estimated mean over the course of follow-up.

3. Results

At baseline, a moderate correlation was seen between the Fried phenotype and the FI (rho = 0.43). This relationship was consistent at waves 3 and 4, where both frailty measures were also available (rho = 0.51 & 0.48, respectively). Baseline CRP and Fibrinogen showed a low positive correlation (rho = 0.28). T-tests found significantly higher levels of baseline FI scores for those who withdrew from the study compared to those who completed all waves (completers mean [SD] = 0.15 [0.08], withdrawers mean [SD] = 0.18 [0.09]; t [1065] = 6.06, $p < .001$). A significant difference between Fried Phenotype category and completers vs withdrawers was also found (t [1080] = 4.43, $p < .001$). Findings showed that 11.3% of withdrawers compared to 5.8% of completers were categorised as frail by the Fried Phenotype at baseline. In total 145 out of a total 550 completers (26%) showed a transition to a worse frailty status over the follow-up period. Additionally, levels of baseline inflammation were higher for those who withdrew (CRP: completers mean [SD] = 3.27 [2.32], withdrawers mean [SD] = 3.69 [2.55]; t[901] = 2.60, $p < .01$, Fibrinogen: completers mean [SD] = 3.22 [0.59], withdrawers mean [SD] = 3.34 [0.68], t[1006] = 3.21, $p < .01$). Over the four waves of data, both CRP and Fibrinogen showed a small decrease, as seen in Figs. A1 and A2.

3.1. Frailty index (FI)

At baseline, no significant sex difference in the FI was observed (male mean [SD] = 0.16 [0.08], female mean [SD] = 0.17 [0.09]; t [1088] = −1.35, $p = .18$). The comparison of fit indices between models describing the trajectory change in FI at a constant rate and models describing an accelerating rate of change showed that the best-fitting model was a model that considers FI change as constant and linear (CRP model BIC = −6826; Fibrinogen model BIC = −7646). Results of both CRP and Fibrinogen models indicated a significant association of time and FI scores, that is, scores increased on average by 0.030 (95% CI:[0.01, 0.05], $p < .01$,) with each wave. Fig. 1 shows this increase across waves. Random effects estimated the average variance of FI at baseline (SD = 0.07) and rate of FI change (SD = 0.02).

Table 2
Results from the linear mixed effects models assessing Frailty Index change in the LBC1936.

	CRP (mg/l) linear mixed effects model (BIC = −6826)			Fibrinogen (g/L) linear mixed effects model (BIC = −7646)		
Fixed effects	β	95% CI	p-Value	β	95% CI	p-Value
Rate of change	0.031	0.008, 0.052	0.006**	0.029	0.008, 0.050	0.007**
Inflammation	0.002	−0.000, 0.004	0.113	0.011	0.002, 0.020	0.016*
Age	0.000	0.000, 0.000	0.000***	0.000	0.000, 0.000	0.000***
Sex	0.012	−0.000, 0.025	0.055	0.013	0.001, 0.025	0.038*
Smoking	0.010	−0.002, 0.022	0.114	0.010	−0.001, 0.022	0.085
Alcohol intake	0.000	−0.000, 0.001	0.800	−0.000	−0.000, 0.000	0.949
Social class	−0.003	−0.009, 0.003	0.343	−0.005	−0.011, 0.001	0.117
Childhood IQ	−0.001	−0.002, −0.001	0.000***	−0.001	−0.002, −0.000	0.000***
Years of education	−0.004	−0.011, 0.002	0.160	−0.005	−0.011, 0.000	0.096
Inflammation over time	0.001	0.000, 0.002	0.021*	0.004	0.001, 0.007	0.014*
Age over time	−0.000	−0.000, 0.000	0.115	−0.000	−0.000, 0.000	0.410
Sex over time	−0.003	−0.007, 0.001	0.193	−0.004	−0.008, 0.000	0.092
Smoking over time	0.004	−0.000, 0.008	0.055	0.005	0.001, 0.009	0.009**
Alcohol intake over time	−0.000	−0.000, 0.000	0.247	−0.000	−0.000, 0.000	0.385
Social class over time	−0.001	−0.003, 0.001	0.311	−0.001	−0.001, 0.009	0.524
Childhood IQ over time	−0.000	−0.000, 0.000	0.538	−0.000	−0.000, 0.000	0.500
Years of education over time	0.001	−0.002, 0.003	0.583	0.000	−0.002, 0.002	0.702

Note. CRP: C - reactive protein; FI: Frailty Index.
Units: Inflammation: CRP or Fibrinogen respectively; Smoking: Current, Ex, Never; Alcohol intake: units per week; Social class: professional, managerial, skilled non-manual, skilled manual, and semiskilled/unskilled.
*** $P < .001$.
** $P < .01$.
* $P < .05$.

Table 3
Results from the fully-adjusted logistic regression models assessing risk of Fried phenotype transition in the LBC1936.

Variables	CRP (mg/l) logistic regression model (AIC = 548)		Fibrinogen (g/L) logistic regression (AIC = 612)	
	Odds ratios (95% CI)	p-Value	Odds ratios (95% CI)	p-Value
Inflammation marker	1.03 (0.93, 1.13)	0.55	0.84 (0.58, 1.20)	0.34
Age	1.21 (0.93, 1.58)	0.16	1.15 (0.89, 1.48)	0.27
Sex	1.01 (0.63, 1.63)	0.96	1.04 (0.66, 1.63)	0.86
Smoking Status	1.19 (0.76, 1.86)	0.44	1.30 (0.86, 1.98)	0.21
Alcohol intake	1.00 (0.98, 1.02)	0.88	1.00 (0.94, 1.02)	0.81
Years of Education	1.07 (0.86, 1.34)	0.52	1.09 (0.88, 1.33)	0.43
Social class	0.89 (0.64, 1.25)	0.51	0.91 (0.64, 1.24)	0.55
Childhood IQ	1.00 (0.98, 1.02)	0.89	1.00 (0.99, 1.08)	0.86
BMI	1.04 (0.98, 1.10)	0.15	1.03 (0.98, 1.08)	0.19
History of diabetes (Yes/No)	0.72 (0.25, 1.86)	0.52	1.24 (0.53, 2.76)	0.60
History of cardiovascular disease (Yes/No)	0.88 (0.50, 1.54)	0.67	0.78 (0.46, 1.31)	0.36
History of high cholesterol (Yes/No)	1.14 (0.69, 1.85)	0.61	1.23 (0.78, 1.93)	0.36
History of stroke (Yes/No)	0.93 (0.19, 3.51)	0.92	1.20 (0.38, 3.49)	0.74
History of thyroid disease (Yes/No)	1.22 (0.57, 2.47)	0.59	0.96 (0.46, 1.89)	0.90
History of cancer (Yes/No)	0.79 (0.35, 1.63)	0.54	0.90 (0.43, 1.77)	0.76
History of Parkinson's disease (Yes/No)	0.00 (N/A[a])	0.98	0.00 (N/A[a])	0.98
History of arthritis (Yes/No)	0.95 (0.61, 1.48)	0.83	0.96 (0.63, 1.45)	0.84
Number of depressive symptoms (HADS)	0.99 (0.88, 1.10)	0.83	0.99 (0.89, 1.10)	0.90

Note. BMI: Body Mass Index; CRP: C - reactive protein; FI: Frailty Index; HADS: Hospital and Anxiety Depression Scale.
Units: Inflammation marker: CRP, Fibrinogen; Smoking: Current, Ex, Never; Alcohol intake: units per week; Social class: professional, managerial, skilled non-manual, skilled manual, and semiskilled/unskilled.
[a] Unable to calculate 95% CI due to small sample of Parkinson's disease case.

Older age and lower childhood IQ were both associated with an increased baseline FI ($p < .001$). In the CRP model, baseline CRP did not have a significant association with baseline FI score but did show a significant association with the slope of FI change longitudinally (β = 0.001, 95% CI: [0.000, 0.002], $p < .05$). In the Fibrinogen model, baseline Fibrinogen was shown to have a significant association with baseline FI score (β = 0.011, 95% CI: [0.002, 0.020], $p < .05$) as well as a significant association with the slope of FI change longitudinally (β = 0.004, 95% CI: [0.001, 0.007], $p < .05$). Full results are reported in Table 2.

3.2. Fried phenotype

At baseline there was a significant difference between Fried phenotype category membership and CRP ($p < .001$) and Fibrinogen ($p < .001$). Non-Frail participants had lower CRP (mean [SD] = 3.16 [2.26]) and Fibrinogen (mean [SD] = 3.17 [0.55]) than Pre-Frail participants (CRP mean [SD] = 3.68 [2.55], Fibrinogen mean [SD] = 3.32 [0.65]) or Frail participants (CRP mean [SD] = 4.07 [2.58], Fibrinogen mean [SD] = 3.60 [0.82]). The distribution of men and women did not differ significantly by baseline Fried phenotype category. Further cross-sectional results showed significant differences between Fried Phenotype categories and several covariates. Those in the Frail category had lower childhood IQ ($p < .001$), less education

($p < .001$), higher BMI ($p < .001$), higher depressive symptoms ($p < .001$), and higher instances of various chronic diseases including diabetes ($p < .001$), cardiovascular disease ($p < .001$), high cholesterol ($p < .01$), stroke ($p < .01$), Parkinson's disease ($p < .05$), and arthritis ($p < .001$). Frail individuals were also more likely to identify as a current smoker ($p < .01$) and more likely to belong to a lower occupational social class ($p < .001$). Full details of baseline Fried Phenotype differences are reported in Table A2.

Longitudinally, sex did not emerge as associated with the rate of transition between Fried phenotype categories. Of the 550 participants who completed follow-up, 5.8% were classified as frail at baseline compared to 12.5% at wave 4. Logistic regression models were used independently for CRP and Fibrinogen. In the baseline models with age and sex as covariates, neither CRP nor Fibrinogen showed a significant association with frailty transitions. Results in the fully-adjusted models remained non-significant both inflammatory biomarkers. Furthermore, no covariates showed significant associations with frailty transition. Full details are reported in Table 3.

4. Discussion

4.1. Summary of findings and comparison with other literature

In this study, we investigated the association between two baseline inflammatory markers CRP and Fibrinogen, and frailty, as measured by the FI and the Fried phenotype, over 12 years of follow-up. Our hypothesis that higher levels of baseline inflammation would be associated with higher baseline frailty scores was partially supported; Fibrinogen, but not CRP, was cross-sectionally associated with FI scores. Whilst for the Fried phenotype both inflammation markers were higher in Pre-Frail and Frail participants compared to Non-Frail, findings which are consistent with previous cross-sectional research (Soysal et al., 2016, 2017). Our longitudinal findings showed no significant associations of inflammation factors and Fried phenotype transitions across the follow-up. These results support previous null findings reported in a meta-analysis of four longitudinal studies (Puts et al., 2005; Reiner et al., 2009; Baylis et al., 2013; Gale et al., 2013). However, we did find significant associations between both CRP and Fibrinogen on the FI slope of change, indicating that higher levels of these markers at baseline increase the gradient of FI score over time. This supports our hypothesis that rate of FI change is influenced by inflammation at baseline. Differences in findings between risk factors and these two frailty measures have been observed previously (Gale et al., 2018) and our findings that FI and Fried phenotype are only moderately correlated reinforces previous comparisons (Aguayo et al., 2017).

4.2. Interpretation

One possibility for the absence of a longitudinal association between inflammatory biomarkers and the Fried phenotype may be the general rates of healthiness in the LBC1936. As the LBC1936 is a self-selected volunteer sample from a relatively affluent area of Scotland, there are, on average, higher levels of healthiness when compared to the general population (Deary et al., 2007; Taylor et al., 2018). Thus, the greater restriction of range in our measures may underestimate the true size of effects in the general population. Furthermore, there was significant attrition which could have led to a healthy survivor effect whereby those who withdrew from the study were more likely to have had worsening frailty. This is congruent with findings that early withdrawers had higher levels of baseline frailty in both the FI and Fried phenotype. Previous analyses of the LBC1936 show that compared to those who stayed in the study, those who dropped out had significantly lower socioeconomic status, fitness levels, grip strength, and cognitive ability, all measures which could contribute to a higher level of Fried phenotype transition (Taylor et al., 2018). Additionally, although women had a marginally higher baseline FI score than men, this did not reach statistical significance. This result is incongruent with previous research which generally finds that women report higher FI levels than men (Gordon et al., 2017), and might reflect further the general healthiness of the LBC1936 (Deary et al., 2007; Taylor et al., 2018).

Another possible explanation for why CRP and Fibrinogen were associated with FI change but not Fried phenotype transitions is the substantial difference in their conceptualisation of frailty. Not only do the FI and Fried phenotype differ in the composition of their measures (biopsychosocial vs purely physical), it may also be that the scale differences (categorical vs continuous) add to our discrepant findings. Previous research has found similar differences, for example, Gale et al. (2018) utilised both the FI and Fried Phenotype to investigate social isolation and loneliness, finding different results depending on the frailty measure used. Aguayo et al. (2017) argued that different frailty scales are often based on different concepts of frailty and that they cannot be compared despite aiming to measure a similar outcome. Accordingly, it may be that inflammation does contribute to increased risk of frailty according to the FI's biopsychosocial definition of frailty but not the Fried Phenotype's physical definition. Further research is required to replicate these findings and tease out the differences between different types of frailty measurements and the associations of inflammatory biomarkers.

4.3. Implications for policy/care

Understanding the association between chronic inflammation and frailty progression may be useful for physicians targeting services for elderly people. For example, elevated inflammation may not indicate the need for immediate clinical care, however it may reinforce the benefit of lifestyle changes to potentially attenuate the risk of worsening frailty. The Fried phenotype, whilst unable to capture the subtle changes, may be more useful for detecting significant shifts in an individual's frailty status, indicating the requirement for immediate care and intervention. It may also be useful in an older population than the LBC1936 where frailty rates are higher and transitions are more substantial.

4.4. Strengths and limitations

A strength of this study is the use of different frailty measurement tools. Whilst the optimal way to measure frailty remains a matter of dispute it is important to consider that not all tools are consistent in their findings, and thus it is important to compare them before reaching firm conclusions. Future research may benefit from this method and reduce the heterogeneity in the field. This study also has limitations. Due to a lack of data at wave 2 we were unable to compute the Fried phenotype at all waves. Accordingly, we calculated transitions over a 12 year period whereby sample attrition took place. Future studies that are able to calculate transitions with less attrition may be able to draw more generalisable conclusions. Additionally, for our logistic regression models we only considered frailty transitions as those who recorded worsening frailty over time. We did not distinguish between those who either stayed healthy or showed improvement in frailty status over time. It may be the case that improvements in frailty are associated with reductions in inflammation. Future research may benefit from exploring this relationship further. A further limitation concerned our lack of inclusion of anti-inflammatory drugs as a covariate, which could have acted as a confounder on our results. Use of anti-inflammatory drugs typically increase in older age (Fowler et al., 2014) and this potentially explains the decreases in Fibrinogen and CRP over time as seen in Figs. A1 and A2.

4.5. Conclusions

We sought to explore the association between inflammation and frailty change over time. As far as we are aware, we are the first study to

explore the longitudinal association between inflammation and FI. We found differing results depending on the frailty measurement tool used; inflammation showed a significant association with frailty over time when measured by the FI but not the Fried phenotype. The differences in frailty conceptualisation (biopsychosocial vs solely physical) may underpin this difference and further research is required to fully understand these differences. The value of comparing different frailty measures has been shown here, and should be continued in future research so that a better understanding of how inflammatory marker associations vary between different frailty conceptualisations can be established. By doing so, it may be possible to facilitate policy and clinical care improvements whereby frailty risk can be identified early, via markers like inflammation, and effective interventions can be implemented.

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Availability of data and material

Data was obtained from the Lothian Birth Cohort 1936, more information can be found at https://www.lothianbirthcohort.ed.ac.uk/.

Code availability

R script can be provided upon request.

Declaration of competing interest

The authors have no competing interests to declare.

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CRediT authorship contribution statement

Miles Welstead: Conceptualisation, Methodology, Software, Formal analysis, Writing – original draft, Writing - review & editing, visualisation, **Graciela Muniz-Terrera**: Conceptualisation, Methodology, Writing - review & editing, Supervision, **Tom Russ**: Conceptualisation, Methodology, Writing - review & editing, Supervision, **Janie Corley**: Writing - review & editing, **Adele Taylor**: Writing - review & editing, Project administration, **Catharine Gale**: Conceptualisation, Writing - review & editing, **Michelle Luciano**: Conceptualisation, Methodology, Writing - review & editing, Supervision.

Appendix A

Table A1
Items constituting the Frailty Index and their coding/cut-off points in the LBC1936.

Items	Coding	Cut-offs based on
Systolic blood pressure	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Diabetes (self-reported)	Yes (1) or No (0)	Already binary variable
High Cholesterol (self-reported)	Yes (1) or No (0)	Already binary variable
Heart problems (self-reported)	Yes (1) or No (0)	Already binary variable
Stroke or mini stroke (self-reported)	Yes (1) or No (0)	Already binary variable
Leg pain (self-reported)	Yes (1) or No (0)	Already binary variable
Blood circulation issues (self-reported)	Yes (1) or No (0)	Already binary variable
Thyroid Disorder (self-reported)	Yes (1) or No (0)	Already binary variable
Cancer (self-reported)	Yes (1) or No (0)	Already binary variable
Parkinson's disease (self-reported)	Yes (1) or No (0)	Already binary variable
Dementia (self-reported)	Yes (1) or No (0)	Already binary variable
Arthritis (self-reported)	Yes (1) or No (0)	Already binary variable
Any other chronic disease (self-reported)	Yes (1) or No (0)	Already binary variable
Polypharmacy (self-reported)	> 4 medications (1), ≤4 medications (0)	Previous literature (Theou et al., 2013)
Body Mass Index (BMI)	18.5 to < 25 (0), 25 to < 30 (0.5), < 18.5 or > equal to 30 (1)	Previous literature (Chamberlain et al., 2016)
6 m walk time (gait speed)	> 10 s or physically unable (1), < 10 s (0)	Previous literature (Hoogendijk et al., 2017)
Able to stand up from a chair	Yes (1) or No (0)	Already binary variable
Grip strength (strongest hand and stratified by sex and BMI)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Townsend Disability Scale (Townsend, 1979)	11–18 (1), 0–10 (0)	Previous literature (Matthews et al., 2016)
Peak Expiratory Flow rate (stratified by sex)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Forced expiratory volume (stratified by sex)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Depression (measured by the HADS) (Zigmond and Snaith, 1983)	11–21 (1), 8–10 (0.5), 0–7 (0)	Previous literature (Zigmond and Snaith, 1983)
Anxiety (measured by the HADS) (Zigmond and Snaith, 1983)	11–21 (1), 8–10 (0.5), 0–7 (0)	Previous literature (Zigmond and Snaith, 1983)
Mini-Mental State Examination (MMSE) (Folstein et al., 1975)	< 10 (1), 11–17 (0.75), 18–20 (0.5), 20–24 (0.25), > 24 (0)	Previous literature (Searle et al., 2008)
Digit Symbol(Wechsler, 2003)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)

(*continued on next page*)

Table A1 (*continued*)

Items	Coding	Cut-offs based on
Block Design(Wechsler, 2003)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Verbal Fluency(Wechsler, 2003)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Matrix Reasoning(Wechsler, 2003)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Reaction time test(Cox et al., 1993)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Delayed recall(Wechsler, 2003)	Bottom 5th percentile (1), 5th–20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)

Note. HADS: Hospital Anxiety and Depression scale.

Deriving the fried criteria

The Fried Criteria was comprised on five dimensions. These were measured in the LBC1936 as follows;

Weight loss

Weight was measured using an electronic weighing scale, and height was measured in metres using a stadiometer. From this, it was possible to compute BMI by dividing weight by height squared. At baseline, weight loss was defined as a BMI less than 18.5 kg/m^2. At waves 3 and 4, weight loss was defined as a loss of weight of 10% or more since their previous visit or a BMI less than 18.5 kg/m^2.

