The course of disability in the very old: drivers and trajectories

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ABSTRACT

In recent decades the rapid growth in the numbers of the very old, those aged 85 years and above, has made them the fastest growing age group of most populations worldwide. Nevertheless we know little about their health and disability, the latter being a particularly important aspect of quality of life for individuals but also more widely as a major determinant for residential care. This thesis uses a unique study, the Newcastle 85+ Study, a longitudinal, population based cohort study of people born in 1921 and aged 85 years at first interview in 2006, to explore the disablement process in very late life through three substantive sub-studies.

In the first sub-study I explore how disability unfolds through the order of loss in basic and instrumental activities of daily living [(I)ADLs, these being the building blocks of disability. (I)ADLs were lost in a specific order, activities requiring long distance mobility and balance (for example shopping) being lost first and those requiring upper body strength (e.g. dressing, feeding) last and with little difference between men and women.

The second sub-study examines the impact of specific diseases on disability onset and finds that arthritis, diabetes and cognitive impairment were similarly disabling for men and women, cardiac disease was more disabling in women, and cardiovascular disease and respiratory disease disabling for women only.

The final sub-study uses novel statistical techniques to uncover patterns of disability from age 85 to 90. Four distinct trajectories of disability were found for both sexes, with a disability-free trajectory being identified in men but not women, and all other trajectories showing increasing levels of disability.

These sub-studies are discussed in the light of other literature, the extent to which they explain the greater disability yet survival of women (the disability-survival paradox), and the implications for the future.

DEDICATION

I dedicate this thesis to my family:

My mother, Elaine – for her love and support, and teaching me not to give up when things get tough.

My grandparents, Jennifer and Bernard – for their love and teaching me the importance of hard work, determination and commitment in all I do.

My aunt, Nicola – for her love, advice, support and guidance throughout my life.

My late great-grandmother, Bella – for leaving me with a spiritual legacy that goes beyond words and showing me the way in life.

I could not have done this without you.

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i) First and foremost I would like to extend a special thanks to Professor Carol Jagger for her supervision, support, guidance and advice throughout this endeavour. Thanks are also extended to my second supervisor Professor Thomas Kirkwood for his advice and guidance at pivotal points along the way.

ii) The participants who gave their time and information so willingly and without whom none of this would have been possible. I would also like to thank those who allowed me to visit them in their home to understand how the data were collected and recorded.

iii) The co-authors of the publications I enclose as part of the thesis and the guidance they gave in terms of pointing me in the direction of literature that would be of benefit as part of the PhD training.

iv) The core Newcastle 85+ Study nurses; Dr Karen Davies, June Edwards, Joan Hughes, Sally Barker and Judith Hunt. Data manager, Pauline Potts and study secretary, Lucy Farfort.

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1 POPULATION AGEING

1.1 Overview

The purpose of this chapter is to give a brief overview of the ageing population of the UK. It will discuss Newcastle upon Tyne as a centre for the study of older people and reveal the need for studies that measure health in the very old. In addition, it will discuss the cohort of people on whom the study is based and detail my contribution. Finally a statement of what the thesis intends to cover will be outlined.

1.2 The ageing population

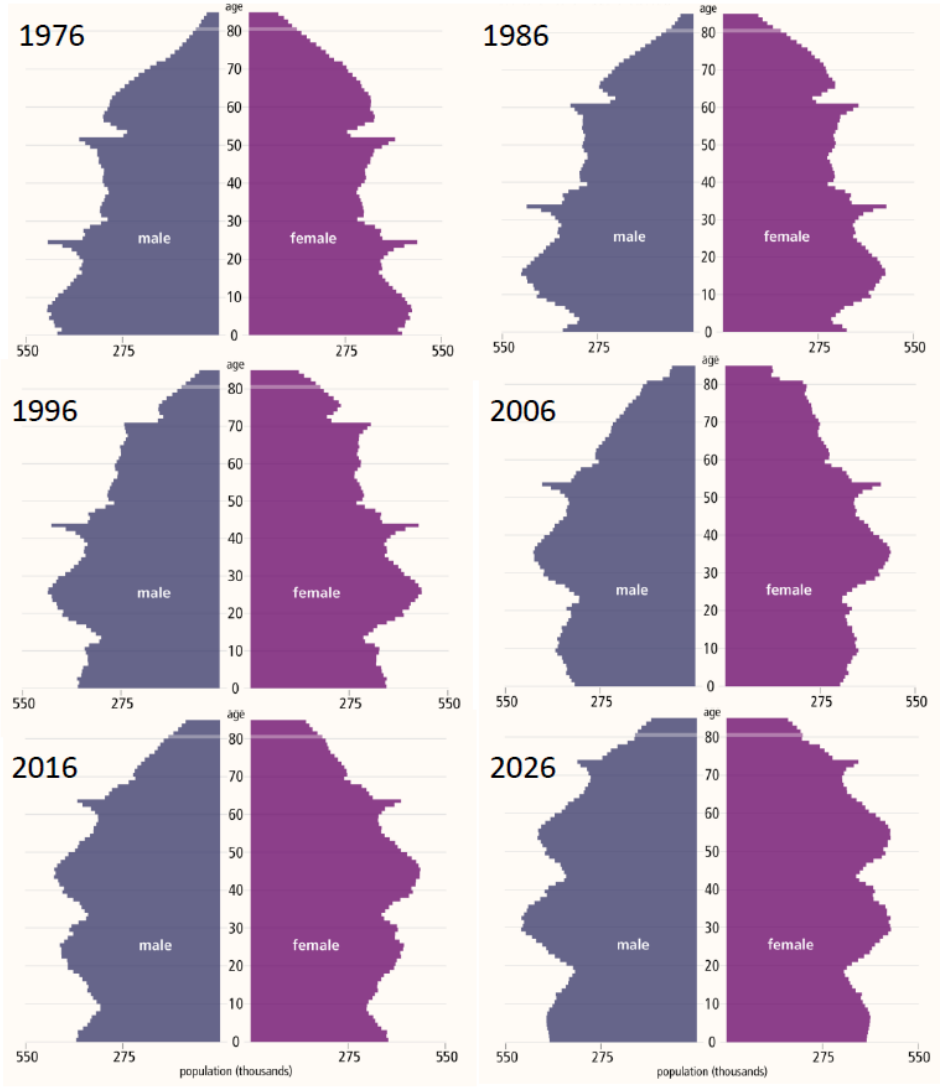
On a global scale the population of the world is ageing. Between 1950 and 2000 the number of people aged over 60 tripled. It is expected that by 2050 it will triple again. This is leading to a marked change in the structure of population that has not been seen throughout history. Ultimately it will lead, for the first time, to a population structure whereby those people aged over 60 outnumber those aged under 15 – a development that has already come to fruition in developed countries (United Nations Department of Economic Social Affairs Population, 2009). During the 19th and 20th centuries these gains were the result of a reduction in infant mortality, reduced infections due to improvements in hygiene, sanitation and health care provision. Further gains in life expectancy since the 1970's have been brought about by a reduction in death rates of older people, notably those aged 80 and over. This was attained through a reduction in deaths caused by vascular diseases and cancer with improvements in health behaviours (Wilmoth, 2000). Furthermore, on a worldwide scale these gains are expected to continue in a linear fashion, adding 2.5 years to life expectancy per decade (up to 2040), and is contrary to the previously expected plateau (Oeppen and Vaupel, 2002).

The most rapidly expanding section of the older population is those aged 85 and over - hereinafter referred to as the very old. Between 1991 and 2031, the total population of England and Wales is projected to rise by 8%, those aged 65-84 years by 46% whilst the 85+ age group will rise by 138% (Office of Population Censuses and Surveys, 1993). Although absolute numbers in the 85+ age group are small, 2001 Census figures show one million aged 85+ (1.9% of the population), (Office for National Statistics, 2003b) and even small increases have major implications for

providers of care. The average annual cost to the NHS of a person aged 85 or over is six times that of someone in the 16-44 age group and four times that of the 45-64 age group (Wanless D., 2001).

Figure 1.1 shows how the structure of the UK population has changed from 1976 and its forecasted distribution by 2026. This exemplifies the growth of people at older ages; shifting its distribution from one that was pyramidal in 1976/86 (i.e. proportions of older people diminish with age) to one that is increasingly becoming rectangular by 2026. This shift in the demographic structure is expected to continue beyond 2026. In addition, the UK is currently experiencing a supplementary surge in the number of people moving into older age (if somewhat transient), primarily driven by the 'baby-boom' generation (those born following the Second World War) with subsequent surges expected as their children and grandchildren move toward older age (Figure 1.1). These factors are the main causes for the expansion in the proportion of people living to an older age.

Figure 1.1: UK population pyramid: 1976 - 2026



Source: ONS - http://www.ons.gov.uk/ons/interactive/uk-population-pyramid---dvc1/index.html

From a public health perspective, there is growing interest in studying in detail what is happening to the health of the very old and the factors that influence individual health trajectories. Factors affecting health operate throughout the life course; yet there is little data on determinants which maintain health in very old age. These insights are important, not only to inform us about the health status of what is demographically the fastest growing section of the population, but also for what they will tell us about the ageing process itself and the factors that affect it. For a very large proportion of medical conditions, age is the single largest risk factor. The rapidly declining mortality rates of the very old suggest a plasticity in the mechanisms of ageing, although it is recognised that there is considerable heterogeneity in health among the very old which has not yet been fully exposed.

1.3 Ageing and society

The expansion in the proportion of the very old is a key societal concern of our time, for a number of reasons. Assumptions about older people often originate in the opinion that the ageing population will result in more people with disabilities and/or poor health. If true, this would place a greater strain on health care providers and increase health care costs; especially given older people have a greater requirement for health related services compared with other ages (de Jouvenel, 1989; Jarvis and Tinker, 1999; Andrews and Phillips, 2004). Likewise, this expansion will shrink the proportion of people remaining of working age and leave them less able to deliver the necessary health care resources, both financially and in terms of an increase in the health care worker to older person ratio. This raises the possibility of increased taxation to meet these growing needs (Bos and Von Weizsacker, 1989; Thane, 1989) potentially impacting intergenerational solidarity (Mullan, 2002). In addition, at the beginning of the 21st century there was little informative data about the health of the very old and there was a pessimistic outlook about their quality of life. This was largely driven by research conducted in 1983 by Kramer, where he suggested that with increasing life expectancy (largely driven by advances in medicine at the time) we did not see associated gains in health and concluded that people were living longer but only in ill health. In other words, people were simply being kept alive in ill health by advances in medicine creating a greater burden on the health service long term (Kramer, 1983).

In contrast, there are optimistic perspectives about future populations of old people. They have a real, valuable and often overlooked input into society in terms of their fiscal contribution to the economy; their involvement in the voluntary sector and their role with childcare and adult care provision. There is also a constant evolution in new medical and assistive technologies which enable people to live for longer and independently within the community (Freer, 1988; Zweifel *et al.*, 1999; Anderson and Hussey, 2000; Evans R.G. *et al.*, 2001; Andrews and Phillips, 2004; Bond and Cabrero, 2007; Robinson *et al.*, 2013). Furthermore, in today's society an older person's mental capital, defined as their cognitive and emotional resources, is largely underutilised, and tapping this vast reservoir of experience, *'…could benefit families, businesses, wider society, and Government, as well as older people themselves…',*

potentially leading net contribution to the public purse (The Goverment Office for Science, 2008).

The societal concerns about the changes in the structure of the population outlined in this section largely arise from supposition about the prevalence of disease and disability in the very old based on a scant literature base. The true amount of disease (or burden of disease) and disability, and what this means for the person and society, are areas where further research is warranted.