Exhaustion

Exhaustion was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Exhaustion was scored as present if the participant responded 'very often' or 'nearly all the time' to the item 'I feel as if I'm slowed down'.

Physical activity

A question asking participants about their usual level of physical activity was used with six responses ranging from moving only when necessary, to heavy exercise or sport several times a week. In line with previous publications (Gale et al., 2017), participants in the lowest sex-specific 20% of the distribution were defined as having low physical activity.

Walking speed

Participants were recorded walking a distance of six metres at maximum speed. After adjusting for sex and height, those in the lowest 20% of the distribution were considered to have a slow walking speed.

Weakness

Maximum grip strength was measured in all participants using a dynamometer. Participants were measured three times with the strongest attempt being used for analysis. After adjusting for sex and BMI, those in the lowest 20% of the distribution were defined as having weakness.

Appendix B. Defining occupational social class

Occupational social class was based upon principal occupation, coded in line with the 1980 census (General, 1991). Five social class categories were used: professional, managerial, skilled non-manual, skilled manual, and semiskilled/unskilled. The women in the cohort were asked for their husband's occupation as well as their own, and they were assigned a social class based on the highest occupation of the household. This was derived from their own occupation for about half of the women, and from their husband's occupation for the remainder.

Childhood IQ was derived from Moray House Test scores at age 11 (Penrose, 1949) as part of the LBC1936. Raw scores were corrected for age in days at time of testing and converted to an IQ scale where mean (SD) = 100 (15).

Table A2
Baseline differences in characteristics for each category of the Fried phenotype in the LBC1936.

Variables	Non-frail (n = 478)	Pre-frail (n = 520)	Frail (n = 93)	p-Value
CRP mg/L: mean (SD)	3.2 (2.3)	3.7 (2.6)	4.1 (2.6)	< 0.001***
Fibrinogen g/L: mean (SD)	3.2 (0.6)	3.3 (0.7)	3.6 (0.8)	< 0.001***
Sex, n (%)				0.8
Male	245 (51%)	259 (50%)	44 (47%)	
Female	233 (49%)	261 (50%)	49 (53%)	
Body mass index (BMI), mean (SD)	27.1 (3.7)	28.2 (4.5)	29.4 (5.8)	< 0.001***
Smoking status, n (%)				< 0.01**
Current	39 (8%)	66 (13%)	20 (21%)	
Ex	203 (43%)	223 (43%)	39 (42%)	
Never	236 (49%)	231 (44%)	34 (37%)	
Alcohol (units per week), mean (SD)	11.4 (14.8)	10.2 (13.8)	7.94 (12.6)	0.1
Social class, n (%)				< 0.001***
Professional	104 (22%)	78 (15%)	8 (9%)	

(*continued on next page*)

Table A2 (*continued*)

Variables	Non-frail (n = 478)	Pre-frail (n = 520)	Frail (n = 93)	p-Value
Managerial	188 (40%)	185 (36%)	29 (33%)	
Skilled non-manual	104 (22%)	122 (24%)	20 (23%)	
Skilled manual	56 (12%)	108 (21%)	24 (27%)	
Semiskilled/Unskilled	18 (4%)	19 (4%)	7 (8%)	
Childhood IQ, mean (SD)	102.1 (14.4)	98.9 (14.8)	95.2 (17.4)	< 0.001***
Years of Education, mean (SD)	10.9 (1.2)	10.7 (1.1)	10.3 (0.9)	< 0.001***
History of diabetes, n (%)				< 0.001***
Yes	18 (4%)	48 (9%)	25 (27%)	
No	460 (96%)	472 (91%)	68 (73%)	
History of cardiovascular disease, n (%)				< 0.001***
Yes	92 (19%)	134 (26%)	42 (45%)	
No	386 (81%)	386 (74%)	51 (55%)	
History of high cholesterol, n (%)				< 0.01**
Yes	147 (31%)	192 (37%)	47 (51%)	
No	330 (69%)	328 (63%)	46 (49%)	
History of stroke, n (%)				< 0.05*
Yes	15 (3%)	30 (6%)	9 (10%)	
No	463 (97%)	490 (94%)	84 (90%)	
History of thyroid disease, n (%)				0.2
Yes	35 (7%)	53 (10%)	11 (12%)	
No	443 (93%)	467 (90%)	81 (88%)	
History of cancer, n (%)				0.4
Yes	61 (13%)	58 (11%)	15 (16%)	
No	417 (87%)	462 (89%)	78 (84%)	
History of Parkinson's disease, n (%)				< 0.05*
Yes	2 (> 1%)	1 (> 1%)	2 (> 1%)	
No	476 (< 99%)	519 (< 99%)	91 (< 99%)	
History of arthritis, n (%)				< 0.001***
Yes	175 (37%)	241 (46%)	61 (66%)	
No	302 (63%)	279 (54%)	32 (34%)	
Depressive symptoms, mean (SD)	1.24 (1.48)	1.69 (1.87)	3.53 (2.61)	< 0.001***

*** $P < .001$.
** $P < .01$.
* $P < .05$.

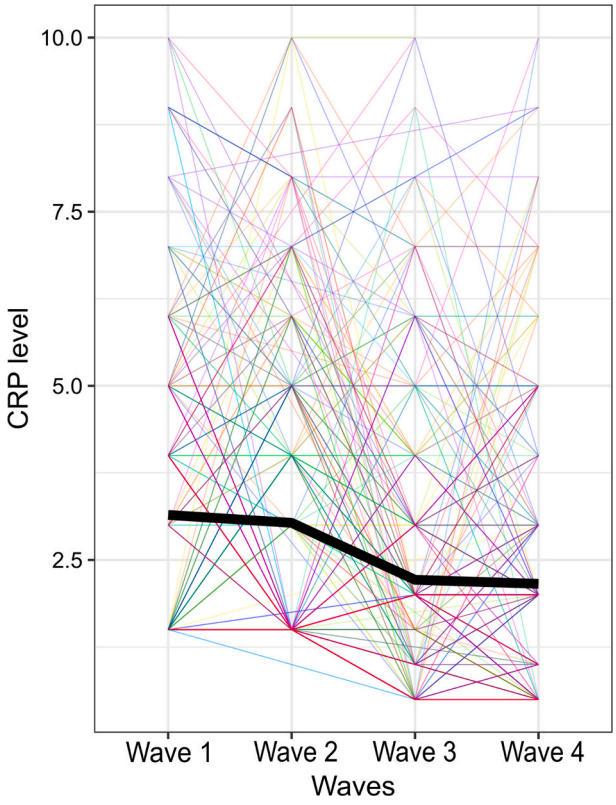

Fig. A1. A plot of CRP levels the course of follow-up.

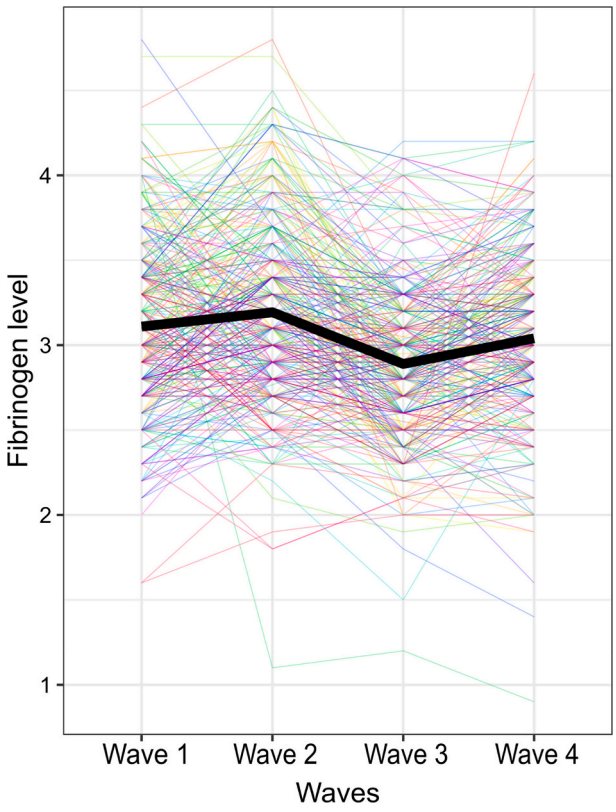

Fig. A2. A plot of Fibrinogen levels over the course of follow-up.

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2020.111055.

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4.3 Concluding remarks

Findings showed that inflammation may act as a marker of frailty progression risk measured by the FI but not the Fried phenotype (higher baseline inflammation was significantly associated with increased change in the FI but not Fried phenotype). The hypothesis that the FI and the Fried phenotype are comparable and measuring the same thing is not supported. This reinforces some previous findings (Aguayo et al., 2017) and suggests that these two measurement tools cannot be reliably used to measure the concept. What remains unclear is exactly what these differences are. As will be discussed more in subsequent chapters, understanding the specific components that make up frailty may help to unlock answers to these questions. Our hypotheses that higher baseline inflammation will be linked to higher baseline frailty and also worse frailty outcomes over time, were only partially supported. Accordingly, whilst Chapter 4.2 has shown that inflammation has an association with the FI and the Fried phenotype, it is not possible to definitively extend this to frailty as a general concept. Future research is still required to create a better understanding of what frailty entails, and then how this relates to inflammation. Despite this, findings here and elsewhere that show associations between inflammation and frailty measurement tools like the FI and Fried phenotype are useful, particularly in a clinical setting whereby it may be possible to identify those at risk of frailty due to increased levels of inflammation in older age.

As discussed in Chapter 4.2, the incorporation of more than one measure of frailty in a study is uncommon in the field, and no research paper included in the systematic review from Chapter 2 did so. As illustrated by the conflicting results, different measures of frailty can influence the results of the study. Whilst some studies may find significant findings using one frailty measure, there may be no effect using another. For example, Rogers and Fancourt (2020) explored the relationship between culture and frailty, finding a dose–

response relationship between older adults with high cultural engagement and lower risk of frailty and frailty progression. Whilst this points towards the beneficial effects of cultural engagement, these findings are based solely on the FI. As far as I am aware, no longitudinal frailty research has investigated the association between cultural engagement and frailty as ascertained by another type of measurement tool such as the Fried phenotype. This highlights one of the major issues with the field of frailty, as it is typically not made clear within research publications that 'frailty' can have different meanings according to the measurement tool. The conflation of different quantification methods into one definition means that there is the danger that research findings using tools like the FI or Fried phenotype may not translate to other clinical or research settings whereby other frailty measures are used. Utilising multiple frailty tools within the same study is one way to help address these issues and work towards finding a more harmonious measure that can be used across a variety of settings.

However, despite our findings that inflammation is associated with FI but not the Fried phenotype over time, it is important to note that this could be due to factors unrelated to the operational definition of frailty. For example, the differing follow-up times that I used could have played a role in the findings. Additionally, covariates like BMI were included in the Fried phenotype analyses but not the FI analyses due to the inclusion of BMI in the FI composition. Considering BMI is associated with inflammation processes (Kantor, Lampe, Kratz, & White, 2013) this could have also impacted the findings. Future research that accounts for these inconsistencies in analytic processes will continue to further our collective understanding of the differences between frailty measures.

The findings that inflammation is associated with frailty is supported by previous research (Soysal et al., 2016). However, frailty research, including my own in Chapter 4.2, typically do not explore the mechanisms underlying these associations. This is a limitation of this study that could be addressed in future research that explores the effect of chronic inflammation on protein degradation or important metabolic pathways (Lang et al., 2009). An

additional limitation was the broad approach to defining inflammation. Additional work is required to home in on the exact aspects of inflammation that are associated with frailty.

Chapter 5: Exploring the subpopulations of frailty trajectories

5.1 Introduction

This chapter builds on Chapter 4 by further exploring frailty progression over time. As detailed in the systematic review from Chapter 2, we know that frailty trajectories differ for a variety of reasons. I recently contributed to the research design of a study that identifies some of the reasons for which frailty trajectories may differ. We explored trajectories of frailty in five independent cohorts using a coordinated analytical approach to evaluate longitudinal frailty changes (Jenkins, Welstead, et al., 2021). We found differences in trajectories according to gender and baseline age. Women showed consistently higher frailty in all cohorts, but there were mixed findings when it came to the association between gender and frailty progression. Baseline age showed a statistically significant association with frailty progression in all cohorts. Figure 5.1 illustrates these differing trajectories.

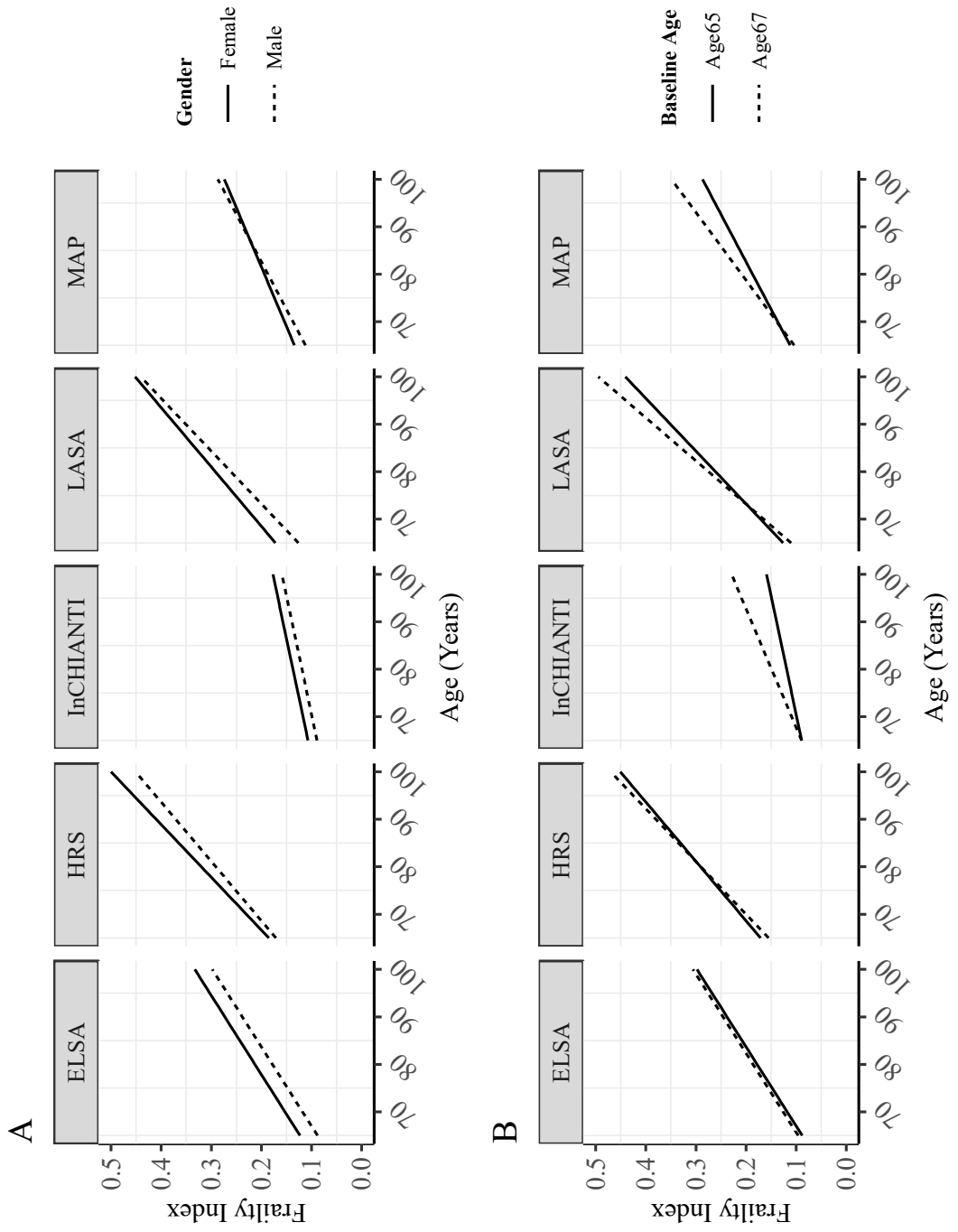

Figure 5.1: Graphical representation of the estimated model trajectory across cohorts for A. Women and Men; B. Individuals aged 65 or 67 years at Baseline (Jenkins, Hoogendijk, et al., 2021).

Another example of the insights to be gained from studying the factors influencing frailty progression was our recent study exploring the effect of neighbourhood social deprivation (Baranyi et al., 2021). Here, the Frailty index (FI) is utilised in the Lothian Birth Cohort 1936 and its findings show that for males, neighbourhood social deprivation in childhood and mid-to-late adulthood was associated with frailty in older age (β = 0.017; 95% CI: 0.005, 0.029; p = 0.007). In females, higher neighbourhood social deprivation in mid-to-late adulthood was associated with steeper frailty trajectories between age 70 and 82 (β = 0.005; 95% CI: 0.0004, 0.009, p = 0.033).

Research like this draws even more attention to the heterogeneity of frailty progression. As we see in Chapter 5.2 and in previous chapters, many factors including cohort, gender, and age influence frailty trajectories. However, research typically treats frailty as a stable factor that affects each individual in the same way; most studies explore the mean change in frailty over time. Recent research suggests that frailty progression is heterogeneous, but that certain groups of individuals follow similar patterns of change over time (Chamberlain, Finney Rutten, et al., 2016). Accordingly, the goal of Chapter 5 was to identify any subpopulations of participants following similar frailty trajectories in LBC1936, and examine what these individuals have in common. This research paper was published in *Gerontology* (M. Welstead et al., 2021).

5.2 Heterogeneity of Frailty Trajectories and associated factors in the Lothian Birth Cohort 1936

Introduction

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Heterogeneity of Frailty Trajectories and Associated Factors in the Lothian Birth Cohort 1936

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Keywords
Latent class mixed models · Subpopulations · Differential ageing · Longitudinal study · Older adults

Abstract
Introduction: Recent research suggests that the experience of frailty progression may be heterogeneous, with latent subpopulations of older adults following distinct trajectories of frailty. We aimed to investigate this notion and determine whether certain factors are associated with the membership of these subpopulations. ***Methods:*** Data from 5 data waves collected over 12 years in participants of the Lothian Birth Cohort 1936, aged 70 at baseline, were used to derive the frailty index (FI) (NW1 = 1,091, NW5 = 431). These were used in latent class mixed modelling to estimate subpopulations of frailty trajectories. ***Results:*** A quadratic latent class mixed model found 3 distinct groupings, which followed a low (61%, *n* = 632), medium (36%, *n* = 368), or high (3%, *n* = 28) FI trajectory. Each grouping had different intercepts and slopes, with the high grouping following the steepest trajectory indicating a rapid increase in frailty. Findings showed that in general, those in the low grouping were younger, had higher education, higher age 11 cognitive ability, and were from a higher social class than those in the medium and high groupings. ***Discussion/Conclusion:*** Our findings demonstrate heterogeneity in frailty trajectories over 12 years in individuals aged 70 years at baseline. Membership of higher frailty trajectory groupings was associated with lower social class, less education, and lower childhood cognitive ability, indicating the potential for future interventions to target individuals who are at the greatest risk of belonging to the high frailty trajectory. Future research is required to continue this line of inquiry by exploring other risk and protective factors, and importantly, to assess whether it is possible to realign an individual's membership to a less detrimental grouping of frailty trajectory.

Introduction

Frailty is characterized by an increased vulnerability to external stressors and a greater risk of disease, disability, and death [1]. It is well established that frailty can affect groups of older people of the same age in different ways [2], and has been shown to be a more reliable indicator of adverse health outcomes than chronological age [3, 4]. Identifying the ways in which frailty affects different groups in different ways at a cross-sectional level is im-

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portant; however, equally important is exploring how longitudinal frailty trajectories differ across different groups.