Newcastle University, including the wider city and hospitals have, over many years, developed expertise and resources to investigate issues of the ageing population. The next section will discuss this in more detail alongside a brief overview of the Newcastle 85+ Study.

1.4 Ageing research in Newcastle

Newcastle University has a rich history of pioneering ageing research stretching back to the 1960's and covering a wide spectrum, including:

i) Understanding the extent of 'old age mental disorders' for both institutionalised and domiciliary based older people (Kay *et al.*, 1964), uncovering a high degree of unmet need in older people with psychiatric conditions.
ii) Integration of geriatric services within hospitals in Newcastle at the acute and rehabilitative care levels to provide more effective delivery of medical care for older people (Evans, 1983).
iii) Spearheading of the identification of different types of dementia, including Lewy body dementia, vascular dementia and Alzheimer's disease.

Newcastle University has also led or contributed to two cohort studies prior to the Newcastle 85+ Study:

i) **The 1000 Families Study** began in Newcastle in 1947 at a time when infant mortality rates were high and its primary objective was to understand the drivers that were causing increased mortality. All those born in Newcastle upon Tyne hospitals in 1947 were recruited into the study (less than 0.5% refused) and a red

sticker was placed on their GP records for identification purposes (hence known as the Red Spot Babies). Participants in this study are now approaching 70 and research from the study has helped understanding of health in early and mid-life (Pearce *et al.*, 2009).

ii) Newcastle was one of six centres in the original **The Cognitive Function and Ageing Study (CFAS)** which began in 1992 to expose the prevalence and incidence of cognitive impairment and dementia in England and Wales. The study consisted of six centres with Newcastle being designated the centre for the north-east of England. A repeat of the CFAS study began in 2011 (CFAS II) in three centres, including Newcastle, to look for changes in the prevalence and incidence of dementia and cognitive impairment (Brayne *et al.*, 2006a).

Although understanding of disease and its impact on health was fairly well researched in the younger old, little was known about the health of the very old (85+). This left medical practitioners / policy makers / researchers with very little knowledge of their health, how it evolves over time and whether services are meeting their needs. To fill this gap, in 2006, Newcastle University began an exciting and novel epidemiological study, **The Newcastle 85+ Study**, whose goal was to investigate the spectrum of health in the very old in unprecedented detail. Participants were all who turned 85 in 2006 (born 1921) and living in Newcastle and North Tyneside. The study ran between 2006 and 2012 and data was collected over four waves. Full details of the study will be discussed in chapter three alongside other worldwide studies of the very old. It is from this source that the data and analyses that form this thesis are based.

This cohort are a unique group to study as they were all born in 1921, meaning they were infants living in the shadow of the 1st World War (1918), spent their adolescent years living with the fallout of the Great Depression (1930s) and turned 18/19 on the eve of the 2nd World War (1939) and so many men went on to fight for their country. Although the period influences of war and depression were experienced by all who were alive at the time, their ages at the events could mean that their exposures shaped their health trajectories in later life. In England as whole only 17.8% of men and 33.3% of women born in 1921 lived to 85 (Office for National Statistics, 2012).

Nevertheless, we will see in chapter 3, that the Newcastle cohort are representative of their birth cohort in and England in terms of demographics.

Furthermore, the UK north-south health divide is well known and therefore the health of the people of Newcastle is generally worse than that of the England average due in part to higher levels of deprivation. Life expectancy is markedly lower than the national average and there is even a striking gradient in life expectancy across the city. Men who live in the most deprived areas of Newcastle live, on average, 12.1 years less than those who live in the most affluent and for women this is 10.1 years (Public Health England, 2015). In addition, the occupations of men and women within Newcastle were markedly different in the early / mid-late 20th century. Many men from this cohort worked long hours in manual occupations (ship building, coal mining) potentially being exposing to hazardous working conditions and, in addition, levels of smoking were higher. This has the potential to set up further gender disparities in health trajectories throughout life. While this paints an unfavourable picture of the health of the people of Newcastle, there have been improvements. Over the previous ten years (to 2011) all-cause mortality rates fell and, although still higher than the national average, death rates from cancer and heart disease fell also (Public Health England, 2011). Whilst these statistics illuminate a picture of the overall general health of the people of Newcastle; none of them are based specifically on the health of the very old (85+) of which we know very little, if anything, on a local or national level.

This thesis is based on the Newcastle 85+ study and the study will be expanded upon in detail in chapter 3.

1.5 My role in the Newcastle 85+ Study

In October 2008 I joined Newcastle University as the statistician for the Newcastle 85+ Study. At this point the study had collected the baseline data and was in the process of implementing the second wave of data collection (18 months from baseline). My role initially was to liaise with the data manager for the cleaning, validation and preparation of datasets and to undertake their analyses. In addition, a sub-study was rolled out (profiling cardiac function in the very old) and I played a key role in the preparation, cleaning, validation and subsequent analysis of this data.

Over the past seven years I have contributed to the writing and analysis of over 20 papers that have been published from the study. These papers are allied to various medical disciplines and my main role was to provide statistical expertise. During my first year, I began to develop an interest in disability and so began my PhD studies (registered October 2009) whose overarching objective was to understand the course of disability in the very old. As I conducted this research, key hypotheses were explored and written up and sent to academic journals for publication. As such, all of the results that form the basis of this thesis are published in peer-reviewed journals. Four manuscripts form the core of this thesis, three of which I led on in terms of the design of the investigation, the conduct of the research, the analytical strategy for the main outcome and the preparation of the manuscripts for publication. These four publications are:

i) **Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study** was published in the British Medical Journal in December 2009 and sets the scene for the study from which the data are drawn alongside the main characteristics at baseline. I was responsible for analysing all the data that are included in the manuscript and writing the statistical methods section as well as critical review of the drafts. Baseline data that was used in subsequent manuscripts are taken from this manuscript and present in results section of chapter 3. The full publication can be found in Appendix A.