A recent systematic review of longitudinal frailty studies [5] found that there is limited evidence of heterogeneity in the field, with most studies exploring mean change over time. For example, previous studies have assessed frailty progression over time accounting for predictive factors such as gender [6], physical activity [7], and inflammation levels [8]. While using a population's mean change in frailty is widely used and effective, it does not always capture the full heterogeneity of a dataset as it estimates the population mean frailty curve under the assumption that all individuals follow a similar pattern of change [9]. Latent class mixed modelling [10], which makes the assumption that there are underlying exclusive latent classes [11], may allow us to better explore the heterogeneity of frailty in a population and isolate frailty trajectories of any underlying subpopulations with distinct patterns of change over time. Identifying subpopulations of frailty change and exploring the factors which may be associated with these trajectories has important implications. Previous studies that have identified distinct frailty trajectories in older adult populations have highlighted the potential role this research may have in targeting high-risk individuals [12]. Understanding these distinct trajectories also improves the ability to design individualized interventions focussed on preventing or delaying the development of numerous adverse outcomes that are associated with frailty [13].

Only a handful of studies using continuous frailty measures have utilized mixture modelling approaches to identify latent trajectories of frailty [5]. Methods of measuring frailty in these studies differed, with most favouring the frailty index (FI), which characterizes frailty as the accumulation of deficits across multiple body systems encompassing physical, social, and cognitive domains [6, 14–16]. For example, FI trajectories were assessed in an English cohort of participants using electronic primary care records [17]. Over the course of 1 year with 12 time points, a latent class mixed model with 3 subpopulations was found to be the best fit (labelled as rapidly rising, moderately increasing, and stable). Comparatively, other studies used a different method to measure frailty, favouring instead the Fried phenotype which measures frailty according to 5 criteria thought to reflect the affected systems of frailty: weight loss; exhaustion; weakness; slowness whilst walking; and low levels of physical activity [18]. For example, 1 longitudinal study [19] used a modified version of the Fried phenotype and found 3 distinct subpopulations in a Mexican-American population over the course of 12 years (labelled as a consistently low group, a progressive moderate group, and a progressive high group).

Although these findings suggest that frailty progression can affect different subpopulations in different ways, further studies are needed [5]. It is important to understand the unique factors associated with these subpopulations, that is, which individuals are more likely to be members of a rapidly rising trajectory opposed to a slow and steady trajectory. Accordingly, here we explored the subpopulations of trajectories in the FI over approximately 12 years in the Lothian Birth Cohort 1936 (LBC1936). FI was used as the measure of frailty as it is measured on a continuous scale, allowing more subtle changes in frailty over time to be detected than a categorical approach [8]. Additionally, it is widely used in the field, allowing comparisons to other studies. We used latent class mixed models to establish a best fitting number of subpopulations, and then explored factors predictive of these subpopulations. In line with previous research [17, 19, 20], we expected to find at least 3 subpopulations of FI trajectories in the LBC1936. We also expected that those individuals allocated to the most detrimental trajectories will have higher rates of the frailty trajectory risk factors that we are already familiar with such as lower education [19, 21], social class [22], and childhood intelligence [23].

Materials and Methods

Study Sample

The LBC1936 is a study based upon the follow-up of participants of the Scottish Mental Survey in 1947 which recruited 70,805 Scottish school children all born in 1936 [24]. The first wave of LBC1936 ran from 2004 to 2007 and consisted of 1,091 participants (mean age, standard deviation [SD] = 69.5 [0.8]). Follow-up testing occurred approximately every 3 years thereafter: wave 2 from 2007 to 2010 (n = 866, mean age [SD] = 72.5 [0.7]), wave 3 from 2011 to 2013 (n = 697, mean age [SD] = 76.3 [0.7]), wave 4 from 2014 to 2017 (n = 550, mean age [SD] = 79.3 [0.6]), and wave 5 from 2017 to 2019 (n = 431, mean age [SD] = 82.0 [0.5]) [25]. Summary data are reported in Table 1. The study followed the Declaration of Helsinki guidelines and obtained ethical permissions from the Multicentre Research Ethics Committee for Scotland (MREC/01/0/56), Lothian Research Ethics Committee (LREC/2003/2/29), and Scotland A Research Ethics Committee (07/MRE00/58). Written consent was obtained from all participants.

Frailty Measure

A FI was derived at each of the 5 waves of the LBC1936 according to standard guidelines [16]. In total, 30 deficits covering psy-

Table 1. Summary characteristics of participants at each LBC1936 wave

Variables	Wave 1 2004–2007	Wave 2 2007–2010	Wave 3 2011–2013	Wave 4 2014–2017	Wave 5 2017–2019
Participants, *n*	1,091	866	697	550	431
Lost to follow-up since previous wave, *n*	0	225	169	147	119
Age, years, mean (SD)	69.5 (0.8)	72.5 (0.7)	76.3 (0.7)	79.3 (0.6)	82.0 (0.5)
Female, *n* (%)	543 (49.8)	418 (48.3)	337 (48.4)	275 (50)	222 (52)
Type of residence, *n* (%)					
Own home	987 (90.5)	791 (91.3)	637 (91.4)	506 (92.0)	400 (92.8)
Rented accommodation	89 (8.2)	67 (7.7)	49 (7.0)	32 (5.8)	24 (5.6)
Residential home	6 (0.5)	6 (0.7)	2 (0.3)	1 (0.2)	1 (0.2)
Nursing home	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (0.4)	2 (0.2)	9 (1.2)	11	6 (1.4)
FI, mean (SD)	0.16 (0.1)	0.18 (0.1)	0.20 (0.1)	0.21 (2.0%)	0.22 (0.1)
Social class, *n* (%)					
Professional	194 (17.8)	170 (19.6)	144 (20.7)	127 (23.1)	102 (23.7)
Managerial	412 (37.8)	331 (38.2)	271 (38.9)	217 (39.5)	171 (39.7)
Skilled nonmanual	249 (22.8)	188 (21.7)	143 (20.5)	109 (19.8)	93 (21.6)
Skilled manual	191 (17.5)	144 (16.6)	111 (15.9)	78 (14.2)	52 (12.1)
Semiskilled/unskilled	45 (4.1)	33 (3.8)	28 (4.0)	19 (3.5)	13 (3.0)
Age 11 cognitive ability, mean (SD)	0.0 (11.6)	0.5 (11.8)	1.2 (11.8)	1.4 (11.8)	1.8 (11.6)
Years of education, mean (SD)	10.7 (1.1)	10.8 (1.1)	10.8 (1.1)	10.9 (1.2)	10.9 (1.2)

FI, frailty index; SD, standard deviation.

chological, cognitive, and physical dimensions were used to construct the measure. A full list of the included deficits and their cutoff values has been described in more detail previously [8]. To calculate an FI score for each participant, their present deficits were summed and divided by the number of total deficits ($n = 30$). For instance, a participant with 12 deficits would have an FI score of 12/30 = 0.4. Scores ranged from 0 to 1 with a higher score indicating a higher level of frailty.

Covariates

Covariates were included to assess differences in subpopulation characteristics. We included: age at baseline, sex, years of education, age 11 cognitive function, and social class (professional/managerial/skilled, nonmanual/skilled manual or semiskilled/unskilled). Age 11 cognitive function was derived as part of the LBC1936 using the Moray House Test at age 11 [24] and standardized into an IQ-type score for age in days on the test date. Social class was derived from the principal occupation of each participant and coded using the 1980 census [26]. More detail has been reported in previous LBC1936 articles [8, 25].

Missing Data

Across the 5 waves of the LBC1936 there were instances where some of the items needed to derive the FI were missing. To address this, we used multiple imputations using the MICE package in R version 4.0.3 to impute these values [27, 28]. Five rounds of imputations estimated the missing data and a total of 49 missing values (4.5%) were replaced with substituted values. Full details of this are published elsewhere [8].

Statistical Analyses

In order to identify latent subpopulations of FI trajectories in the LBC1936, latent class mixed models were used. Of the 1,091 participants, 63 had missing covariate data. Accordingly, 1,028 participants were included in the latent class mixed models. To establish which model was best fitting for the data, it was necessary to compare models describing different functional shapes for the frailty trajectories. First, models describing linear rate of change and with an increasing number of classes were estimated. Next, we estimated models describing quadratic change with an increasing number of classes. The best fitting model was identified comparing values for Akaike information criterion (AIC) and Bayesian information criterion (BIC) [29], indices that help identify the most parsimonious model. Models with the lowest AIC and BIC are preferred. Posterior probabilities were calculated for each participant, and participants were assigned to a certain trajectory group according to the class with the highest probability [30]. As a measure of fit, average posterior probabilities were calculated and reported.

Comparisons of the AIC and BIC of different models revealed that a quadratic model with either 3 or 4 classes of FI trajectories showed the best fit. A model with 4 classes of latent FI trajectories showed a marginally better fit according to the BIC value (−9,995.12) and AIC value (−10,105.01) than a 3-class model (BIC: −9,979.04, AIC: −10,068.94). However, the 4-group model had relatively low posterior probabilities for each of the group memberships (0.71 in 2 cases), whilst the 3-group model showed posterior probabilities above 0.83 (group 1: 0.90, group 2: 0.84, group 3: 0.95). Typically probabilities above 0.80 indicate a strong fitting model [31], and accordingly, the posterior probabilities indicate that discrimination of individuals into groups in the 4-group mod-

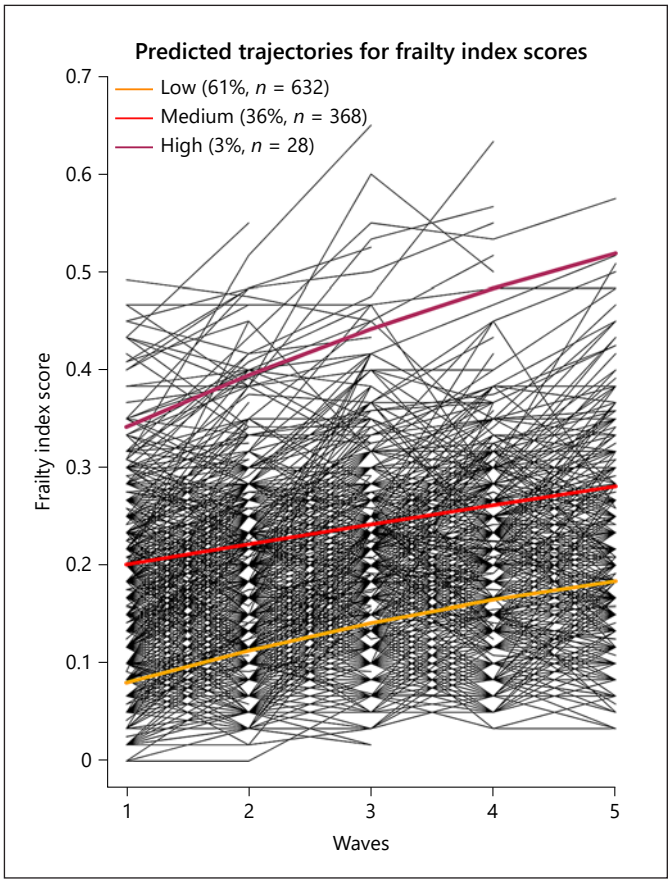

Fig. 1. FI scores for each individual of the LBC1936 over the 5 waves. Three trend lines show differing trajectories for different subpopulations. FI, frailty index.

el was fuzzier than in the 3-group model. Additionally, upon further inspection, all individuals assigned to the smallest grouping in the 4-group model were also assigned to the smallest grouping in the 3-group model. Subsequently, taking into account each of these indicators, preference was given to the 3 group quadratic model, as it was the most parsimonious. AIC and BIC values for each model are reported in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519240. Comparisons of the covariates across different trajectory groupings were assessed by ANOVAs, *t* tests, and Pearson's χ^2 tests. All analyses and figure creation were undertaken in R Version 3.6.1 [28] with the latent class mixed models using the Hlme package, and Figure 1 using the Spaghettiplot function.

Results

Of the 1,028 participants with complete data, 520 (51%) were male and 508 (49%) were female. The mean age of these participants at baseline was 69.58 (SD 0.84). Using a quadratic latent class mixed model, 3 groupings of latent FI trajectories were identified. As illustrated in Figure 1, findings show 3 distinct FI trajectories with differing intercepts and slopes. For ease of understanding, these 3 trajectory groups will henceforth be referred to as groups Low, Medium, and High.

In the quadratic model the intercept represented the baseline FI, the linear slope corresponded to the rate of change over time, and the quadratic term indicated the change in the rate of change, that is, the acceleration or deceleration over time. The low grouping was most common with 61% (n = 632) of participants. Participants in this grouping showed a baseline FI of 0.08 (SE = 0.01) with a linear slope of 0.04 (SE = 0.00). However, the quadratic term indicated that this increase significantly slowed over the course of the 5 waves (q = −0.002). Accordingly, by the final wave the low grouping had increased by 0.10 to a FI score of 0.18. The medium grouping contained 36% (n = 368) of the sample, showing a baseline FI of 0.20 (SE = 0.01) with a linear slope of 0.02 (SE = 0.01). By the final wave, the medium grouping had increased by 0.08 to a FI score of 0.28. The high grouping held only a small minority of the sample with the remaining 3% (n = 28). This grouping showed the highest baseline FI of 0.34 (SE = 0.03) and the steepest trajectory with a linear slope of 0.06 (SE = 0.02) which equated to an overall increase of 0.18 by the final wave to a FI score of 0.52.

Probability of Classification

Results estimating the probability of group membership as a function of age, sex, education, age 11 cognitive functions, and social class, indicated that there were significant differences between the 3 groups. As reported in Table 2, associations between the covariates and FI trajectory group were significant for age at baseline, social class, age 11 cognitive ability, and years of education. No sex differences were found. Post hoc *t* tests and Pearson's χ^2 tests were used to assess the difference between specific FI trajectory groups and the covariates (low vs. medium/low vs. high/medium vs. high). Significant differences indicated that members of the low grouping were significantly more likely to come from a higher occupational social class than those in the medium ($\chi^2[5] = 67.67$, $p < 0.001$) or high grouping ($\chi^2[5] = 51.72$, $p < 0.001$). Those in the low grouping were also significantly younger at baseline than those in the medium grouping ($t[998] = -10.31$, $p < 0.001$), but not the high grouping. Baseline age did not significantly differ between the medium and high groups. Years of education was significantly higher in the

Table 2. A comparison of covariate characteristics between latent classes

Variables	Low (n = 632)	Medium (n = 368)	High (n = 28)	p value
Age at baseline, mean (SD)	69.38 (0.83)	69.92 (0.75)	69.62 (0.74)	<0.001[1]*
Sex, *n* (%)				
Male	324 (51.3)	182 (49.5)	14 (50.0)	0.857[2]
Female	308 (48.7)	186 (50.5)	14 (50.0)	
Social class, *n* (%)				
Professional	145 (23.0)	37 (10.1)	1 (3.6)	<0.001[2]*
Managerial	261 (41.3)	120 (32.6)	7 (25.0)	
Skilled nonmanual	140 (22.2)	92 (25.0)	3 (10.7)	
Skilled manual	68 (10.8)	98 (26.6)	13 (46.4)	
Semiskilled/unskilled	18 (2.9%)	21 (5.7%)	4 (14.3%)	
Age 11 cognitive ability, mean (SD)	3.95 (9.08)	−5.57 (11.80)	−15.96 (15.30)	<0.001[1]*
Years of education, mean (SD)	10.99 (1.16)	10.29 (0.90)	10.14 (0.89)	<0.001[1]*

* $p < 0.001$. [1] Linear model ANOVA. [2] Pearson's χ^2 test. SD, standard deviation.

low grouping than both the medium (t[998] = 9.98, p < 0.001) and high grouping (t[658] = 3.82, p < 0.001). Age 11 cognitive ability was significantly higher in the low grouping than both the medium (t[998] = 14.28, p < 0.001) and high groupings (t[658] = 10.95, p < 0.001), and also significantly higher in the medium grouping than the high grouping (t[394] = 4.39, p < 0.001). No other statistically significant findings between specific FI trajectory groups and covariates were found.

Discussion/Conclusion

In this study, we investigated the existence of subgroups of individuals with distinct patterns of frailty change over time using data from the LBC1936. Using a growth mixture model, we found that participants of the LBC1936 tend to fit into one of 3 trajectory groups. Of the population, 61% fit into the low grouping, 36% into the medium grouping, and 3% into the high grouping. Each grouping showed significantly different baseline FI scores and differing slopes of change over time. The high grouping showed both the highest baseline FI score and steepest slope of change, indicating a rapid increase in frailty over the 5 waves. Whilst the low and medium groupings have significantly different baseline FI scores, over the 5 waves, they gradually begin to take converge due to a marginally steeper FI trajectory in the low grouping. Further analysis revealed that membership of these 3 groupings of FI trajectory were affected by social class, years of education, age at baseline, and age 11 cognitive ability.

Comparison with Other Literature and Interpretation

Comparisons with similar literature prove difficult due to differing frailty outcome measures and time scales. For example, 2 longitudinal studies [19, 20] found 3 distinct frailty trajectories in a group of older adults. However, both of these studies utilized the Fried phenotype, which not only conceptualizes frailty in a different way to the FI, but it also measures frailty as a categorical variable. Comparatively, 1 longitudinal study [17] utilized the FI and similar statistical analyses as our study, finding 3 frailty trajectories. However, this study followed participants in the year preceding the participant's death, meaning that the trajectories will presumably be higher and more pronounced than a relatively healthy older adult sample like the LBC1936. However, despite these substantial methodological differences between previous studies, it is notable that our findings of 3 distinct trajectories are consistent with all of these mentioned studies. This indicates that frailty does seem to affect 3 subpopulations of older adults in different ways. It is unsurprising to observe that those in the low grouping had a steeper FI trajectory than those in the medium grouping as this supports previous findings and the notion that those with the most to lose tend to show steeper slopes of decline. For example, 1 study which identified 3 distinct frailty trajectories [17] found that the grouping with the lowest baseline frailty rate also showed the steepest trajectory.

Our findings indicated that social class, years of education, age at baseline, and age 11 cognitive ability all significantly differed according to FI trajectory grouping. These findings reinforce previous research which impli-

cates these factors as predictors of frailty, largely finding that younger, more educated individuals from a higher social class are less likely to become frail [5]. These findings are significant as they indicate that modifiable factors such as education may be able to provide an effective way to help reduce an individual's risk of higher levels of frailty. It seems probable that there may be other underlying factors that we have not tested for which help explain trajectory group membership. Further research is required to assess other factors and explore the causality of these in relation to FI trajectory group membership.

Irrespective of the potential factors associated with FI trajectory groupings, it is clear that a certain subpopulation of older adults is at great risk of developing frailty and rapidly declining, presumably until death occurs. By understanding these trajectories and mapping out the pathways to which these subpopulations follow, it will be better possible to put in place effective early interventions and implement frailty treatment measures. A crucial question for future research is whether individuals are able to change between FI trajectory groupings, for example, with early intervention is it possible for an individual in the high grouping to shift into the medium or low grouping. Additionally, it would be highly informative to further explore the associations between frailty trajectory groupings and clinical data such as mortality, disability, and health-care use.

Limitations and Strengths

There are several limitations to consider in this study. Firstly, it has been well established that the participants of the LBC1936 have higher levels of physical health and cognitive ability than the general population [25, 32]. Physical health and cognitive ability both contribute to frailty risk [5], and accordingly, our results may be conservative when considering the general population whereby a larger proportion may be at risk of falling into the medium or high groupings. Secondly, after splitting the sample into the 3 groupings, the high grouping contained only 28 participants, and accordingly, larger studies are required to validate our results. Thirdly, as with most longitudinal studies in older adults, due to significant rates of attrition or loss to follow-up due to death, LBC1936 has a healthy survivor effect whereby those who remain in the study throughout follow-up are also the participants with better overall health. Previous LBC1936 has shown that those who dropout of the study had lower socioeconomic status, physical fitness, and cognitive ability [25]. Subsequently, this study may also underestimate how steep the frailty trajectories are in the general population. Fourthly, due to the FI's biopsychosocial approach of including a wide range of variables from various domains, and due to small sample sizes reducing the analysis power, it was not feasible to control some important factors such as physical activity levels, body mass index, or polypharmacy. Accordingly, it may be necessary for future research to undertake a similar analysis in a larger cohort using a frailty measure, such as the Fried phenotype [18] which focusses purely on physical domains, and would subsequently allow for more covariates to be considered. And finally, whilst the FI has been shown to have good reliability and validity as a measure of frailty, there are many different ways of measuring frailty, and it is important to acknowledge that studies like this one which uses the FI may not be comparable to other studies using different frailty measurement tools [33].