ii) **Losing the ability in activities of daily living in the oldest old: a hierarchic disability scale from the Newcastle 85+ study** was published by the Public Library of Science (PLoS) in January 2012 and I was first author. For this publication I was responsible for a full review of the current literature, conducting the research, the analytical strategy and preparing the manuscript for publication and responding to reviewer comments. The full publication can be found in Appendix B.

iii) **The contribution of diseases to the male-female disability-survival paradox in the very old: results from the Newcastle 85+ study** was published by the Public Library of Science (PLoS) in February 2014 and I was first author. For this

publication I was responsible for a full review of the current literature, conducting the research, the analytical strategy and preparing the manuscript for publication and responding to reviewer comments. The full publication can be found in Appendix C.

iv) **The enduring effect of education–socioeconomic differences in disability trajectories from age 85 years in the Newcastle 85+ study** was published by the Archives of Gerontology and Geriatrics in March 2015 and I was first author. For this publication I was responsible for a full review of the current literature, conducting the research, the analytical strategy and preparing the manuscript for publication and responding to reviewer comments. The full publication can be found in Appendix D.

In addition, I have also presented the results from publications two to four at scientific conferences [REVES network on healthy life expectancy (Paris, 2011), Gerontological Society of America (San Diego, 2012 and Washington DC, 2014) and the Wellcome Trust Longitudinal Studies Conference (Cambridge, 2015)] over the course of the PhD.

1.6 Thesis structure

The second chapter of this thesis will cover the background to disability. It will be discussed in terms of its conceptualisation and how this has evolved over the years and, in so doing, will detail risk factors and how people are now beginning to rethink disability prediction in preclinical terms.

The third chapter will give a comprehensive overview of the study in terms of recruitment, retention, response rates and the baseline findings related to disease, geriatric syndromes and demography. All of the results that form this chapter come from publication one.

The next three chapters will broadly follow the order of the publications and form the main results chapters (four-six).

The primary and overarching objective of this thesis is to understand the course of disability in those aged 85 and over and it will do this by:

i) Testing whether the measurement of disability used in the Newcastle 85+ Study is appropriate for the very old and whether there is distinct pattern, or order, to how people become disabled – chapter four (publication two).

ii) Determining if particular diseases drive incident disability and death, and whether these are these gender specific – chapter five (publication three).

iii) Determining whether distinct trajectories of disability exist in the very old and how are these associated with sociodemography, life-course socioeconomic status, geriatric syndromes, disease and a selection of inflammatory biomarkers – chapter six (publication four).

The final chapter (seven) will discuss all of the results focusing on the course and development of disability in the very old in view of existing literature. It will also discuss the strengths and limitations of the study and potential future directions from this research.

2 DISABILITY AND HEALTH

This chapter explores issues of population health and its evolution with particular reference to disability - a common indicator used to measure the health and dependency of the ageing population. It will discuss disability as a theoretical concept, its measurement in practice and associations with disease, socioeconomic status and a selection of inflammatory biomarkers.

2.1 Ageing and the measurement of health

In itself, age is a risk factor for ill health; inferring that the very old are likely to be burdened with greater levels of disease, disability and frailty, thus utilising more health care resources then their younger old counterparts (Allen *et al.*, 2001; Covinsky *et al.*, 2003; Burden of Disease Network Project, 2004; Bootsma-van der Wiel *et al.*, 2005; Klein *et al.*, 2005; Collerton *et al.*, 2012). It is also posited that inter-person disease burden is likely to be highly variable (Suzman and Manton, 1992; Motta *et al.*, 2005; Jopp and Rott, 2006). In addition, in the very old, the ratio of men to women will have reduced; driven by increased mortality in men (Office for National Statistics, 2003a) and as current research suggests that women suffer more non-fatal disease than men, then their health care utilisation has the potential to be greater (Wray and Blaum, 2001; Crimmins *et al.*, 2002; Murtagh and Hubert, 2004). Irrespective of the increase in ill health with age, current research suggests it is not all bad news and that older people continue to perceive health in encouraging terms (Leinonen *et al.*, 1999; Andersen-Ranberg *et al.*, 2001; Jopp and Rott, 2006). However, the emerging concern about the growing proportion of older people is that with increasing life expectancy we have not seen associated expansions in healthy life expectancy, forcing more older people to confront disease, disability and social care reliance as they age and live for longer (Kelly and Baken, 2000; Jagger *et al.*, 2008).

Measuring health in very old people poses many challenges related to sampling errors, non-response and non-random subject attrition. The error source (in terms of sampling errors) is largely related (but not limited to) individual enthusiasm to take part in epidemiological studies; the quality of the information collected (especially from those whose health is compromised) and the exclusion of particular individuals

based on specific circumstances (e.g. those living in institutions). Non-response errors generally occur where an individual does not have the capacity to answer or refuses to answer for personal or disease specific reasons that principally relate to cognition, frailty, multimorbidity, disability and visual/auditory difficulties (Rodgers and Herzog, 1992; Carsjo *et al.*, 1994; Leahy *et al.*, 2005; Larsson and Thorslund, 2006; Davies *et al.*, 2010). Consequently, studies of the very old which assess health and account for these potential sources of error are needed. Furthermore, the assessment of health in the very old has previously been conducted via a series of tools that are useful in a clinical setting, evaluating areas related to cognition, frailty and physical performance (Katz *et al.*, 1963; Lawton and Brody, 1969; Folstein *et al.*, 1975; Jette *et al.*, 1986; Nelson *et al.*, 1990; Fried *et al.*, 2001; Rockwood *et al.*, 2005; Ng *et al.*, 2006) but some of these tools are not appropriate for research in the very old. The reasons principally relate to the readiness of the very old to participate in research programs that take them away from their home into formal settings.