This study also had several strengths. The follow-up period was around 12 years with 5 time points (age ~69 to ~82 years old). Amongst community dwelling individuals, it is thought that around 10% of 65 year olds are frail [34], with this percentage increasing significantly over the following decades. With this in mind, our follow-up period allowed us to track frailty in later life over a critical period of frailty progression. Additionally, by utilizing latent class mixed models, we were able to capture the heterogeneity of frailty progression in later life. By doing so, we provide a more individualized approach to frailty, acknowledging that not all groups of people will be the same. This approach has the potential to inform and optimize future prevention strategies with a more targeted approach.

Conclusions

This study identified 3 trajectories of frailty in the Lothian Birth Cohort 1936 across approximately 12 years of data collection. Low, medium, and high trajectories were found to differ significantly on a number of factors including social class, education, and age 11 cognitive ability. Addressing education and social class disparities may help to close the gap between the most detrimental frailty trajectories and improve health outcomes. Our findings are a preliminary indication of heterogeneity in the progression of frailty in later life. Future research should continue to develop this line of research by implementing consistent frailty measures in different samples and utilizing latent class mixed model analysis to reveal any trajectories of subpopulations. By exploring the heterogeneity of frailty trajectories in different populations, and factoring in variables such as social class, education, and age

11 cognitive ability, this study sheds further light on how frailty influences certain groups of people over time. Further work into these avenues of research are imperative in furthering our understanding of frailty and informing therapeutic and preventative interventions.

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Statement of Ethics

The study followed the Declaration of Helsinki guidelines and obtained ethical permissions from the Multicentre Research Ethics Committee for Scotland (MREC/01/0/56), Lothian Research Ethics Committee (LREC/2003/2/29), and Scotland A Research Ethics Committee (07/MRE00/58). Written consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Miles Welstead contributed to conceptualization, methodology, software, formal analysis, writing – original draft, writing – review and editing, and visualization. Graciela Muniz-Terrera contributed to conceptualization, methodology, writing – review and editing, and supervision. Tom C. Russ contributed to conceptualization, methodology, writing – review & editing, and supervision. Michelle Luciano contributed to conceptualization, methodology, writing – review and editing, and supervision.

Data Availability Statement

All data generated or analysed during this study are included in this article (and/or) its online suppl. files. Further enquiries can be directed to the corresponding author.

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5.3 Concluding remarks

The purpose of this study was to explore subpopulations of frailty trajectories. The hypothesis that there would be at least three subpopulations of FI trajectories was supported and helps to demonstrate the heterogeneous nature of frailty progression by indicating that not all older adults will follow a similar path. Further research is required to understand whether these subpopulations are present in other settings. The second hypothesis that those on the most detrimental frailty trajectories would have lower education, social class, and childhood intelligence was also supported. This adds to our collective knowledge about the risk factors associated with increases in frailty. Future research that identifies more of these factors will help to develop a portfolio of frailty trajectory associated risk factors, all of which will feed into prevention strategies.

A limitation of the approach taken in Chapter 5.2 is the choice to use continuous measures, only the FI was utilised. Assessing the subpopulations of frailty trajectories using other measures such as the Fried phenotype may be enlightening, as it would allow us to gain a better understanding of how the physical component of frailty changes over time. Future research could also explore the possibility of using a modification of the Fried phenotype, which transforms it to a continuous composite variable. As discussed in Chapter 2, various studies have trialled using such a modification (Buchman, Wilson, Bienias, & Bennett, 2009; Liu et al., 2018; Peek, Howrey, Ternent, Ray, & Ottenbacher, 2012). Further work is required to explore these modifications and assess how they correlate to other continuous measures such as the FI.

This highlights an unknown aspect of the FI: each deficit included in the index is unweighted and treated equally and so it is unable to identify which domains of frailty an individual is affected by the most. One way in which to assess specific domains of frailty is to explore their trajectories

independently. How and why particular deficits accumulate over time whilst others either stay the same or improve is unclear. For instance, if it transpires that deficit X tends to accumulate in a cohort over time, whereas deficit Y tends to drop off over time, this is surely an important consideration to take into account when calculating frailty. A component of the FI that can be further explored in the LBC1936 is that of cognitive impairment.

Whilst frailty and cognitive impairment have typically been studied separately, recent work has focussed on the close interaction that these two phenomena may have (Liu et al., 2018). In particular there has been the recognition that cognitive impairment and physical frailty are often both simultaneously present in older age (Morley et al., 2015). As a result of this focus an International Consensus group, the IANA-IAGG, put forward the definition of 'cognitive frailty', a concept to refer to an individual with both physical frailty and cognitive impairment (Kelaiditi, Cesari, Canevelli, Van Kan, et al., 2013). Cognitive frailty reinforces the view that 'things that are bad for the body, are likely to be bad for the brain' (Searle & Rockwood, 2015), indicating that whilst frailty and cognitive impairment may be distinct factors, they may be interlinked in later life. The first operational definition, proposed by Kelaiditi, Cesari, Canevelli, Abellan Van Kan, et al. (2013), used the simultaneous presence of physical frailty and cognitive impairment in the absence of dementia to indicate cognitive frailty. Several studies have quantified cognitive frailty using different models based on coexisting physical frailty and cognitive impairment (Panza et al., 2018; Sugimoto et al., 2018). However, the concept has yet to be embraced by all, with some researchers pointing to the use of 'cognitive frailty' as a common general description of those in older age with cognitive impairment (Woods, Cohen, & Pahor, 2013). Additionally, as reported by Sargent and Brown (2017), consistent and widely accepted operational definitions for cognitive frailty and psychometrically appropriate clinical measures are currently lacking. One prominent issue is that there remains a need for gold standard measurements for the individual components of cognitive frailty – i.e. physical frailty and cognitive impairment (Panza et al., 2018). Accordingly, future research is required to assess the

best way to measure cognitive frailty. A follow-up to the 2013 IANA-IAGG consensus may help to establish a more consistent operationalisation and answer the questions raised since the initial operational definition was proposed. In lieu of a valid and reliable measure of cognitive frailty, a preliminary step in fully understanding how cognitive impairment changes over time in the LBC1936 and how frailty may affect this change was to explore a health state known as mild cognitive impairment.

Chapter 6: Mild cognitive impairment over time

6.1 Introduction

This chapter introduces research into MCI in the LBC1936. MCI is a commonly used concept in older adult research and clinical settings, but had not previously been examined in the LBC1936. In addition to a 'general' MCI, I specify specific subtypes of cognitive impairment: amnestic MCI, which includes only memory related decline, and non-amnestic MCI, which includes non-memory related cognitive impairment (executive function, attention, language, and visuospatial skills). The aim of this chapter is to introduce the concept of MCI and its subtypes, and detail the process of deriving the measure in the LBC1936. I also aimed to compare LBC1936 prevalence with the general UK population to understand the generalisability of the results. Identifying and reporting these data also enabled the research in Chapter 7 to identify those at highest risk of progressing to and reverting from MCI, and assessing the influence of factors such as physical frailty. This research paper was published in *Alzheimer's Disease and Associated Disorders* (Miles Welstead, Luciano, Muniz-Terrera, & Russ, 2021).

6.2 Prevalence of mild cognitive impairment in the Lothian Birth Cohort 1936

OPEN

Prevalence of Mild Cognitive Impairment in the Lothian Birth Cohort 1936

Miles Welstead, MSc, Michelle Luciano, PhD,* Graciela Muniz-Terrera, PhD,† Adele M. Taylor, MA,* and Tom C. Russ, PhD, MRCPsych*†‡*

Background: The Lothian Birth Cohort 1936 (LBC1936) is a highly phenotyped longitudinal study of cognitive and brain ageing. Given its substantial clinical importance, we derived an indicator of mild cognitive impairment (MCI) and amnestic and nonamnestic subtypes at 3 time points.

Methods: MCI status was derived at 3 waves of the LBC1936 at ages 76 (n = 567), 79 (n = 441), and 82 years (n = 341). A general MCI category was derived as well as amnestic MCI (aMCI) and nonamnestic MCI (naMCI). A comparison was made between MCI derivations using normative data from the LBC1936 cohort versus the general UK population.

Results: MCI rates showed a proportional increase at each wave between 76 and 82 years from 15% to 18%. Rates of MCI subtypes also showed a proportional increase over time: aMCI 4% to 6%; naMCI 12% to 16%. Higher rates of MCI were found when using the LBC1936 normative data to derive MCI classification rather than UK-wide norms.

Conclusions: We found that MCI and aMCI rates in the LBC1936 were consistent with previous research. However, naMCI rates were higher than expected. Future LBC1936 research should assess the predictive factors associated with MCI prevalence to validate previous findings and identify novel risk factors.

Key Words: MCI, cognitive aging, amnestic, nonamnestic, prevalence

(*Alzheimer Dis Assoc Disord* 2021;35:230–236)

BACKGROUND

In conjunction with advancements in health and social care in the past century, life expectancy has improved dramatically and contributed to a rapidly increasing older population.[1] A consequence of this demographic shift is the challenge we now face to care for a larger number of older adults with susceptibility to cognitive deterioration.[2] Understanding how cognitive decline affects older people is imperative in order to design interventions to slow or delay decline and ensure individuals are on the healthiest aging trajectory possible.[3] Decline in memory is a key indicator of dementia; however, it is common in older age, and differences between normal age-related decline and the early stages of dementia can be difficult to differentiate.[4]

The concept of mild cognitive impairment (MCI) traces back many years but has gained particular traction over the past few decades.[5] Petersen et al[6] popularized the concept as a distinct clinical condition and established a set of criteria based on memory changes without loss of ability to undertake normal activities. These criteria heavily influenced the way in which MCI was, and continues to be, identified in research and clinical settings. However, other researchers such as Dubois and Albert[7] disputed the notion of MCI as a distinct clinical entity, instead proposing it as a stage of severity for particular disorders. Accordingly, they proposed a "prodromal Alzheimer disease" based upon subjective memory complaints with progressive onset, preserved ability to undertake activities of daily living, neuroimaging, and biomarker testing. Disagreement on how MCI should be conceptualized has led to multiple attempts at an international consensus. Winblad et al[8] reached consensus that MCI criteria should assess whether an individual has a dementia diagnosis, whether their cognition has shown subjective and/or objective decline over time, and whether their activities of daily living are significantly affected —and, indeed, how this latter criterion is judged.

This groundwork informed the most recent guidelines proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines for Alzheimer disease.[9] These guidelines propose 4 criteria based on: (1) concern regarding a change in cognition, (2) impairment in 1 or more cognitive domains, (3) preservation of independence in functional abilities, and (4) no diagnosis of dementia. In addition to identifying general MCI, there has also been increased interest in identifying specific subtypes of MCI that may precede certain types of dementia. For instance, amnestic MCI (aMCI) focuses solely on memory-related cognitive impairment, whereas nonamnestic MCI (naMCI) focusses on cognitive impairment in other domains such as processing speed, attention, and executive functions.[10] Associations found between these subtypes and the risk of converting to dementia depend heavily on how the measures are defined and the population in which they are implemented. With this in mind, some research has indicated that aMCI may be associated with an increased risk of converting to Alzheimer disease, while naMCI is linked with other types of dementia such as diffuse Lewy body dementia.[11] Another caveat of using MCI and its subtypes as a measure of subclinical cognitive impairment is

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that there is great debate surrounding its clinical utility. It remains contested as to how useful MCI is in a clinical context, what it actually captures, and whether other measures such as other cognitive impairment no dementia, which does not factor in functionality, may in fact provide a better estimate of those at high risk of developing dementia.[12] Despite this, MCI can be a useful tool to capture cognitive decline in research. By identifying MCI and its subtypes it will potentially allow for improved knowledge on how early prevention strategies can identify individuals who are at high risk of cognitive decline and subsequent dementia. Here we use the NIA-AA guidelines to derive an identification of MCI and its subtypes using data from the Lothian Birth Cohort 1936.[13,14] We hypothesize that MCI rates will be similar to those found in other older adult cohorts and that prevalence of all types of MCI will be higher in later data waves.

METHODS

At Wave 1, the LBC1936 study consisted of 1091 participants, born in 1936 with a mean age of 69 (SD = 0.89) years, mostly surviving members of the Scottish Mental Survey 1947.[15] Wave 1 took place between 2004 and 2007, with follow-up waves approximately every 3 years thereafter at ages: 73 (n = 866), 76 (n = 697), 79 (n = 550), and 82 years (n = 431). More details on recruitment and testing procedures have been published previously.[13,14,16] The LBC1936 study was conducted according to the Declaration of Helsinki guidelines. Ethical permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (Wave 1: MREC/01/0/56), the Lothian Research Ethics Committee (Wave 1: LREC/2003/2/29), and the Scotland A Research Ethics Committee (Waves 2, 3, 4 and 5: 07/MRE00/58). Written consent was obtained from participants at each of the waves.

Identification of MCI

Using data previously collected in the LBC1936, an algorithm was created which identifies participants who fulfill the MCI criteria as outlined by the NIA-AA workgroups on diagnostic guidelines for Alzheimer's disease.[9] Variables necessary to conduct MCI coding were collected from Wave 3 (age 76) onwards. In order to be classified in the MCI category, participants must have shown met all 4 criteria reported below:

(1) Concern regarding a change in cognition: self-reported memory problems that are interfering with their life, as recorded in a questionnaire at each wave.
(2) Impairment in 1 or more cognitive domains: scores at least 1.5 SD below the mean on at least 1 cognitive domain (memory, executive function, attention, language, or visuospatial skills) *and* either shows a decline from the previous wave to below the 10th percentile on 1 test, a decline from wave 1 to below the 20th percentile on 1 test, or a decline from the previous wave to below the 20th percentile on 2 tests.
(3) Preservation of independence in functional abilities: scores at least 1.5 SD below the mean on the Townsend Disability Scale overall score.[17]
(4) No diagnosis of dementia: does not self-report or have a formal diagnosis of dementia *and* scores at least 24 on the Mini-Mental State Examination (MMSE).[18]

Cognitive domains were assessed using the following cognitive tests: Symbol Search, Digit Symbol Coding, Matrix Reasoning, Letter-Number Sequencing, and Block Design from the Wechsler Adult Intelligence Scale III (WAIS) and Logical Memory I & II from the Wechsler Memory Scale III (WMS-III).[19] A cut-off of ≥ 1.5 SD below the mean or scoring below specific percentiles was used to indicate cognitive impairment. Consistent with previous research co-authored by the creators of the NIA-AA guidelines,[20] cognitive decline was determined as a decline from the previous wave to below the 10th percentile on 1 test, a decline from wave 1 to below the 20th percentile on 1 test, or a decline from the previous wave to below the 20th percentile on 2 tests. Two versions of the cognitive impairment criterion were conducted using the means and SD of individual tests from (1) the LBC1936 sample at each wave and (2) a more representative UK sample provided by the WAIS-III-WMS-III technical manual.[19] Preliminary comparisons showed that fewer participants were identified as having MCI using the general population norms, likely due to the higher rates of overall healthiness in the LBC1936.[14] Therefore, the definition using UK normative data were used here as they were more reflective of the general population.

We also coded 2 subtypes of MCI: aMCI and naMCI. Creation of these subtypes followed the same procedure as for the general MCI; however, aMCI was only identified if the participant showed impairment in the memory domain. Similarly, classification for naMCI was met if the participant showed impairment in cognitive domains other than memory (executive function, attention, language, or visuospatial skills).

Covariates

We examined the association between a range of covariates and MCI status. Covariates included: age, sex, years of education, age 11 cognitive function, body mass index; calculated in the standard way of kg/m^2), occupational social class (professional/managerial/skilled, nonmanual/skilled manual or semiskilled/unskilled), *APOE* ε4 status (allele present/absent), self-reported history of cardiovascular disease, self-reported history of stroke, depression, and physical frailty level (not frail/prefrail/frail). Physical frailty was derived using the Fried Phenotype guidelines,[21] for information on how this was calculated in LBC1936 see Welstead et al.[22] Depression was measured using the Hospital Anxiety and Depression scale.[23] Age 11 cognitive function was based on LBC1936 participant's scores on the Moray House Test (MHT) at age 11[24]; for more detail see Taylor et al.[14] To adjust for age in days at time of testing, MHT11 scores were residualized for age at 11 years.

Statistical Analysis

Three participants had been diagnosed with dementia before age 76 (wave 3) by the LBC1936 study doctor and were excluded, leaving 694 participants at that wave. In addition, since a wide variety of variables were required in order to derive an MCI coding, missing data at each wave meant that some participants were excluded from analyses (wave 3; n = 127, wave 4; n = 106, wave 5; n = 87). Accordingly, MCI status was coded for 567 participants at wave 3 (age 76), 441 at wave 4 (age 79), and 341 at wave 5 (age 82). Descriptive analyses including number and percentages of people with MCI were used to characterize the study sample. Linear model analysis of variance and Pearson χ^2 tests were used to assess characteristics associated with MCI and

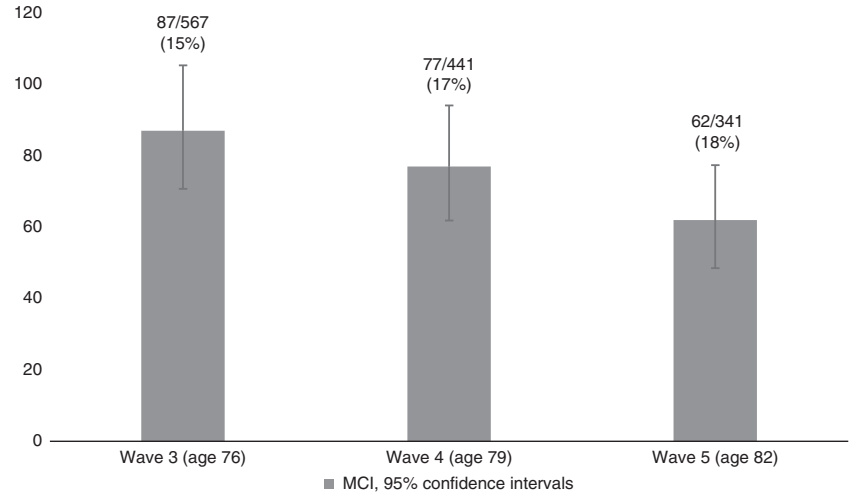

FIGURE 1. Comparisons of MCI rates in the Lothian Birth Cohort 1936 study across waves using UK wide normative data. MCI indicates mild cognitive impairment.

non-MCI participants. All statistical analyses were conducted in R Version 3.6.1.[25]

RESULTS

Figure 1 show the rates of MCI in the LBC1936. There was an increase in people with MCI over time with 15% at wave 3 (n = 87/567), 17% at wave 4 (n = 77/441), and 18% at wave 5 (n = 62/341) having MCI. As there were a substantial number of participants who withdrew from the study between baseline and final follow-up, we also looked at MCI rates for completers only, that is, those who completed waves 3, 4, and 5. Results showed an overall proportional increase over follow-up with 14% of completers identified as having MCI at wave 3 (n = 38/271) and wave 4 (n = 38/271), and then a rise to 21% at wave 5 (n = 57/271).

MCI rates did not differ significantly by sex at any of the waves. The only significant differences found indicated that higher rates of MCI were associated with *APOE* ε4 status at wave 3 ($P < 0.001$) and wave 5 ($P < 0.05$), and history of stroke at wave 3 ($P < 0.01$) and wave 5 ($P < 0.05$). Covariate differences according to MCI status are reported in Table 1.