Functional status (and physical performance) is a field that has received much attention in the younger old (<85 years) but less so in the very old (≥85 years) and the measurement of health using this component is often defined in terms of disability. It is through this mechanism that data can highlight deteriorations or improvements in health, providing important information to healthcare providers and help design interventions where data are showing a worsening health profile. Until recently most studies considered people in the 65 years and over age bracket to be 'the old', but as the population ages (§1.2 & §2.1), research in the very old is becoming increasingly important. As a society there is now a growing need for informative data describing the multiplicity of health, disease and disability in this age group. Collecting data from this age demographic will inform our understanding of the spectrum of health and how it changes over time and in doing so will fill the lacuna where knowledge is limited.

2.2 The importance of disability

From the perspective of individuals who are currently experiencing (and those who will at some point move into) older age, personal fears about what remaining lifetimes have in store is an important consideration. The biggest fear (aside from concerns about ill-health) is the loss of independence in daily activities. A study by the

Disability Living Foundation in December 2009 indicated that 68% of older adults feared a dependence on others more than death itself (29%) and, furthermore, 44% had concerns about moving into a care home. This has significant and understandable implications for their psychological wellbeing (e.g. depression, loneliness) (Disability Living Foundation, 2009; Mangoni, 2014).

Disability is often defined in terms of the ability to carry out activities related to daily tasks (Jagger *et al.*, 2001b) and is a precursor for numerous important outcomes such as health service use (both primary and secondary care), institutionalisation and mortality (Branch *et al.*, 1981; Wan and Odell, 1981; Branch and Jette, 1982; Manton, 1988; Branch and Ku, 1989; Reuben *et al.*, 1992; Keller and Potter, 1994; Mor *et al.*, 1994; Severson *et al.*, 1994; Stuck *et al.*, 1999; Li, 2005a; Li, 2005b), and it has been used to assess levels of dependency (Isaacs and Neville, 1976; Jagger *et al.*, 2011) (dependency will be discussed further in §2.2.2). Within the younger old it also has many important associations with other significant global health measures such as self-rated health, socialisation and physical (and leisure) activity (Pope and Tarlov, 1991). Therefore, the identification of factors which predict disability onset and progression is of paramount importance, not least in the very old where research and understanding of the disablement process itself (and indeed the ageing journey) is at a nascent stage of understanding. Firstly however, the measurement of disability must be conceptualised.

2.2.1 Models of disability

Standard measures revealing the prevalence or incidence of disease have relatively unopposed meaning. However, shifting measurement to a concept such as disability comes with inherent difficulties such as characterisation and conceptualisation (to individuals/researchers/clinicians/policy makers) and what biological / socio-demographic / environmental features should be used in its quantification (Abberley, 1997; Davidson, 2003). Initially, the concept of disability gave rise to two main models; the frame of reference for which arose from a social or medical perspective and so their rationale lay either with society (social) or the individual (medical).
The social model of disability uses society as its locus (rather than individual) and the obstacles disabled people face in their ability to function within the community (in comparison to their non-disabled counterparts). Disability is considered as a failure

by society to provide environments which cater for the needs of disabled people and where social/physical structures are constructed without disability in mind. These structures can be environmentally based, for example limited access to public buildings, perhaps caused by restricted entrance, thus affecting a person who may require the services that are located within. It can also be defined by public attitudes, where assumptions are made by lack of knowledge, low expectations, or even anxiety providing for disabled people. Similarly, people with disabilities can be excluded on discriminatory basis, for example restricted access to education or employment (Harris and Enfield, 2003). These damaging attitudes, often invoked by the non-disabled mainstream, and their associated exclusions generally present as a function of the aforementioned reasons (Abberley, 1997; Davidson, 2003; Thomas, 2004; Watson *et al.*, 2014).

In contrast the medical model has a physiological perspective. It views disability as a product of impairments that cause an individual to live life at a disadvantage compared to their non-disabled counterparts (Watson *et al.*, 2014). The foundation of this model's framework lies in a 'norm' based context, whereby people are classified according to established and accepted levels. For example, assessing the hearing ability of an individual will be contrasted against a recognised and acceptable level of normal hearing, and people who depart from this norm (in a way that does not reach conventional levels) are considered impaired (Rothman, 2003) i.e. the observed condition is considered as the 'problem' - put another way, the condition or the individual is considered as the locus of disability (Areheart, 2008). Generally speaking, the medical framework of disability acts as a sentinel for access to specialised and supporting facilities, and places a professional at the centre of established assessment protocols (Barnes *et al.*, 1999). In this framework little consideration is given to social, environmental or individual circumstances and a person is seen as someone who can be re-abled or supported by ameliorating the effects of diseases or conditions.

Furthermore, the perspective (whether medical or sociological) from which a researcher approaches the measurement of disability unavoidably impacts the phraseology and nature of questions that assess the disabled status of individuals. The medical model will focus questions around the person and their ability to

complete routine daily activities assessing disability through the lens of functional limitation. In contrast, assessing the same concept via the social model will centre questions on the physical/attitudinal/social obstructions present in society that limit an individual to carry out the same task. Instances of the differences in the phraseology and perspective were outlined by Abberley in 1992, for example, from a medical stance, "*What complaint causes you difficulty in holding, gripping and turning things?",* and the equivalent question from a sociological stance, *"What defects in the design of everyday equipment like jars, bottles and lids causes you difficulty in holding, gripping and turning them?"* (Abberley, 1992).

To date, few studies have approached disability from a sociological perspective and as such the majority of data gathered have been almost entirely focused on the medical model (Purdon *et al.*, 2005). That being said, there is evidence to suggest the medical model does accurately capture disability; this being validated (and found to correlate well) against social welfare and heath episode statistics (Dale and Marsh, 1993; Bajekal *et al.*, 2004). Often the pragmatism of large scale data collection exercises is the force that motivates the collection of information related to disability with a medical outlook; distinguishing those with medical disabilities and informing the delivery of required resources. Nevertheless, neither the medical nor the social model are sufficient to capture disability as a whole and it is the complex interface between environment, social situations, impairments and disease that is needed for it to be fully elucidated (WHO, 2001).