MCI Subtypes

We also derived 2 subtypes of MCI: aMCI and naMCI. As reported in Figure 2, proportions of aMCI remained fairly low across follow-up from 4% at wave 3 (n = 24/604), to 4% at wave 4 (n = 21/484), and 6% at wave 5 (n = 24/376). Prevalence of naMCI was higher and showed a gradual proportional increase over follow-up from 12% at wave 3 (n = 73/609), to 14% at wave 4 (n = 63/466), and 16% at wave 5 (n = 56/361).

Normative Data Comparisons

We compared whether MCI rates were sensitive to the use of different normative data. Comparisons were made between MCI rates when using normative data based on the LBC1936 and a UK-wide sample to derive the identification of MCI. As might be expected with a healthy cohort, at all waves there were higher proportions of MCI when using the LBC1936 norms compared with the UK based norms. Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/WAD/A319) reports MCI rates at each wave according to the LBC1936 normative data.

DISCUSSION

We found MCI proportions in the LBC1936 study of 15%, 17%, and 18% at ages 76, 79, 82 years, respectively. Similar proportions were found when looking only at the individuals who attended all waves. MCI status at wave 3 and wave 5 (but not wave 4) was significantly associated with *APOE* ε4 status and history of stroke. Proportions of people with aMCI were 4% at ages 76 and 79 years and 6% at 82 years, whereas rates of naMCI were higher but still showed an increase in proportions from 12% at age 76 years to 14% and 16% at 79 and 82 years, respectively.

Comparison With Other Literature

We observed higher rates of MCI in men, albeit not at a statistically significant level, a finding that is consistent with some previous research,[26,27] but not all.[28,29] As discussed by Xue et al,[29] sex differences in MCI research are inconsistent and may differ according to alternate methods of deriving MCI. Importantly, the assessment of day-to-day function in men and women presents different challenges, and perhaps surprisingly, there were minimal significant associations between groups of individuals defined by key features. At 2 of the time points *APOE* ε4 status was associated with having MCI, a finding which has been consistently found in previous MCI research and is also strongly linked to the risk of progression to dementia.[30] The only other characteristic associated with MCI change was having a history of stroke, again somewhat unsurprising given the extensive evidence that stroke patients have higher risk for developing of MCI and dementia.[31] The lack of significant association between these factors and MCI status at wave 4 is unexpected and not readily explained. However, it may be related to attrition or other factors leading to sample differences at wave 4; the proportion of participants with MCI who had an *APOE* ε4 allele

TABLE 1. Covariate Descriptive Statistics for Participants With MCI Present Versus Absent

	Wave 3			Wave 4			Wave 5		
Variables	**MCI Absent (N = 480)**	**MCI Present (N = 87)**	***P***	**MCI Absent (N = 364)**	**MCI Present (N = 77)**	***P***	**MCI Absent (N = 279)**	**MCI Present (N = 62)**	***P***
Age at wave 3, mean (SD)	76.25 (0.68)	76.21 (0.66)	0.55*	76.23 (0.68)	76.13 (0.69)	0.24*	76.20 (0.69)	76.17 (0.72)	0.75*
Sex, n (%)			0.07†			0.37†			0.05†
Male	248 (52)	54 (62)		183 (50)	43 (56)		133 (48)	38 (61)	
Female	232 (48)	33 (38)		181 (50)	34 (44)		146 (52)	24 (39)	
Years of education, mean (SD)	10.81 (1.13)	10.76 (1.16)	0.70*	10.90 (1.19)	10.87 (1.14)	0.85*	10.91 (1.17)	11.10 (1.17)	0.25*
Age 11 cognitive function, mean (SD)	1.21 (11.70)	1.30 (11.28)	0.95*	1.75 (11.41)	1.73 (12.01)	0.99*	2.30 (11.24)	2.34 (10.91)	0.98*
Missing data	29	7		25	3		16	6	
Depressive symptoms, mean (SD)	2.68 (2.20)	3.00 (2.13)	0.23*	2.55 (2.13)	3.04 (2.30)	0.07*	2.42 (1.95)	2.97 (2.04)	0.05*
Missing data	1	0		3	0		3	1	
BMI, mean (SD)	27.71 (4.41)	27.66 (4.23)	0.92*	27.53 (4.35)	27.85 (4.25)	0.55*	27.44 (3.91)	27.77 (4.13)	0.56*
Missing data	2	0		3	1		3	1	
History of cardiovascular disease, n (%)			0.05†			0.63†			0.34†
No	327 (68)	50 (58)		240 (67)	49 (64)		185 (67)	37 (61)	
Yes	153 (32)	37 (42)		121 (33)	28 (36)		91 (33)	24 (39)	
Missing data	0	0		3	0		3	1	
History of stroke, n (%)			0.003†			0.71†			0.017†
No	433 (90)	69 (79)		323 (89)	70 (91)		254 (92)	50 (82)	
Yes	47 (10)	18 (21)		38 (11)	7 (9)		22 (8)	11 (18)	
Missing data				3	0		3	1	
Social class, n (%)			0.364†			0.22†			0.85†
Professional	98 (21)	19 (22)		88 (24)	16 (21)		68 (25)	16 (27)	
Managerial	189 (40)	35 (41)		136 (38)	36 (47)		106 (38)	24 (41)	
Skilled nonmanual	102 (21)	11 (13)		76 (21)	10 (13)		62 (23)	12 (20)	
Skilled manual	70 (15)	18 (21)		50 (14)	14 (19)		32 (11)	7 (12)	
Semiskilled/unskilled	16 (3)	3 (3)		11 (3)	0		8 (3)	0	
Missing data	5	1		3	1		3	3	
APOE ε4 status, n (%)			< 0.001†			0.22†			0.018†
Absent	332 (74)	47 (55)		241 (70)	46 (63)		195 (74)	34 (59)	
Present	118 (26)	38 (45)		102 (30)	27 (37)		68 (26)	24 (41)	
Missing data	30	2		21	4		16	4	
Fried phenotype status, n (%)			0.75†			0.36†			0.89†
Not frail	197 (41)	33 (38)		160 (45)	30 (39)		135 (49)	29 (47)	
Prefrail	224 (47)	41 (47)		164 (45)	35 (45)		119 (43)	26 (43)	
Frail	59 (12)	13 (15)		37 (10)	12 (16)		22 (8)	6 (10)	
Missing data	0	0		3	0		3	1	

*Linear model analysis of variance.
†Pearson χ^2 test.
MCI indicates mild cognitive impairment.

present or a history of stroke was lower at wave 4 than waves 3 or 5.

As expected, findings also showed an increase in proportion of participants with MCI at wave 5 compared with wave 3. The rates of MCI we find are consistent with previous research using the same MCI coding guidelines which reports an average prevalence of 14.8% for 70 to 75 year olds.[32] The rates of 2 subtypes of MCI—aMCI and naMCI—were in partial agreement with previous literature. Some previous research[10] has found rates of around 3% to 4% of both aMCI and naMCI in older populations, while others have found 11% for aMCI and 5% prevalence for naMCI.[28] Thus, while the aMCI results are expected, the rates of naMCI in the LBC1936 are higher than anticipated. Higher rates of naMCI than aMCI may indicate that participants of the LBC1936 are more prone to nonamnestic cognitive impairment in areas such as language, visual-spatial skills, attention, or executive functioning. Another possibility is that the salient memory problems associated with aMCI may make participants more likely to withdraw from the study, whereas the cognitive problems associated with naMCI (executive function, attention, language, or visuospatial skills) may more often go unnoticed by the participant. However, it is also important to note that making comparisons between our proportions of aMCI and naMCI cannot be done entirely accurately given that cases of missing data differed between them.

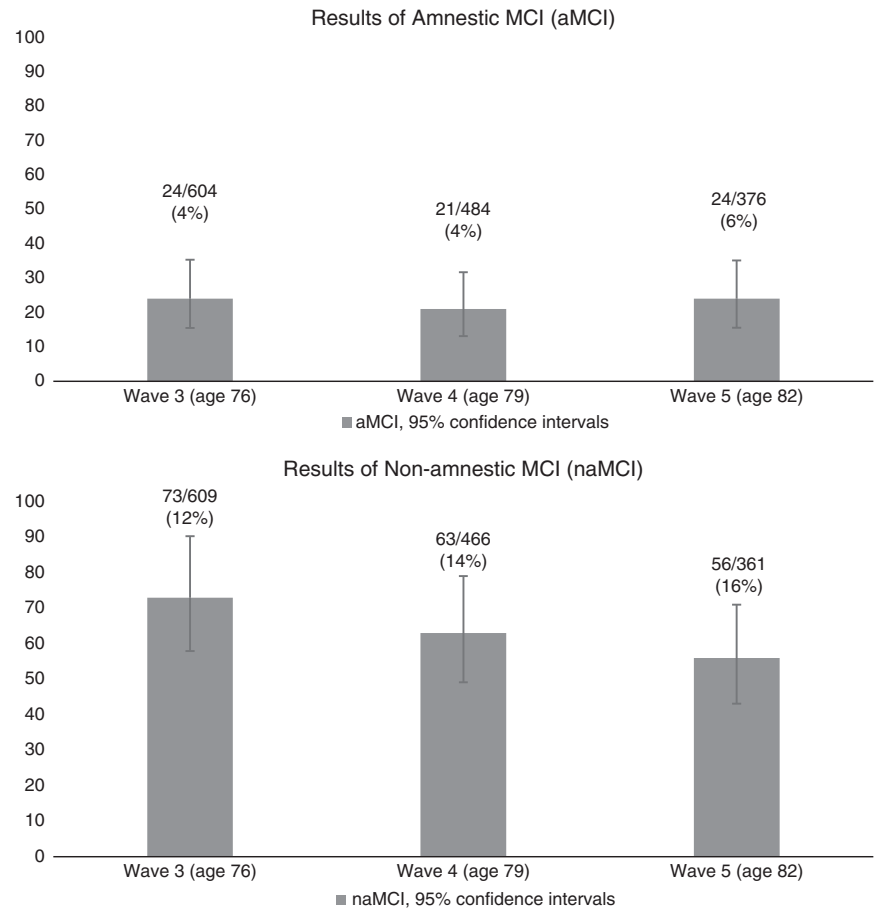

FIGURE 2. Comparisons of amnestic mild cognitive impairment (aMCI) versus nonamnestic mild cognitive impairment (naMCI) rates in the Lothian Birth Cohort 1936 study across waves.

Limitations and Strengths

LBC1936's rates of high physical health and cognitive ability is well documented,[14,16] and highlights a limitation of this study: our sample is less representative of the general population who likely have higher rates of MCI. An additional limitation that affects the accuracy of our results was that there was a relatively small number of participants who were identified as having aMCI, which introduces an element of uncertainty into our results. For the participants who withdrew from the study, we did not have systematic information on their reason for dropping out. It is likely that at least some of these participants dropped out due to MCI or dementia, and accordingly we were unable to consider these cases in our analyses. Related to this, other than 3 cases in which we had confirmation from the LBC1936 study doctor, we relied primarily on the self-reporting of dementia diagnoses for part of the MCI criteria. This could have introduced bias if additional participants had a dementia diagnosis but did not report it. While self-reporting is used extensively in epidemiological studies and biases are usually insignificant,[33] given the nature of dementia, using these measures may have introduced inaccuracies. Current work is being undertaken in the LBC1936 to ascertain dementia status for every participant and so future research will be able to revisit this.

The strengths of this study are our use of data collected at multiple time points over the course of ~6 years in a well-characterized longitudinal cohort study. Using more than 1 time point gives us better insight into how MCI proportions change over time in the LBC1936. An additional strength is that we derived and compared an MCI coding using normative cognitive data from the LBC1936 sample and the UK wide norms. By doing so, we were able to assess the extent to which the LBC1936 data are representative of the wider population. As anticipated, MCI rates were higher at all waves when using the LBC1936 norms, presumably due to an overestimation caused by the higher rates of healthiness found in the LBC1936 when compared with the general population. Deriving MCI using the cohort's own normative data will cause the cognitive impairment cut-off points to be more lenient than using normative data from the UK population as we see in our results.

Implications

This study adds to the field by providing a picture of MCI at various time points in a cohort whereby all participants were born in the same year and same country/region, and thus have had similar life experiences.[14] Our research contributes to the global effort to understand how subclinical cognitive impairment affects older adults. However, this study also highlights the imprecision of MCI, with factors such as the normative data used, or the types of cognitive tests used, significantly affecting MCI rates. This has major practical implications for the use of MCI in a

clinical setting. Future research should establish a more precise definition of subclinical cognitive impairment with more consistency in measurement approaches. By doing so, research may be able to provide evidence leading to improved clinical tools.

The identification of individuals with MCI in the LBC1936 and their comparison with findings in similar cohorts provides opportunities for future research to further explore MCI in this cohort. In particular, utilizing the wealth of longitudinal data in the LBC1936 could prove insightful. MCI has been shown to be relatively fluid over time with both declines and reversions being common.[34–36] Accordingly, understanding this fluidity and the predictive factors associated with MCI change will be insightful for future interventions and prevention strategies that aim to lower the risk of MCI developing and progressing. However, our results do deviate in some ways from previous research. This inconsistency is not uncommon in the field of MCI and dementia research and highlights the issue with using diagnostic criteria which leave room for interpretation without clear cut-offs or specified measures.[37] Indeed, definitions of dementia have continued to evolve over the past decade, causing has a knock on effect on how MCI can be identified.[37] Accordingly, comparisons between studies need to be made with caution. Recent research has proposed that future research may benefit from exploring data driven computer algorithms for identifying MCI which may subsequently provide greater validity and enable data synthesis to be more accurate.[37,38] Furthermore, some criticism aimed at measures of MCI suggest that it is a somewhat restrictive perspective of subclinical cognitive impairment.[12,39] As previously mentioned, there are other ways to identify these subpopulations, and accordingly, future LBC1936 research may benefit from considering other less restrictive measures such as other cognitive impairment no dementia which does not rely on functional impairment as a factor.[12]

CONCLUSION

This study is largely consistent with previous research, finding MCI rates of 15% to 18% in the LBC1936 at ages 76 to 82. When considering subtypes of MCI, nonamnestic MCI is more likely to affect participants than aMCI indicating that perhaps this population is more prone to cognitive decline in nonamnestic cognitive domains. These results help highlight the prevalence of MCI in the LBC1936 and allow for future studies to explore cognitive trajectories over time and the predictive factors which may increase the risk of developing MCI.

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6.3 Concluding remarks

The primary aim of implementing the MCI measure in the LBC1936 was to provide an insight into the prevalence of cognitive impairment in the cohort over the five waves of data, and provide a foundation for the work in Chapter 7. The hypothesis that MCI rates will be consistent with previous findings in longitudinal cohorts was largely supported. This contributes to our understanding of how many people are affected by MCI in later life. However, the MCI coding also opens the door for an array of further LBC1936 research outwith this thesis. The MCI coding has already begun to show its worth by way of an analysis in which I contributed LBC1936 summary Genome-wide association study (GWAS) results to a larger consortium effort led by members of the NeuroCHARGE cognitive working group. The primary aim of this research is to identify common and low frequency variants associated with MCI using GWAS data. The hope is that this MCI measure in the LBC1936 will continue to show such value in future research.

The next step was to explore individual change over time. Contributing to our understanding of how and why individuals shift in and out of MCI states will enhance our understanding of ageing trajectories and pave the way for future research.

Chapter 7: Why does mild cognitive impairment change over time?

7.1 Introduction

This chapter builds upon Chapter 6 by utilising the general MCI coding and investigates how and why MCI changes over time. Previous research has drawn attention to several factors that seem to be associated with MCI status change over time. The main aim was to explore several of these factors in the LBC1936. One predictor, which has particular relevance to this thesis, is that of physical frailty.

One way in which I could have approached this area of research is to explore the notion of cognitive frailty whereby the two factors coexist. It is possible using the measurement tools derived throughout this thesis to develop a measure of cognitive frailty in line with previous research (Ruan et al., 2015). This measure is based on an individual having MCI, being Frail or Pre-frail according to the Fried phenotype, and not having a diagnosis of dementia. For example, if we look at those in the LBC1936 with these criteria, then we see a cognitive frailty prevalence of 9% at Wave 3, 11% at Wave 4, and 14% at Wave 5. However, as discussed in Chapter 5.3, implementing a measure of cognitive frailty at this point is premature due to the unresolved nature of cognitive frailty definitions. Instead, physical frailty is included as one of the predictors of MCI change over time, extending previous longitudinal research, which has found links between the two factors (Borges, de Castro Cezar, et al., 2019; Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010). For example, Boyle et al. (2010) found a strong association showing that for each one-unit increase in baseline physical frailty there was a 63% increase in MCI risk over a 12-year period. Frailty as assessed by the Frailty index (FI) was not included due to the cognitive component of its composition, therefore the Fried phenotype was solely used. In the most recent practice guidelines for the operation of MCI, Petersen et al. (2018) recommend that future studies explore the effects of early life factors on cognitive decline.

Accordingly, I also utilised the unique aspect of the LBC1936 by controlling for early life cognitive ability.

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7.2 Predictors of mild cognitive impairment stability, progression, or reversion in the Lothian Birth Cohort 1936

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Predictors of Mild Cognitive Impairment Stability, Progression, or Reversion in the Lothian Birth Cohort 1936

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Abstract.
Background: Mild cognitive impairment (MCI) describes a borderland between healthy cognition and dementia. Progression to and reversion from MCI is relatively common but more research is required to understand the factors affecting this fluidity and improve clinical care interventions.
Objective: We explore these transitions in MCI status and their predictive factors over a six-year period in a highly-phenotyped longitudinal study, the Lothian Birth Cohort 1936.
Methods: MCI status was derived in the LBC1936 at ages 76 ($n = 567$) and 82 years ($n = 341$) using NIA-AA diagnostic guidelines. Progressions and reversions between healthy cognition and MCI over the follow-up period were assessed. Multinomial logistic regression assessed the effect of various predictors on the likelihood of progressing, reverting, or maintaining cognitive status.
Results: Of the 292 participants who completed both time points, 41 (14%) participants had MCI at T1 and 56 (19%) at T2. Over the follow-up period, 74% remained cognitively healthy, 12% transitioned to MCI, 7% reverted to healthy cognition, and 7% maintained their baseline MCI status. Findings indicated that membership of these transition groups was affected by age, cardiovascular disease, and number of depressive symptoms.
Conclusion: Findings that higher baseline depressive symptoms increase the likelihood of reverting from MCI to healthy cognition indicate that there may be an important role for the treatment of depression for those with MCI. However, further research is required to identify prevention strategies for those at high risk of MCI and inform effective interventions that increase the likelihood of reversion to, and maintenance of healthy cognition.

Keywords: Aged, cognitive dysfunction, memory, public health

INTRODUCTION

Mild cognitive impairment (MCI) is used to describe individuals presenting with cognitive decline above what would be expected of normal ageing but not severe enough to warrant a diagnosis of dementia [1, 2]. Prevalence of MCI in older adults for individuals in their 70s and 80s is typically reported

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to be 10–25% [3–5]. However, these MCI prevalence rates are cross-sectional and do not account for changes over time. Overton et al. [6] report that MCI status is not stable and both progression to and reversion from an MCI state can occur. Thus, longitudinal studies with repeated measures have particular value.

Progression from healthy cognition to MCI is common and well documented in the longitudinal literature [7, 8]. It has been established that the cognition of those with MCI frequently remains stable [9]. Reversion from MCI to healthy cognition is also relatively frequent, with several studies reporting that those with MCI are more likely to revert to healthy cognition than progress to dementia [6, 10, 11]. Subsequent research has focused on understanding why certain individuals progress to, revert from, or maintain MCI whereas others do not. Higher rates of MCI conversion and maintenance are associated with a plethora of factors including age, education, race, cardiovascular risk factors, diabetes, depression, *APOE* $\varepsilon 4$ status, Parkinson's disease, and sleep disorders [6, 12–17].