Whilst the medical and social models of disability are not completely discordant and efforts to unite the two have been made, contention still exists between research groups. From a medical perspective recognition has been given to the social constructs and barriers that influence disability; however the locus still rests firmly with the individual. Conversely, sociological researchers now lend credence to impairments but similarly their causal locus has not shifted from society (Thomas, 2004). The merger of the two models is often referred to as the biopsychosocial model (Engel, 1977) or the sociomedical model (Verbrugge and Jette, 1994).

Initial efforts to expand the conceptualisation of disability started with the World Health Organisation in 1980 and its rationale was grounded in the International

Classification of Impairments, Disability and Handicaps (WHO, 1980). Although this schema was widely accepted by the scientific community, concern grew around its use for hypothesis generation, as a tool for the design of studies and as a measurement instrument to understand the development of disability (Grimby *et al.*, 1988). At around the same time another model was being developed by Saad Nagi (1979) from a sociological perspective with four fundamental themes: active pathology, impairment, functional limitations and disability (Nagi, 1979). This model's foundation is ostensibly the same as that developed by the WHO (without a one-to-one association for handicaps) but its theoretical underpinning lay within sociological theory. Over time, Nagi's scheme gained much ground as a tool to understand the development of disability, eventually being endorsed by the Institute of Medicine (Pope and Tarlov, 1991).

In 1994 Verbrugge *et al.* embarked on a project to unify the two models and take into account the medical and sociological aspects (Verbrugge and Jette, 1994). This model built upon that posited by Nagi but also incorporated the detail put forward by the World Health Organisation. Its main goal was to describe a conduit through which disability can be defined, beginning with a pathological element and leading to a variety of intermediary outcomes before disability itself. This process is outlined in figure 2.2 below.

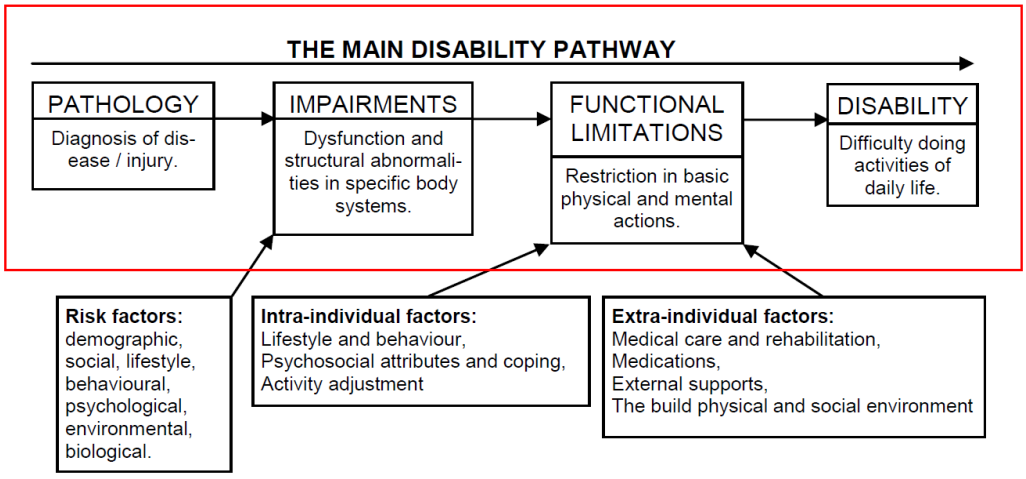


Figure 2.1: Verbrugge and Jette model of disablement

The pathology element of the disability pathway refers to the biological irregularities that can be identified medically and their potential sequelae. Impairment follows

pathology, whereby the diagnosis of a particular condition will impact the function of a certain body system or area. For example a diagnosis of arthritis may cause impairment in joint flexibility. As such, this leads to functional limitations; for instance the capability to grip, reach or stretch. This can then give rise to a failure carrying out housework or dressing oneself, i.e. disability. This model of disability allows investigation from a more diverse perspective and acknowledges that it does not evolve in a regular fashion but can be influenced by various risk factors. These risk factors can be intra and/or extra-individual and operate to influence how disability acts on a person-specific and population level. Using the example of arthritis outlined above; disability could be ameliorated by changes to lifestyle behaviour, for example by increasing physical activity and actively trying to maintain function at the 'functional limitation' level thus halting (or decelerating) the process in a person before they actually reach a disabled juncture.

Models considered so far have considered disability from the point at which disease is diagnosed, and the two (disease and disability) are seen as separate entities with the interaction of various features resulting in disablement i.e. a unidirectional process. The conceptualisation of disability has been acknowledged to be a more complex affair than these models can explain (Verbrugge and Jette, 1994; Fougeyrollas *et al.*, 1998) and criticisms of their structure have been voiced (A.M. and Badley, 2002). This prompted the World Health Organisation to revise their model of the disability process; the outcome of which was the International Classification of Functioning, Disability and Health (ICF) in 2001 (WHO, 2001). It suggested a paradigm shift by postulating that disability is a common experience and a product of decremented declines in health, this being a property of the mainstream and not just the minority. The result of this change meant that the emphasis shifted to the impact of disorders rather that the causal effect. The revised model is outlined in figure 2.3. Similar to the construct of the disablement process that was outlined by Verbrugge and Jette (1994), the ICF describes decreases in function as the complex and dynamic interaction of health conditions with extra and intra individual factors acting together to mitigate or exacerbate the process. However, where the endpoint of the Verbrugge and Jette model was disablement, the ICF outline considers interactions between the health conditions (and potential feedback mechanisms) and the contextual factors (environmental and personal) which can be thought of as intra-

individual (personal) and extra-individual (environmental) in addition. The process of disablement is therefore no longer thought of as a linear route (and just the reaction to illness); but a dynamic process that can change in severity over the life course.