Previous research into transition from normal cognition to MCI is inconsistent and focused primarily on either progression or reversion rather than considering them both simultaneously. Accordingly, further research, which considers transitions both to and from an MCI state, may allow for better data synthesis in the future. By understanding the key factors associated with MCI state transitions, it may be possible to improve the ability for interventions to lessen an individual's risk of developing MCI, but also to facilitate reversion from it or stability in those who already have it. Here we explore the predictive factors which are associated with MCI stability, progression to MCI, and reversion from MCI over approximately six years in the Lothian Birth Cohort 1936 (LBC1936) [18, 19]. One of the key differences between the LBC1936 and other longitudinal cohorts used in this field is that all participants were born in 1936 in Scotland. Accordingly, due to the narrow age gap and similar geographical area, participants have had similar life experiences, for instance, living through the introduction of a National Health Service or World War II. Thus, the homogeneity of their experiences makes them more suitable for modelling some aspects of ageing compared to a broader sample whereby cohort effects may complicate such analyses. Additionally, the wealth of information collected by the study enables us to explore MCI transitions while controlling for not only a range of previously researched biopsychosocial factors, but also novel risk factors such as age 11 cognitive function. Using this wealth of information, we hypothesize that several risk factors will emerge that influence MCI stability over follow-up.

METHODS

Study sample

The LBC1936 study consists of 1091 participants, almost all born in 1936 with a mean age of 69.5 years (SD = 0.9) at recruitment. Wave 1 took place from 2004–2007, with follow-up visits approximately every three years thereafter (wave 2 $n = 866$, wave 3 $n = 697$, wave 4 $n = 550$, wave 5 $n = 431$). For more details on recruitment and testing procedures, see [19, 20]. MCI status could only be determined at Wave 3 (mean age [SD] = 76.3 [0.7]) and Wave 5 (mean age [SD] = 82.1 [0.5]) allowing a follow-up period of approximately six years. The LBC1936 study was conducted according to the Declaration of Helsinki guidelines. Ethical permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland (Wave 1: MREC/01/0/56), the Lothian Research Ethics Committee (Wave 1: LREC/2003/2/29), and the Scotland A Research Ethics Committee (Waves 2, 3, 4, & 5:07/MRE00/58). Written consent was obtained from participants at each of the waves.

MCI coding

MCI was coded in the LBC1936 according to the criteria outlined by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines for Alzheimer's disease [1]. Accordingly, MCI was based on subjective concern regarding a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, and no diagnosis of dementia. Further detail has been previously reported [21]. In the following analyses, MCI codings were used at Wave 3 (T1) & Wave 5 (T2). Missing data meant that not all participants received an MCI coding. Additionally, of those participants who had MCI coding at T2, 49 had missing data at T1 and accordingly were excluded as this prevented the calculation of change in MCI status over time. Accordingly, MCI was coded for 567 participants at T1 and 292 at T2. Figure 1 illustrates the number of participants recruited, assessed, followed-up and excluded, at both time points.

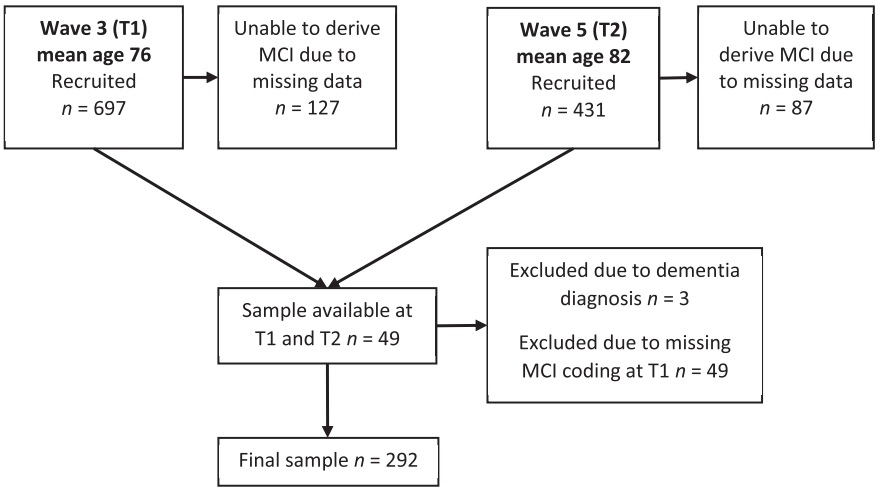

Fig. 1. A flow chart to demonstrate how many participants were recruited and assessed at each time point.

Covariates

T1 predictors of MCI change over the follow-up period were chosen based on previous research showing associations between them and cognitive decline [16, 22–25]. These included: age at T1 (range = 74.59–77.70), sex, years of full-time education, age 11 cognitive function (calculated from the Moray House Test score at age 11 years [26] and standardized for age in days on the test-date), occupational social class (professional/managerial/skilled, non-manual/skilled manual or semi-skilled/unskilled), *APOE* ε4 status (gene present/absent), self-reported history of cardiovascular disease (coded yes or no), number of depressive symptoms, body mass index (BMI calculated as kg/m2), and physical frailty level (not frail/pre-frail/frail). Number of depressive symptoms were obtained from the Hospital Anxiety and Depression scale (HADS) [27]. Physical frailty status (not frail/pre-frail/frail) was derived for each participant using the Fried Phenotype guidelines [28], for more detail see Welstead et al. [29]. For the purposes of our longitudinal analysis, this was recoded as a binary variable (not frail versus pre-frail/frail).

Statistical analysis

Comparisons of the predictors across different MCI transition states were assessed by ANOVAs and Pearson's Chi-squared tests. Multinomial logistic regression models were fit in order to assess the effect of various predictors on the likelihood of fitting into one of three potential outcomes between T1 and T2 compared to the reference group of those who remained cognitively healthy. Outcomes were: 1) Participant remains categorized as having MCI, 2) Participant reverts from MCI to healthy cognition, 3) Participant transitions from healthy cognition to MCI. Participants may have progressed to dementia over follow-up; however, they would then not have been eligible to take part in the next data wave, or if they did, they would be excluded from our analyses. Participants who withdrew from the study were not assessed as an outcome as the reason for withdrawal was not known. Risk of fitting in to each of these categories was calculated in a baseline model controlled for age and sex before computing a full model with adjustment for all covariates. Associations between the covariates were below 0.4, indicating that that the variance of the model's regression coefficient was not inflated by multicollinearity. Goodness of model fit was assessed using McFadden's R-squared [30] and found to have a value of 0.31, between the typical 'very good fit range' of 0.2 to 0.4. All analyses were conducted in R version 3.5.3 [31].

RESULTS

Of 697 participants at T1, 127 were excluded because of missing data, and three were excluded as they had developed dementia. MCI was coded for 567 participants at T1 and 341 at T2, but 49 of those individuals did not have MCI status at T1 so the final number of participants with MCI status ascertained at both time points was 292. At T1, 41 (14%) participants were categorized as having MCI, while at

T2 there were 56 (19%) participants with MCI. MCI status at each time point for the 292 participants is reported in Table 1.

74% ($n = 215$) remained cognitively healthy, 7% ($n = 20$) remained MCI, 7% ($n = 21$) reverted from MCI to healthy cognition, and 12% ($n = 36$) transitioned to MCI. Figure 2 illustrates these transition rates.

Associations between covariates and MCI transition status were significant for number of depressive symptoms and cardiovascular history (see Table 2). *Post-hoc t*-tests tested the difference in cardiovascular history between specific MCI transition groups. Individuals who remained cognitively healthy between T1 and T2 had significantly lower rates of cardiovascular disease (33.5% of participants) compared to those who remained MCI at both time points (60.0% of participants) ($t(233) = 2.38$, $p = 0.018$). Similarly, those who remained cognitively healthy had significantly fewer T1 depressive symptoms than those who remained MCI stable ($t(233) = 15.49$, $p < 0.001$), and those who reverted from MCI to healthy cognition ($t(233) = 2.60$, $p < 0.01$).

Table 1
MCI status at T1 and T2 for participants who completed both time points

		T2 MCI status		
		Healthy cognition	MCI	*Total*
T1 MCI status	Healthy cognition	215	36	251
	MCI	21	20	41
	Total	236	56	292

Significant differences were noted between completers and withdrawers. Specifically, those who withdrew from the study had a lower age 11 cognitive function (completers M[SD] = 2.42 [11.01], withdrawers M[SD] = –0.02 [12.14], F(1, 529) = 5.88, $p = 0.016$), fewer years of education (completers M[SD] = 10.98 [1.17], withdrawers M[SD] = 10.61 [1.07], F(1, 565) = 15.54, $p < 0.001$), more depressive symptoms (completers M[SD] = 2.47 [1.96], withdrawers M[SD] = 3.00 [2.38], F(1, 529) = 5.88, $p = 0.004$), were more likely to come from a lower occupational social class ($\chi^2(5) = 22.94$, $p < 0.001$), and were more likely to be frail (completers = 43.2% pre-frail/frail, withdrawers = 57.8% pre-frail/frail, $\chi^2(1) = 18.38$, $p < 0.001$). Full comparisons are reported in Supplementary Table 1.

A baseline multinomial logistic regression model was fitted using sex and age as covariates and comparing three MCI transition statuses (MCI stable, healthy cognition to MCI, MCI to healthy cognition) against a reference group (remained cognitively healthy). Odds ratios and 95% confidence intervals were calculated to determine the effect of a one-unit increase in predictor variables on the odds of being in a particular MCI transition category. In the baseline model, age showed a significant association with MCI status transition, but sex did not. A fully adjusted model with all of the predictors was then computed. It showed that, compared to staying cognitively healthy, participants who were older at T1 were less likely to maintain an MCI status (OR = 0.57 [0.51–0.64], $p < 0.001$), revert from MCI to healthy cognition (OR = 0.24 [0.21–0.26], $p < 0.001$), or progress from healthy

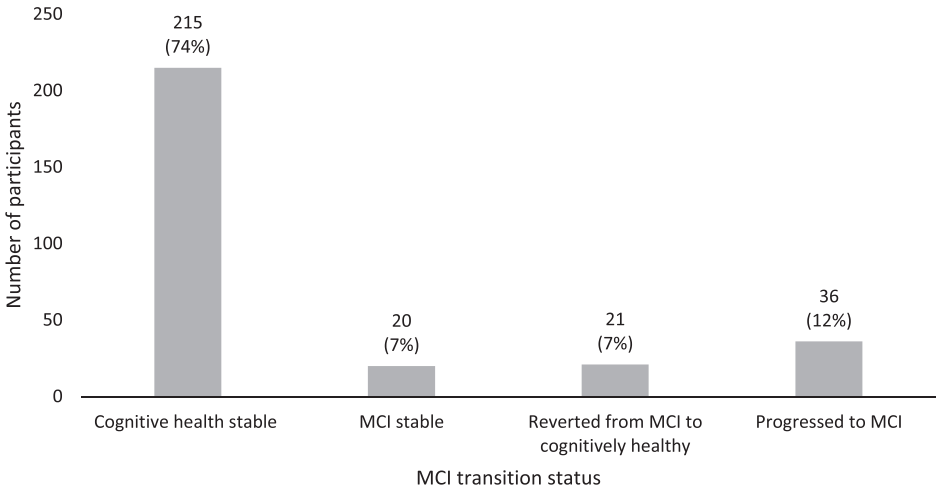

Fig. 2. MCI transition rates over six-year follow-up (T1 and T2).

Table 2
Predictor variables according to MCI Transition Status

Variables	Maintained healthy cognition status (N = 215)	Maintained MCI status (N = 20)	Transitioned from healthy cognition to MCI (N = 36)	Reverted from MCI to healthy cognition (N = 21)	*p*
Age at T1, mean (SD)	76.24 (0.68)	76.13 (0.69)	76.25 (0.72)	75.99 (0.74)	0.389[1]
Sex, *n* (%)					0.233[2]
Male	100 (46.5%)	13 (65.0%)	21 (58.3%)	12 (57.1%)	
Female	115 (53.5%)	7 (35.0%)	15 (41.7%)	9 (42.9%)	
Age 11 cognitive function, mean (SD)	2.50 (11.06)	3.17 (11.81)	1.39 (10.92)	2.61 (10.66)	0.943[1]
Missing data	13	2	3	2	
Years of education, mean (SD)	10.94 (1.16)	11.20 (1.06)	11.06 (1.26)	11.05 (1.32)	0.774[1]
Depressive symptoms, mean (SD)	2.28 (1.86)	2.75 (2.92)	2.92 (2.58)	2.47 (1.96)	0.024[1]*
Body mass index, mean (SD)	27.52 (4.02)	26.96 (3.40)	27.67 (3.89)	27.51 (3.93)	0.920[1]
Social class, *n* (%)					0.903[2]
Professional	57 (26.6%)	7 (35.0%)	8 (23.5%)	3 (15.0%)	
Managerial	80 (37.4%)	7 (35.0%)	13 (38.2%)	13 (65.0%)	
Skilled non-manual	48 (22.4%)	2 (10.0%)	10 (29.4%)	3 (15.0%)	
Skilled manual	25 (11.7%)	4 (20.0%)	3 (8.8%)	1 (5.0%)	
Semiskilled/Unskilled	4 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Missing data	1	0	2	1	
History of cardiovascular disease, *n* (%)					0.028[2]*
No	143 (66.5%)	8 (40.0%)	26 (72.2%)	10 (47.6%)	
Yes	72 (33.5%)	12 (60.0%)	10 (27.8%)	11 (52.4%)	
History of stroke, *n* (%)					0.052[2]
No	198 (92.1%)	15 (75.0%)	30 (83.3%)	18 (85.7%)	
Yes	17 (7.9%)	5 (25.0%)	6 (16.7%)	3 (14.3%)	
APOE ε4 status, *n* (%)					0.056[2]
Absent	155 (76.7%)	11 (57.9%)	19 (57.6%)	15 (71.4%)	
Present	47 (23.3%)	8 (42.1%)	14 (42.4%)	6 (28.6%)	
Missing data	13	1	3	0	
Fried Phenotype Status, *n* (%)					0.767[2]
Not Frail	108 (50.2%)	10 (50.0%)	18 (50.0%)	8 (38.1%)	
Pre-Frail/Frail	107 (49.8%)	10 (50.0%)	18 (50.0%)	13 (61.9%)	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; [1]Linear Model ANOVA; [2]Pearson's Chi-squared test.

cognition to MCI (OR = 0.91 [0.84–0.99], $p < 0.05$) over the follow-up period. Furthermore, compared with remaining cognitively healthy, every unit increase in depressive symptoms significantly increased the likelihood that a participant would revert from MCI to healthy cognition (OR = 1.37 [1.05–1.80], $p < 0.05$). A history of cardiovascular disease was also shown to increase the likelihood of a participant maintaining an MCI status across follow-up (OR = 3.13 [1.01–9.70], $p < 0.05$). No further significant associations were found, individual odds ratios are reported in Table 3.

DISCUSSION

In this study, we found that, of those with MCI at T1, half remained so but half returned to healthy cognition. Of those who were cognitively healthy at T1, the majority stayed this way at T2 with a smaller proportion progressing to MCI. Age, history of cardiovascular disease, and number of depressive symptoms significantly differed between MCI transition groups. The effect of age was such that those who were older at T1 were less likely to remain MCI stable, revert to healthy cognition, or progress to MCI. Higher number of depressive symptoms increased the likelihood of reverting from MCI to healthy cognition and having a history of cardiovascular disease increased the likelihood of remaining MCI stable across follow-up. We discuss next the potential reasons behind our findings and how they compare in a wider research context.

Comparison with other literature and interpretation

Our findings of MCI progression and stability rates aligned with previous findings. While rates of reversion seem lower than in other studies, which report anywhere between 14% and 57% [16, 17, 32], this is likely due to our inclusion of cognitively healthy participants at baseline. Findings indicated that older

Table 3
Odds ratios of MCI status compared to the 'remained cognitively healthy' reference group

Covariates	MCI stable ($n = 20$)		Transitioned healthy cognition to MCI ($n = 36$)		Reverted MCI to healthy cognition ($n = 21$)	
	Odds Ratios (95% CI)	*p*	*Odds Ratios (95% CI)*	*p*	*Odds Ratios (95% CI)*	*p*
Age	0.57 (0.51–0.64)	< 0.001***	0.91 (0.84–0.99)	< 0.001***	0.24 (0.21–0.26)	< 0.001***
Sex (1 = male/2 = female)	1.16 (0.30–4.44)	0.83	0.79 (0.29–2.15)	0.65	1.44 (0.40–5.23)	0.58
Age 11 cognitive function	0.99 (0.95–1.03)	0.58	0.98 (0.94–1.02)	0.28	0.99 (0.95–1.03)	0.66
Years of education	1.39 (0.78–2.45)	0.26	1.18 0.75–1.87)	0.47	1.43 (0.81–2.52)	0.21
Depressive symptoms	1.15 (0.85–1.57)	0.36	1.01 (0.79–1.28)	0.96	1.37 (1.05–1.80)	0.04*
Body mass index	0.95 (0.80–1.11)	0.50	1.06 (0.95–1.20)	0.29	0.99 (0.86–1.14)	0.90
Social class	1.27 (0.58–2.82)	0.55	1.05 (0.56–1.97)	0.87	1.21 (0.54–2.75)	0.64
History of cardiovascular disease	1.55 (0.44–5.48)	0.50	3.13 (1.01–9.70)	0.04*	0.58 (0.15–2.22)	0.42
APOE ε4 carrier	1.91 (0.55–6.65)	0.31	2.60 (0.98–6.91)	0.06	1.36 (0.36–5.20)	0.65
Fried Phenotype (non-frail versus pre-frail/frail)	1.16 (0.33–4.14)	0.82	2.00 (0.72–5.52)	0.18	1.11 (0.29–4.22)	0.88

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

age at T1 was a significant factor decreasing the likelihood of maintaining, reverting from, or progressing to MCI compared to remaining in cognitively healthy. This is somewhat surprising for two reasons. Firstly, the variance in T1 age is small as the LBC1936 is a narrow age cohort. Secondly, while we would expect increased age to have negative effects on MCI transition, the positive effects found do not fit with previous findings that increased age increases MCI risk [33]. Further research is required to investigate this more thoroughly.

Additional logistic regression findings showed that higher depressive symptoms at T1 increased likelihood of reverting from MCI to healthy cognition. Our results may reflect a pseudo-dementia, whereby the symptoms of depression in older age mirror those of cognitive decline. [34]. In theory, as these depressive symptoms improve, their negative cognitive impact will be ameliorated. Sugarman et al. [35] reported that successful treatment of depression increased probability of reverting from MCI to healthy cognition. Accordingly, clinical care interventions targeted at treating depression may help to reduce risk of cognitive decline. However, another interpretation of our results is to consider is that depression not cause cognitive impairment, but may exacerbate cognitive impairment by uncovering decline caused by neurodegenerative processes that had until then be unobserved [36]. Accordingly, while treating depression may provide a short reprieve, the underlying cause may remain.

The final findings from our regression analyses indicated that cardiovascular history increases the likelihood of remaining with MCI status at follow-up. This is perhaps unsurprising considering the previous research indicating that cardiovascular health issues are associated with cognitive decline [13, 37], as well as current clinical guidelines that endorse the reduction of cardiovascular risk as a method of tackling dementia risk [38].

Strengths and limitations

This study has several limitations. Firstly, while our sample was of reasonable size, when this was broken down into different MCI transition categories the number of participants in some groups was small and potentially limited the power and accuracy of our statistical analyses. Secondly, participants with dementia were ineligible and accordingly this study was not able to consider those who progressed to or reverted from a dementia diagnosis. The dataset also lacked information on why participants withdrew from the study leaving us unable to differentiate between those who died from those who were diagnosed with dementia or simply withdrew without reason. Thirdly, the LBC1936 has been shown to be skewed towards those with higher socio-economic status [20], which could affect the results and make them less generalizable to the general population. Fourthly, cardiovascular disease was assessed categorically as a Yes/No self-report question. While self-report measures can be highly efficient, they may also introduce a level of inaccuracy when compared to using medical records or physical examination. Finally, due to a lack of cases we were unable to assess the effect of having a history of stroke on MCI transition, which is an important consideration

due to previously established associations between stroke and cognitive impairment [39]. This study also had strengths and benefitted from considering both progressions to, and reversions from MCI. Most previous research focusses on one of these two processes rather than both simultaneously and subsequently may be missing salient information. Additionally, this study utilized a relatively long follow-up period of six years, allowing for a better understanding of the long-term fluidity of MCI, and considered factors such as childhood cognitive function that have not previously been investigated.

Future directions

Future research is required to delineate the predictive factors that can influence MCI transition between healthy cognition and cognitive impairment. A particularly interesting question is whether MCI progression and reversion have the same predictive factors. Our findings indicate that this may not be the case, which has important ramifications for the differential treatment of those at risk of developing MCI and those with MCI. Future research may also benefit from using additional time points to further examine the fluid nature of MCI status; it would be particularly interesting to see whether those reverting from MCI to healthy cognition remain that way over time.

CONCLUSION

While a considerable amount of longitudinal research has investigated the factors associated with dementia risk, fewer studies have focused on the progression and reversion transitions between a healthy cognition and MCI. Our findings indicate a slow but consistent increase in MCI rates over a six-year period in the LBC1936. Despite the overall increase, we also find that around 4% of participants actually show an improvement over time and revert from MCI to healthy cognition. Higher instances of baseline depressive symptoms were associated with an increased likelihood to revert from MCI to healthy cognition over follow-up. These findings potentially indicate the important role of early identification and treatment of depression in clinical care to help address cognitive decline. Our findings add to previous literature and highlight the potential for a two-pronged approach to addressing MCI: 1) effectively designing prevention strategies that target risk factors between healthy cognition and progression to MCI, and 2) implementing interventions for those living with MCI to facilitate reversion to healthy cognition. Future research should continue exploring these factors and the fluid nature of MCI in older adults.

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SUPPLEMENTARY MATERIAL

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7.3 Concluding remarks

Findings from Chapter 7.2 reinforce the notion that cognitive status in later life is unstable and that there are several factors that may influence this change. Chapter 7.2 helps to enhance our collective understanding of these associated factors, however, much more clarity is required before firm conclusions can be made. Despite this, it is promising that somewhat modifiable health factors such as depression and cardiovascular disease seem to be associated with cognitive status. Prioritising treatment of these health conditions for those with MCI may be an effective strategy to help increase the likelihood of reversion to a healthy cognitive state. However, in the case of depression, it is a distinct possibility that the findings in Chapter 7.2 are a result of participants who were depressed at baseline but were misclassified as having MCI. This relates to a critique of the concept of MCI in general. MCI often cannot distinguish between cognitive impairment that is a result of health conditions like early dementia, depression, anxiety, or attentional issues (Mourao, Mansur, Malloy-Diniz, Castro Costa, & Diniz, 2016). Accordingly, further research is required to explore the findings that MCI is associated with depression. Interestingly, physical frailty did not have a significant association with developing MCI. Taking into account previous research, I would have expected an association between these two factors (Boyle et al., 2010). A previous systematic review found that those with higher physical frailty are at higher risk of developing cognitive disorders than those without frailty (Borges, Canevelli, Cesari, & Aprahamian, 2019). The lack of an association may reflect the relatively small sample sizes or it may indicate that the relationship between these factors is not as clear-cut as would be suggested by a cognitive frailty framework. Some recent cross-sectional research indicates that whilst frailty is significantly associated with dementia risk, it may not be associated with MCI (Shah, Morani, Rodriguez-Suarez, Apracio-Ugarriza, & Ruiz, 2019). Accordingly, further study is required to work towards a better understanding of how these two factors are associated over time in later life. An additional avenue for future research, which was not possible in the LBC1936 due to small sample sizes,

would be to use a larger sample and split the sample at baseline to assess the predictors of transition to MCI in a healthy baseline group and predictors of transition to healthy in a MCI baseline group.

Chapter 8: Discussion

In this thesis, I aimed to explore the health declines associated with later life ageing trajectories. Specifically, I sought to use the operational concepts of frailty and MCI to capture age-related decline with the goals of:

- Improving our understanding of how these health states change over time.
- Identifying the salient factors associated with these changes.
- Facilitating future research using these measures in the LBC1936.

The purpose of undertaking this research was to contribute to a burgeoning field of research, and ultimately identify the ways in which we improve quality of life for older adults and ensure that everyone follows their healthiest ageing trajectory.

8.1 Summary of findings

I explored two methods of measuring age-related health declines and this thesis is broadly split into two halves with the first exploring frailty trajectories and the second investigating MCI change over time. I began by conducting a systematic review of frailty trajectories. The purpose of this review was to explore what is currently known about frailty rate of change and which factors contribute to or moderate these changes. Considering the vast amount of research into frailty, there are a limited number of studies exploring the shape of frailty longitudinally. Accordingly, the systematic review in Chapter 2 proved to be highly informative as the foundation of this thesis. Findings from the review indicated that there is a great degree of heterogeneity in the field with studies using different frailty measurement tools, different participant

demographics, and different types of statistical analyses. Despite this, it was possible to make several conclusions. Firstly, frailty shows a steady progression with age in most populations. Secondly, this progression is consistently associated with various risk and protective factors. In particular, socioeconomic factors, social support, brain pathology, and level of physical activity are significantly associated with frailty progression. I conclude by suggesting that future studies explore this line of research further with the aim of establishing a better understanding of exactly which factors are linked to worsening frailty. Furthermore, it is proposed that one way of working towards a more coherent frailty definition is to include multiple measures of frailty in the same study to allow contrasts to be made. An additional benefit is the additional robustness given to any findings if multiple frailty measures show similar results.

Chapter 4 detailed the first empirical study, which aimed to address Chapter 2's conclusions by assessing the association between frailty and inflammation. The particularly unique aspect of this study was the use of dual frailty measures: the Frailty index (FI) and the Fried phenotype. By doing so, it was possible to assess the differences between frailty measures and highlight the limitations of using only one frailty measure. Based upon recent literature searches there are currently no other research studies which have employed this method apart from a study by Gale et al. (2018). Using blood-based markers for inflammation in the LBC1936, higher Fibrinogen was shown to be significantly associated with higher FI scores at baseline (β = 0.011, 95% CI [0.002, 0.020], $p < .05$). Additionally, higher baseline levels of CRP (β = 0.001, 95% CI [0.000, 0.002], $p < .05$) and Fibrinogen (β = 0.004, 95% CI [0.001, 0.007], $p < .05$) were associated with an increase in the gradient of FI over a 12-year follow-up. However, when analysing the Fried phenotype it was found that although higher CRP and Fibrinogen were associated with higher baseline frailty, there were no significant associations over the follow-up period. Accordingly, differing results were found dependant on the way in which frailty is operationally conceptualised. This has important ramifications for the field of frailty research and it is suggested that future

research should aim to incorporate multiple frailty measures where possible to allow further comparisons.

An assumption made by the majority of frailty trajectory research - including the study in Chapter 4 - is that every individual follows a similar gradient of frailty trajectory. In fact, it is possible that there are multiple subpopulations of people on the same trajectories. Identifying these subpopulations has important implications for prevention strategies. To address this I explored the heterogeneity of frailty trajectories in the LBC1936. Findings showed three classes of frailty trajectories with different intercepts and slopes: Low (61%, n=632), Medium (36%, n=368), and High (3%, n=28). Those in the Low group tended to be marginally younger and from a higher social class, with higher education and higher age 11 cognitive ability. The identification of these groups helps to illustrate the heterogeneity of frailty trajectories. I conclude by suggesting that future research should focus on replicating these findings and exploring other factors, which may influence subgroup membership.

Chapter 6 marked a shift in focus to study cognitive impairment trajectories in later life. I began by exploring the prevalence of MCI in the LBC1936. Findings were largely in line with previous research, showing a gradual proportional increase over time from 15% to 18%. I then subdivided MCI into two subtypes: amnestic MCI and non-amnestic MCI. The subtypes showed similar increases over time but non-amnestic MCI rates were slightly higher than I expected in relation to other studies. With the coding derived, Chapter 7 focussed on assessing how MCI changes over time and which factors were associated with this change. Findings showed that over six years 74% remained cognitively healthy, 12% transitioned to MCI, 7% reverted to healthy cognition, and 7% maintained their baseline MCI status. The factors significantly associated with these changes were age, cardiovascular disease, and number of depressive symptoms, but not physical frailty. I suggest that future research should continue to explore the factors affecting MCI change, and that research into physical frailty and MCI may help to clarify the link between these two factors.

8.2 The implications of measuring age-related decline

Implementing measures of frailty and MCI has been critical for the empirical aspects of this thesis. Additionally, the derivation of these measures has proved useful for other researchers who have utilised the measures in their own studies. For instance, the FI measure in the LBC1936 was used to explore frailty's association with neighbourhood deprivation (Baranyi et al., 2021), and the MCI measure derived is included in a current NeuroCHARGE cognitive working group analysis. This illustrates the beneficial and collaborative aspect of deriving these types of age trajectory measures, and it is hoped that these measurement tools will continue to be useful in future studies. However, whilst there are many positive aspects of these measures, the findings in this thesis raise several important discussion points and implications to consider. Many of these considerations are discussed in previous chapters, but in the following sections, the salient issues surrounding the quantification of frailty and MCI are reviewed, and recommendations for future research are made.

8.2.1 Considerations of measuring frailty

As discussed in Chapter 3, the operational definition of frailty remains ambiguous and there lacks consistency in the field. Numerous frailty measurement tools exist and this thesis has only considered only a few of the options available (Russ & Welstead, 2020). In Chapter 1, it was detailed that there are two main operationalisation approaches to frailty, either to consider it a purely physical condition, or to take a multidimensional accumulation of deficits approach. Due to the strong outlooks on both sides, it seems unlikely that a definitive consensus will be made in the near future. The field of frailty research is rife with inconsistency between frailty measurement tools (Aguayo et al., 2017). This divergence is demonstrated in Chapter 4 in which frailty associations differed when using different measurement tools despite

the conditions being the same. These differences in operationalisation and findings have ramifications for the interpretation of frailty research. Most research studies utilise only one measure; however, this approach increases the risk of frailty becoming conflated whereby two distinct models are being used to measure the same concept. It remains unclear as to whether frailty is a singular concept, but given this thesis' results and others (Cesari et al., 2013), there is evidence to suggest that physical frailty and multidimensional frailty are distinct and should be treated as separate concepts. To help address this issue it is proposed that utilising more than one frailty measure in a research study is currently the best way to control for differences between frailty tools. By doing so, it allows more opportunity to compare and contrast the different ways of measuring frailty and potentially paves the way for more precise definitions to be made in the future. A further recommendation is that researchers are more specific about the type of frailty that they are testing – i.e. multidimensional accumulation of deficits frailty, physical frailty etc. This will help to ameliorate confusion over which operational definition of frailty is being used. By undertaking these actions and continuing to contrast frailty measurement tools, future research may reach a point at which a fundamental difference between physical and multidimensional accumulation of deficits frailty is certain, and subsequent research acknowledges them as distinct entities.

Another significant issue facing the measurement of frailty is the translation of these tools into efficient and operational tools in a clinical setting. Whilst research may often have the option to choose between frailty measures, in a clinical setting the requirement of an accurate and reliable tool is often dictated by time and financial pressures (Russ & Welstead, 2020). The choice of tool generally comes down to the resources available at each primary care service, and so whilst a tool like the FI may provide great insight, its practicality in a clinical setting is uncertain as it requires time and resources to derive. As discussed by De Lepeleire, Iliffe, Mann, and Degryse (2009), frailty offers clinicians a useful tool for patient care and for targeting resources at older adults. However, they note that simple scales are required

to effectively identify frailty. Potential solutions to this issue have been developed. For example, Wallace et al. (2020) developed the Pictorial Fit-Frail Scale which uses an image based questionnaire that allows a rapid assessment of frailty in under five minutes. Another example is the electronic FI, which is based on the FI created by Rockwood and Mitnitski (2007), but is adapted to utilise existing primary care health records that are available to every UK general practice (Clegg et al., 2016). Finally, additional research may be necessary to explore the inclusion of social vulnerability in frailty measures. Tools like the Groningen Frailty Indicator (Peters, Boter, Burgerhof, Slaets, & Buskens, 2015) and Tilburg Frailty Indicator (Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010) are used more in clinical settings due to their insight into an individual's social vulnerability eg. Their social support networks. Further study of these tools is required, however, as we point out in our recent commentary (Russ & Welstead, 2020), this avenue of research represents a promising future whereby tools are developed to improve efficiency in a clinical setting.

The accurate measurement of frailty is still very much in development. However, as numerous research studies have shown, frailty presents a useful method of identifying vulnerability in later life. Accessing this information enables research to explore the causes of late life health vulnerabilities and seek effective prevention strategies. Additionally, being able to identify those with frailty allows for more targeted care plans that ultimately improve quality of life and reduce the burden on healthcare systems.

8.2.2 Considerations of measuring MCI

There are several important considerations to bear in mind when deriving and utilising an MCI measure. As discussed in Chapter 6, MCI prevalence can change according to how the measure is constructed. Prevalence will differ according to the normative data and type of cognitive tests used, and

the way in which impairments to the activities of daily living are defined (Dunne et al., 2021). A recent systematic review of MCI showed that there is a great heterogeneity in MCI incidence across studies, likely due to the inconsistencies in methodologies and the settings in which they were testing (i.e. clinical or community) (Gillis, Mirzaei, Potashman, Ikram, & Maserejian, 2019). These inconsistencies can also be seen in the systematic review of frailty trajectories in Chapter 2 and once again highlights the importance of developing consistent approaches to measuring age-related health declines. Despite these inconsistencies, in a research setting MCI can provide important insights into how cognitive status changes over time and often provides a target population for dementia clinical trials (Cummings et al., 2016).

However, the translation of MCI identification to a clinical setting has proved particularly controversial. Disputes primarily come from the standpoint that MCI is a rudimental concept which is open to clinical interpretation and produces variations in prevalence depending on the clinician (Saunders, Ritchie, Russ, Muniz-Terrera, & Ritchie, 2018). Currently in the UK there are no guidelines for clinicians to manage MCI, consequently, there are great inconsistencies between practices (Dunne et al., 2021), and many emphasise the prognostic uncertainty of the concept (Wang, Page, & Etherton-Beer, 2021). Accordingly, some propose that MCI is not a particularly useful tool for clinicians to use to help their patients, and instead it is suggested that future cognitive impairment identification focusses more on the precursors to specific diseases like Alzheimer's disease (Dunne et al., 2021). As with the debates surrounding the measurement of frailty, these differences in opinion are unlikely to be resolved imminently and so it is necessary for future research to work towards a more consistent definition of MCI, whilst also exploring criteria that are more specific to certain causes of MCI such as Alzheimer's disease, Vascular dementia, or Frontotemporal dementia. Some researchers have also considered that MCI may have better utility if it is viewed as an entity on the neurodegenerative disease spectrum rather than the current categorical approach of it being deemed either

present or absent (Saunders et al., 2018). A focus on continuous measures may allow for more precision in research exploring the trajectories of cognitive impairment in later life and the factors that affect it.

Taken as a whole, whilst the current model of MCI is imperfect, the ongoing evolution of the concept enables it to continue to be a useful tool for identifying those who fit into the critical stage for intervention between normal cognitive functioning and dementia. Identifying someone with MCI or at risk of further decline can be crucial. Therefore, future research is vital to define what constitutes MCI, addressing its current limitations, and working towards a more consistent and efficient concept that has utility both in a clinical and a research setting.

8.2.3 Remembering to consider the central issue of measuring age-related declines

Perhaps unsurprisingly, the parallels between frailty and MCI are strong. However, an important consideration when deriving and interpreting any measure of age-related health decline is to bear in mind the central objective of this line of research: to improve quality of life in older adults. One way in which to address these issues is to explore quality of life and wellbeing measures in relation to concepts like frailty and MCI. Some research has found that psychological wellbeing can protect against the development of physical frailty (Gale, Cooper, Deary, & Sayer, 2014) and MCI (Gates, Valenzuela, Sachdev, & Singh, 2014), but more research, particularly longitudinal studies, is required.

Linking measures such as frailty or MCI back to the human experience is imperative. For instance, in Chapter 3, it is reported that on average LBC1936 participants show an increase in FI from 0.16 to 0.22 over approximately 15 years, but how does this increase in frailty relate to difficulties in daily living for individuals? Moreover, should patients be

informed that they are on a steep trajectory of frailty decline? Similarly, in a clinical setting is it helpful for an individual to be informed that they have MCI? This steers into a philosophical and well-trodden debate whereby it is necessary to consider the ethical implications of disclosing concepts that, whilst useful in a research setting, may have limited use for the patient (Frederiksen et al., 2021; Nielsen et al., 2020).

A better understanding of the diagnostic disclosure of health states like frailty or MCI is urgently required. Linking quantitative research studies to the human experience can be difficult. For that reason, it may be useful to undertake qualitative studies alongside patients and clinicians to develop evidence based models addressing the disclosure of age-related decline (Nielsen et al., 2020). Gaining a better understanding of how much information patients want from their clinician is a major aspect of the health care experience. Using focus groups may be one way to gain a better understanding of the attitudes held towards concepts such as frailty or MCI (Gregory et al., 2021). In addition to this, it may also be beneficial to incorporate patient contributions into the research design process itself. By doing so, it may be possible to work towards a more informed approach to how concepts like frailty and MCI are conveyed to a patient.

8.2.4 The fluctuations of age-related health trajectories

Bearing in mind the results from Chapters 3, 4, 5, and 7 it is evident that both frailty and MCI show substantial fluctuations over time. In Chapter 7, it is demonstrated that individuals with MCI are able to revert to healthy cognitive ability over time, and accordingly, cross-sectional data may miss these important transitions and make their conclusions less precise. With this in mind it seems that longitudinal research is the optimal way to provide a holistic approach to age-related decline as it allows us to assess the vacillating nature of late life health trajectories.

However, it is possible that latent classes of frailty trajectories exist whereby certain individuals group together into similar classes of trajectory. Chapter 5 explores this heterogeneity by uncovering the latent subpopulations of frailty trajectories rather than using the population mean like most other longitudinal studies do. It is not possible to definitively say that all older adults fit into one of the three frailty trajectory classes that were identified. However, the fact that several previous publications have also found three distinct classes adds strength to the findings (Chamberlain, Finney Rutten, et al., 2016; Stow, Matthews, & Hanratty, 2018), as do the high posterior probabilities of an individual falling into one of the three groups. It is suggested that future studies consider this approach more often to account for the vast differences there are between individual trajectories and to help reinforce findings like those in this thesis. Specifically, this method could be undertaken more often in the field of cognitive impairment research. Exploring the heterogeneity of MCI is something which previous research has studied in depth (Nordlund et al., 2005). Whilst some research has identified latent subpopulations of cognitive decline (Wilkosz et al., 2010), these studies are rare. It would be insightful to continue to develop our understanding of the latent subpopulations of cognitive trajectories in different populations, and furthermore, explore the trajectories from healthy cognitive status to MCI to dementia. Of particular interest may be looking at the trajectories of particular types of cognitive abilities, breaking it down into amnestic MCI and non-amnestic MCI may be an initial step in doing so. Improving our understanding of latent subpopulations of decline will potentially enable a more individualised approach to realigning individual ageing trajectories onto the healthiest pathways.

One area that I had hoped to explore further was the relationship between frailty and cognitive impairment, specifically through the concept of cognitive frailty. As discussed, whilst cognitive frailty is a promising area of focus, we currently do not have the consensus or accurate measurement tools to be able to conduct high quality research. The first step in improving our ability to accurately test for cognitive frailty is to gain better understanding of each

separate component and have a better knowledge of what frailty and MCI actually entail. At that point, it may be possible to create a concept and measure for cognitive frailty.