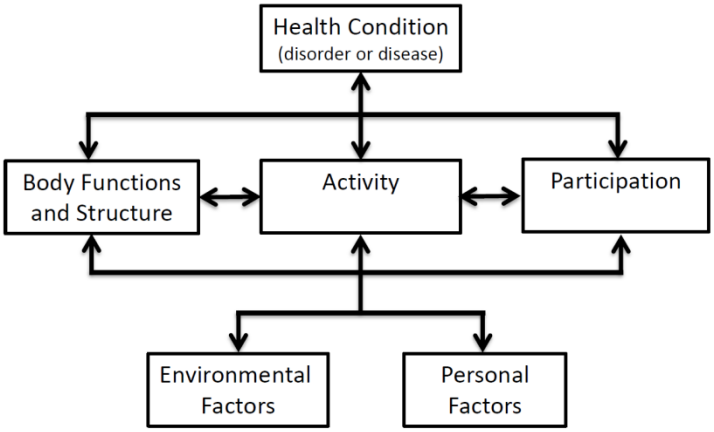


Figure 2.2: ICF model of disability

The ICF framework is described by three levels of functioning; the level of the body (or body structure), the whole person and the whole person in their social milieu. Consequently, this extends the meaning of disability into dysfunction at any or all of these levels. Whilst this model allows a user to investigate the impact of diseases (or conditions) it also allows further exploration of secondary disorders (or sequelae) that may arise as the consequence of the primary factor under question (Pope and Tarlov, 1991).

For the purposes of this thesis and because of the nature of the study from which the data are drawn, disability in the very old will be analysed from a sociomedical perspective.

In later life the process of disablement frequently begins with the onset of chronic disease leading to a loss of function and so restricting the ability to perform standard daily routine tasks (Verbrugge and Jette, 1994). Often it is found that the diseases which lead to disability are non-fatal such as arthritis, hypertension, cardiovascular disease, cognitive impairment, diabetes and visual impairment (Verbrugge and Jette, 1994). By their nature, people tend to live with these chronic conditions rather than die from them (Rothenberg and Koplan, 1990) and a major outcome is disability. However, disability in itself is not an irreversible process (Crimmins *et al.*, 1997) and

it can be ameliorated or exacerbated by both intra and extra-individual factors, such as those outlined in figure 2.2. The ICF model lends understanding to the process of prevention, deceleration or reversibility in crossing thresholds that would carry an individual through to disability (Peres *et al.*, 2005). It allows a method of examining the disablement process from a life course perspective and given the case put forward that biological, behavioural and psychosocial pathways interact to influence health in later life (Ben-Shlomo and Kuh, 2002), it is central to understand disability mechanisms. Where a medical model of disablement only allows one to consider the proximate determinants of disability, the fuller model allows the examination of the causes and lifestyle choices that can lead to the proximate determinants themselves (Lynch and Smith, 2005). Furthermore, it has been reported that major illnesses, in early, mid and late life increase the risk of illnesses later and therefore corroborate the argument for the study of disability from a life course approach (Barker, 1998; Costa, 2000; Blackwell *et al.*, 2001; Caljouw *et al.*, 2013). However, before this life-course approach can begin, the measurement of disability must be further defined.

2.2.2 Measuring disability

From a medical perspective disability is often defined in terms of the ability to carry out activities related to daily tasks (Jagger *et al.*, 2001b). These tasks are frequently subdivided into two types. The first considers items which are connected to an individual's ability to maintain the status quo in relation to their basic functioning care (i.e. survival) and include items such as the capability to feed oneself, bathe, transfer to and from the toilet, bed and chair and dressing. Occasionally, questions pertaining to bladder and faecal incontinence are also included. Questions focused around these items were initially developed into a survey instrument in 1963 to form an index from which a measure of disability could be ascertained (Katz *et al.*, 1963), known as the Katz ADL index. The items that encompass the Katz index are often referred to as Basic Activities of Daily Living (BADLs or ADLs) and respondents often rate themselves on a Likert scale with a foundation in difficulty or the need for help in carrying out these tasks.

Several years later (1969) an additional scale was developed by Lawton and Brody. This new scale was constructed to measure a more complex set of behaviours associated with disability and focused on the capability of an individual to preserve

independence within the larger community (including their own home) rather than focus on basic care (Lawton and Brody, 1969). This index consists of items that measure the ability to use the telephone, shopping, the management of medications and finances and housekeeping and are referred to as Instrumental Activities of Daily Living (IADLs). Measurement of the index is comparable to that used for ADLs. It has been postulated that the IADL scale is the less discriminatory of the two indices in terms of its facility to accurately evaluate the capacity of the less disabled (LaPlante, 2010). In addition some IADL items have the power to measure high order cognitive ability (the management of medications and finances). Use of the ADL index alone has been suggested to discriminate against the less disabled who remain living independently within the community. However, the use of both indices together facilitates the description of a greater range of disability for a broader range of people (Kempen, 1995). Furthermore, the use of the combined index is not found to be biased by age, whereas this cannot be said for the use of the ADL index alone (LaPlante, 2010).