8.3 Strengths and Limitations

Specific strengths and limitations in relation to the studies conducted in this thesis are discussed in their respective chapters. The work in this thesis had numerous strengths. I approached the field of frailty with a critical eye. The vast majority of frailty research selects a single frailty tool with which to conduct their research, but I felt it was important to explore the differences between the different operationalisations of frailty. By doing so, an important difference between two of the main methods of operationalising frailty was exposed and it was brought into question whether or not frailty as a concept needs to be re-evaluated. Another strength of the empirical studies in this thesis is the use of the LBC1936, which benefits from the unique inclusion of intelligence test scores at age 11 for all participants, allowing the studies to control for early life cognitive ability. Additionally, all participants were born in 1936, in the same location, with similar environmental factors, reducing the likelihood of confounding factors. The fact that participants were so close in age means that the findings reflect differential age rather than chronological age which can confound the influence of other variables (McGrory et al., 2019).

A limitation of the research in this thesis relates to the reliability of the measurement tools that were utilised. The frailty measurement tools used in this thesis were chosen because they represent the two major frameworks that underpin the current understanding of frailty (Nguyen, Moodie, Keezer, & Wolfson, 2021). This allowed comparisons to be made to other cohorts and populations. However, despite this widespread use, there was the concern particularly with the FI, which varies in number of items and composition between studies, about the reliability of the construct. Ultimately, it was decided to include the FI despite these concerns due to its widespread use

and evidence from a systematic review of 35 frailty measurement tools that the FI had the highest level of agreement across studies (Aguayo et al., 2017). However, recent research has called into question the reliability of the FI, with findings indicating that the number and composition of deficits in the FI can significantly affect their reliability (Nguyen et al., 2021). Accordingly, future research is required to further explore the psychometric properties of this tool, and potentially work towards refining the FI guidelines created by (Searle et al., 2008).

One noteworthy limitation of this thesis is that the empirical research relied solely on analysing data from one cohort. Whilst the LBC1936 is an ideal basis for this type of research, future work is required to replicate the results in different populations. As discussed in previous chapters, the LBC1936 is comprised of white Caucasians with a skew towards those with a higher socioeconomic status (Taylor et al., 2018). Replicating the results in other cohorts is important, particularly by using cohorts made up of different ethnic groups and from different backgrounds. It may also be necessary to look to larger samples, as we have done with two upcoming studies in using data from SHARE (Jenkins, Hoogendijk, et al., 2021; Jenkins, Welstead, et al., 2021).

A further limitation with using this cohort was the inability to derive measures of frailty and MCI at several of the waves due to missing data. Whereas the FI was derived at all five waves, the Fried phenotype could only be implemented at waves 1, 3, 4, and 5. This made comparisons between the two measures less consistent and introduced a longer period between wave 1 and 3 in which unobserved frailty changes could have occurred. Similarly, due to missing data, MCI status was derived at waves 3, 4, and 5 meaning that it was not possible to observe MCI rates at the younger ages. Whilst it is unlikely that there would be high numbers of participants with MCI at earlier waves, early identification of those with MCI is important for several reasons. Recent clinical trials aiming to tackle MCI and dementia have increasingly started to focus on earlier stages of the disease progress for treatment intervention (M. Albert et al., 2018). Accordingly, studying the transference

from normal cognitive ability to MCI at earlier ages is crucial to predict which individuals are most likely to progress. Disease modifying interventions are thought to be more successful early in the disease progression. Therefore, the lack of information about MCI at earlier waves of the LBC1936 may miss this crucial period. More research into the early stages of cognitive decline are paramount to determine the efficacy of prevention strategies and interventions.

Related to this is the lack of information about participants who go on to develop dementia. As discussed in Chapter 7.2, the lack of information on dementia status is a significant limitation. Understanding the fluidity between normal cognitive ability, MCI, and dementia would be incredibly informative. Whilst these data are currently unavailable, the LBC1936 research team are in the process of ascertaining dementia status for each participant. Plans are underway to incorporate this data into a validated model in the future and extend the current findings. Finally, the studies were likely to have a degree of bias due to the attrition rates at each wave. Sample attrition is likely to create a healthy survivor effect whereby the healthier participants remain in the study for longer. Indeed some of the empirical chapters identified such an effect (see Chapter 4). Additionally, the details for participants withdrawing from the study are not recorded in the Lothian Birth Cohort 1936 making it difficult to assess the reasons for attrition. Therefore, it is important to bear in mind that the results may underestimate the prevalence of frailty and MCI in the general population.

8.4 Final remarks

In conjunction with advancements in health and social care over the past century, life expectancy has improved dramatically and caused an exponentially ageing population. A consequence of this demographic shift are the challenges we now face to care for a larger older generation with susceptibility to cognitive and physical deterioration. Understanding how these declines affect older adults and how age-related impairments interact

across time is imperative to intervene early and ensure individuals follow the healthiest ageing trajectory possible. The purpose of this thesis was to provide further information on the age trajectories of later life, specifically through the eyes of frailty and MCI. I approached this goal systematically and developed a body of work that extends our collective knowledge of how frailty and MCI develop over time, who are the individuals at highest risk of decline, and which factors contribute to these differences. Whilst I deemed that the research into the crossover between these two factors – cognitive frailty – is not yet sufficient, I hope that research such as this will be useful in refining our understanding of precisely what frailty and MCI entail, subsequently paving the way for definitions that are more precise. Quantifying age-related declines comes with limitations as there lacks consensus on what concepts like frailty and MCI entail. Accordingly, future research is crucial to allow us to hone these concepts and subsequently be able to provide consistent and replicable research. It is the hope that this information will encourage future researchers and policy makers to design and implement evidence-based interventions that ultimately improve quality of life and relieve the burden on healthcare systems.

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Appendices

Appendix 1. Supplementary material for Chapter 2.2

Supplementary Text S1

Search strategy; Phrase truncation was used to pick up on all forms of the selected words. The following search terms were included: 'frailty' OR 'frail*' OR 'frail elderly' AND 'longitudinal study' OR 'trajector*' OR 'prospective study' OR 'change'. For a link to the search strategy see: https://www.crd.york.ac.uk/PROSPEROFILES/126334_STRATEGY_20190227.pdf

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#5-6

Section/topic	#	Checklist item	Reported on page #
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	#7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl #1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#9

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#29-31

Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#10-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	#10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#21-23
FUNDING			

Section/topic	#	Checklist item	Reported on page #
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#1

Supplementary Table S1. PRISMA 2009 Checklist (Moher, Liberati, Tetzlaff, & Altman, 2009)

Appendix 2. Supplementary material for Chapter 4.2

Items	Coding	Cut-offs based on
Systolic Blood Pressure	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Diabetes (self-reported)	Yes (1) or No (0)	Already binary variable
High Cholesterol (self-reported)	Yes (1) or No (0)	Already binary variable
Heart problems (self-reported)	Yes (1) or No (0)	Already binary variable
Stroke or mini stroke (self-reported)	Yes (1) or No (0)	Already binary variable
Leg pain (self-reported)	Yes (1) or No (0)	Already binary variable
Blood circulation issues (self-reported)	Yes (1) or No (0)	Already binary variable
Thyroid Disorder (self-reported)	Yes (1) or No (0)	Already binary variable
Cancer (self-reported)	Yes (1) or No (0)	Already binary variable

Parkinson's disease (self-reported)	Yes (1) or No (0)	Already binary variable
Dementia (self-reported)	Yes (1) or No (0)	Already binary variable
Arthritis (self-reported)	Yes (1) or No (0)	Already binary variable
Any other chronic disease (self-reported)	Yes (1) or No (0)	Already binary variable
Polypharmacy (self-reported)	>4 medications (1), ≤4 medications (0)	Previous literature (Theou et al., 2013)
Body Mass Index (BMI)	18.5 to <25 (0), 25 to <30 (0.5), <18.5 or >equal to 30 (1)	Previous literature (Chamberlain, Sauver, et al., 2016)
6m walk time (gait speed)	>10 seconds or physically unable (1), <10 seconds (0)	Previous literature (Hoogendijk et al., 2017)
Able to stand up from a chair	Yes (1) or No (0)	Already binary variable
Grip strength (strongest hand and stratified by sex and BMI)	Bottom 5^{th} percentile (1), 5^{th}-20^{th} percentile (0.5), Above 20^{th} percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Townsend Disability Scale (Townsend, 1979)	11 – 18 (1), 0 -10 (0)	Previous literature (Fiona Elaine Matthews et al., 2016)
Peak Expiratory Flow rate (stratified by sex)	Bottom 5^{th} percentile (1), 5^{th}-20^{th} percentile (0.5), Above 20^{th} percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)

Forced expiratory volume (stratified by sex)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Depression (measured by the HADS)(Zigmond & Snaith, 1983)	11 -21 (1), 8 – 10 (0.5), 0 – 7 (0)	Previous literature (Zigmond & Snaith, 1983)
Anxiety (measured by the HADS)(Zigmond & Snaith, 1983)	11 -21 (1), 8 – 10 (0.5), 0 – 7 (0)	Previous literature (Zigmond & Snaith, 1983)
Mini-Mental State Examination (MMSE)(Folstein, Folstein, & McHugh, 1975)	<10 (1), 11-17 (0.75), 18 – 20 (0.5), 20 – 24 (0.25), >24 (0)	Previous literature (Searle et al., 2008)
Digit Symbol(Wechsler, 2003)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Block Design(Wechsler, 2003)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Verbal Fluency(Wechsler, 2003)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)

Matrix Reasoning(Wechsler, 2003)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Reaction time test(Cox, Huppert, & Whichelow, 1993)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)
Delayed recall(Wechsler, 2003)	Bottom 5th percentile (1), 5th-20th percentile (0.5), Above 20th percentile (0)	Recommended technique where no established cut-offs available (Theou et al., 2015)

Note. HADS: Hospital Anxiety and Depression scale

Online Resource 1: Items constituting the Frailty Index and their coding/cut-off points in the LBC1936

Online Resource 2: Deriving the Fried Criteria

The Fried Criteria was comprised on five dimensions. These were measured in the LBC1936 as follows;

Weight loss; Weight was measured using an electronic weighing scale, and height was measured in metres using a stadiometer. From this, it was possible to compute BMI by dividing weight by height squared. At baseline, weight loss was defined as a BMI less than 18.5 kg/m^2. At waves 3 and 4, weight loss was defined as a loss of weight of 10% or more since their previous visit or a BMI less than 18.5 kg/m^2.

Exhaustion;

Exhaustion was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Exhaustion was scored as present if the participant responded ‘very often’ or ‘nearly all the time’ to the item ‘I feel as if I’m slowed down’.

Physical activity;

A question asking participants about their usual level of physical activity was used with six responses ranging from moving only when necessary, to heavy exercise or sport several times a week. In line with previous publications (Gale et al., 2017), participants in the lowest sex-specific 20% of the distribution were defined as having low physical activity.

Walking speed;

Participants were recorded walking a distance of six metres at maximum speed. After adjusting for sex and height, those in the lowest 20% of the distribution were considered to have a slow walking speed.

Weakness;

Maximum grip strength was measured in all participants using a dynamometer. Participants were measured three times with the strongest attempt being used for analysis. After adjusting for sex and BMI, those in the lowest 20% of the distribution were defined as having weakness.

Online Resource 3: Defining occupational social class

Occupational social class was based upon principal occupation, coded in line with the 1980 census (General, 1991). Five social class categories were used: professional, managerial, skilled non-manual, skilled manual, and semiskilled/unskilled. The women in the cohort were asked for their husband's occupation as well as their own, and they were assigned a social class based on the highest occupation of the household. This was derived from their own occupation for about half of the women, and from their husband's occupation for the remainder.

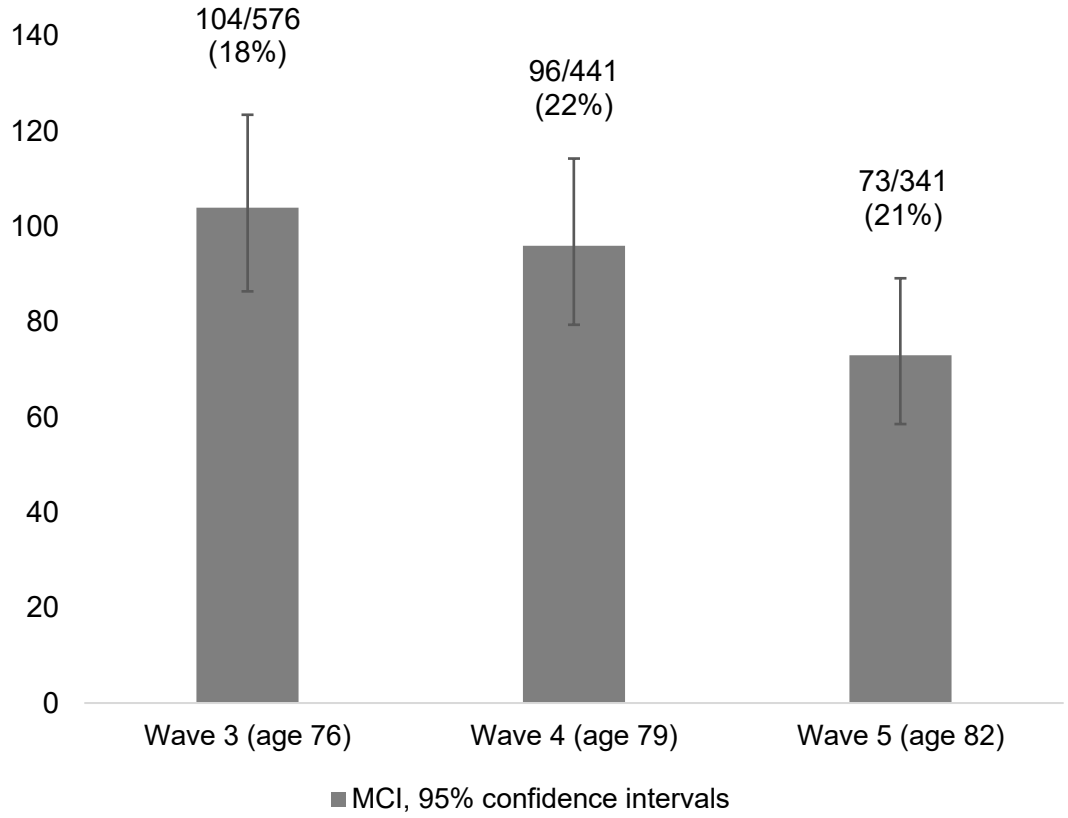
Childhood IQ was derived from Moray House Test scores at age 11 (Penrose, 1949). Raw scores were corrected for age in days at time of testing and converted to an IQ scale where mean (SD) = 100 (15).

Appendix 3. Supplementary material for Chapter 5.2

	Type of model	Number of classes specified			
		2	**3**	**4**	**5**
AIC	Linear	-9903.26	-9995.01	-9989.01	-9983.01
	Quadratic	-10025.94	-10068.94	-10105.01	-10097.01
BIC	Linear	-9858.31	-9935.08	-9914.09	-9893.11
	Quadratic	-9956.01	-9979.04	-9995.12	-9967.14

Supplementary Table 1: A comparison of AICs and BICs in baseline model with no covariates

Appendix 4. Supplementary material for Chapter 6.2



Supplementary figure 1: MCI rates using normative data from the Lothian Birth Cohort 1936

Appendix 5. Supplementary material for Chapter 7.2

Supplementary text 1

Each of the MCI criteria were established by following the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines for Alzheimer's disease (Albert et al., 2011):

1. *Concern regarding a change in cognition*: To retrospectively assess this criterion I identified a question in the LBC1936 that has also been used in previous MCI classifications (Fiona E Matthews, Stephan, Bond, &

McKeith, 2007). The self-reported question asks ‘Do you have any problems with your memory?’

2. *Impairment in one of more cognitive domains*: Due to the longitudinal nature of the LBC1936, it is possible to assess cognitive change over time. Consistent with the NIA-AA workgroup guidelines (Albert et al., 2011), I defined the cognitive impairment criterion as: At least one cognitive domain score scoring ≥1.5 standard deviations lower than the mean **OR** A decline below the 10th percentile on one test since the previous wave **AND** below the 20th percentile on two tests since the previous wave **AND** a decline below the 20th percentile on one test since wave 1. These percentile cut offs were chosen to reflect evidence of a lower than expected performance in cognitive ability since their previous visit given their age. The cut offs are consistent with previous research (Knopman et al., 2016). I purposefully included both a cross-sectional measure of cognitive impairment as well as a measure of cognitive decline that captures those with slow decline (since wave 1) as well as a more rapid decline (since previous wave). The following cognitive tests were used: Wechsler Adult Intelligence Scale III (WAIS-III) - Symbol Search, Digit Symbol Coding, Matrix Reasoning, Letter-Number Sequencing, Block Design, and Wechsler Memory Scale III (WMS-III) Logical Memory I & II (Psychological Corporation, 1997).
3. *Preservation of independence in functional abilities*: In the LBC1936 we have the Townsend Disability Scale (Townsend, 1979) which scores participants out of 18, with higher scores reflecting greater disability. The criterion is met if the participant has little decline (≤1 point negative change) since the previous wave on the Townsend Disability Scale, reflecting a general maintenance in their independence of function. Alternatively, the participant can also meet the criteria if they answered ‘No’ to the question ‘Are your memory problems affecting your life’.
4. *No diagnosis of dementia*: The fourth and final criterion is met if the participant does not self-report a diagnosis of dementia (or for the sample who have been assessed clinically, do not have a formal

diagnosis of dementia made by a research doctor) **AND** scores ≥24 on the MMSE.

Variables	**Withdrew from study (*n*=275)**	**Completed both time points (*n*=292)**	***p*-value**
Age at T1, mean (SD)	76.278 (0.652)	76.217 (0.690)	0.280[1]
Sex, *n* (%)			0.109[2]
Male	156 (56.7%)	146 (50.0%)	
Female	119 (43.3%)	146 (50.0%)	
Age 11 cognitive function, mean (SD)	-0.021 (12.137)	2.415 (11.011)	0.016*[1]
Missing data	16	20	
Years of education, mean (SD)	10.611 (1.066)	10.983 (1.174)	< 0.001***[1]
Depressive symptoms, mean (SD)	3.000 (2.380)	2.473 (1.959)	0.004**[1]
Missing data	1	0	
Body Mass Index (BMI), mean (SD)	27.913 (4.811)	27.512 (3.930)	0.277[1]
Missing data	2	0	
Social class, *n* (%)			< 0.001***[2]
Professional	42 (15.4%)	75 (26.0%)	
Managerial	111 (40.7%)	113 (39.2%)	
Skilled non-manual	50 (18.3%)	63 (21.9%)	
Skilled manual	55 (20.1%)	33 (11.5%)	
Semiskilled/Unskilled	15 (5.5%)	4 (1.4%)	
Missing data	2	4	
History of cardiovascular disease, *n* (%)			0.203[2]
No	190 (69.1%)	187 (64.0%)	
Yes	85 (30.9%)	105 (36.0%)	

Variables	**Withdrew from study (*n*=275)**	**Completed both time points (*n*=292)**	***p*-value**
History of stroke, *n* (%)			0.514[2]
No	241 (87.6%)	261 (89.4%)	
Yes	34 (12.4%)	31 (10.6%)	
APOE ε4 status, *n* (%)			0.324[2]
Absent	179 (68.8%)	200 (72.7%)	
Present	81 (31.2%)	75 (27.3%)	
Missing data	15	17	
Fried Phenotype Status, *n* (%)			< 0.001***[2]
Not Frail	86 (31.3%)	144 (49.3%)	
Pre-Frail/Frail	189 (68.7%)	148 (50.7%)	

**p<0.05, **p<0.01, ***p<0.001*

[1] Linear Model ANOVA; [2] Pearson's Chi-squared test

Supplementary table 1: Comparisons between completers and withdrawers