Several other scales have been constructed over the years to measure the burden of disability. Some of these have used isolated ADL or IADL scales whilst others have combined items and others still have included additional items such as continence, hearing and vision. A summary of the main scales are detailed below:

i) The **Barthel Index** (Mahoney and Barthel, 1965) is an index that measures functional independence in personal care and mobility and include items relating to feeding, transfers, toileting, bathing, walking on a level surface, using steps, dressing and bowel control. This scale is widely respected and used throughout the research community. However, as this scale was designed for institutionalised populations it may not detect low levels of disability.

ii) The **Health Assessment Questionnaire (HAQ)** (Fries *et al.*, 1982) is a scale that has been used for people who are compromised by disease and to examine the impact of disease on disability outcomes. It has been implemented widely throughout the world, particularly related to outcomes of clinical trials involving specific arthritides and other diseases (HIV). Whilst this scale is popular, there is little evidence of validity and reliability.

iii) The **Functional Activities Questionnaire** (Pfeffer *et al.*, 1982) is a scale pertaining to items that are in the IADL domain and has been used extensively in studies into normal ageing, in particular to examine mild cognitive impairment (MCI). The sensitivity and specificity of its ability to discriminate between normal controls and those who exhibit symptoms of MCI is 85%-98% and 71%-91% respectively.

iv) The **Townsend Disability Scale** (McGee *et al.*, 1998) is a scale comprised of 9 items and are a mix of ADL and IADL items. It has been used extensively within the UK as it is easy to administer and concise. However, although its use is wide, there has been little work on the validity and reliability of the results mainly caused by many modifications of its use.

v) The **Office of Population Census Surveys (OPCS) Disability Scale** was originally developed as a tool to evaluate the prevalence of disability amongst UK adults it measures dimensions such as locomotion, reaching and stretching, dexterity, personal care, continence, visions and hearing, communication, behaviour, intellectual functioning, consciousness, eating and drinking, and disfigurement. This scale was based on the WHO disability classification.

vi) The **Lambeth Disability Screening Questionnaire** (Charlton *et al.*, 1983) is a 22 item screening tool used to assess the level of disability within the community via postal survey. However, this scale has not been used extensively and requires testing in more environments than just a postal survey.

vii) The **Short Form (36) Health Survey** (Anderson *et al.*, 1996) consists of eight domains (all measured on their own scale) relating to items that examine physical functioning, pain, self-rated health, physical activity and mental health, vitality, emotion and social interaction.

viii) The **Groningen Activity Restriction Scale (GARS)** (Kempen *et al.*, 1996) is used to assess seven IADL items and 11 ADL items and is non-disease specific

i.e. it is usable in the general population. It has been used extensively to measure disability in general populations and shows strong internal validity.

Irrespective of the type of scale that is being used, the measurement of disability should assess the execution of activities that form part of the everyday milieu. The responses to (I)ADL items (and other items if collected) are often combined to form a scale where a higher score indicates greater levels of disability. In the first instance, however, what constitutes disability must be clearly defined and this is determined by how questions are phrased and their possible response categories. Performance of activities is frequently measured via 'difficulty' and responses regularly form an ordinal scale related to that difficulty (i.e. none, some, a lot, cannot do). Additionally, some use dependency as their measure (the need for help) although it is debated that this does not truly reflect level the level of disability within an individual and what it really measures is, *"…the presence of an intervention to reduce disability. It measures the buffer to disability and not disability itself."* (Verbrugge and Jette, 1994). With that in mind the classification or measurement of disability is assessed by one (or more) of three important qualifiers that relate to performance, capacity and ability. The ability qualifier pertains to whether an individual 'can' carry out particular activities that may or may not be impacted by disease or disorders. The performance qualifier is related to whether an individual 'does' carry out a particular task and the capacity qualifier, whether an individual 'could' carry out a particular task. The use of different qualifiers exposes different aspects of disability. Where the performance qualifier is used it will expose disability and vulnerability; the ability qualifier will expose self-reported disability with the potential to expose what people 'think' versus what they 'can' actually do. The collection of both types of information can also yield important information in terms of 'incapacity yet performance' and/or reflect gender specific roles found in older people such as cooking or housework (Hubert *et al.*, 1993; Murtagh and Hubert, 2004).

Using items to form a scale in this way (whether based on difficulty or dependency) has caused controversy amongst researchers, in particular regarding the issue of unidimensionality – that is whether all items are measuring the same latent trait, in this case, disability. Some suggest that the scales are bidimensional as the IADLs are a more complex set of tasks that are environmentally and culturally influenced

(Breithaupt and McDowell, 2001) compared to ADLs. Others suggest it may be tridimensional, this being a function of the more cognitive elements items that form the scale (managing medications or money and using a telephone) (Thomas *et al.*, 1998; Ng *et al.*, 2006). However, some refute these assertions and maintain it is unidimensional, arguing that as all items are highly correlated then the use of a single scale is sufficient to capture the variance. Therefore the use of all IADLs and ADLs are a sufficient measuring instrument to capture the level of disability in the population (Asberg and Sonn, 1989; Kempen and Suurmeijer, 1990; Fleishman *et al.*, 2002). Before an investigator begins in-depth analyses of disability (measured through (I)ADLs), it is therefore important that the concerns around their dimensional construct is tackled. As such, the structure of the (I)ADL items used in the Newcastle 85+ Study and whether they form single or multiple health dimensions will be examined in detail in chapter four of this thesis, which aims to validate the use of a combined (I)ADL scale through robust statistical techniques.

2.2.3 Hierarchy of disability

Another issue of using (I)ADLs to form a scale surrounds the subject of whether greater scores truly measure the severity of disability i.e. are people with higher scores more disabled than those with lower ones or is it just a random mix of items? This issue can be thought of in terms of a hierarchy of disability i.e. are some items more 'difficult' to complete and is the ability to carry them out lost first, before more 'easy' items? If this is true, then a constructed score is likely to contain a hidden hierarchical property which includes information about the severity of disability. Furthermore, using items to form a scale without consideration of a potential hierarchy loses information about the disablement process, information that could prove valuable in targeting interventions to maintain function.

The acquisition of skill in completing ADLs in childhood follows a distinct pattern (eating, toileting, dressing and bathing) all ordered by increasing difficulty (Katz and Akpom, 1976). Conversely, as a person becomes disabled in later life, the capability to complete similar tasks is commonly lost opposite in order to which they are gained in childhood. Due to the nature of the items that form the ADL and IADL indices, it is generally accepted that the IADL items are more difficulty to complete than the ADLs and as such one would expect that the loss in ability in IADLs would precede the loss

of ability in ADLs. Although a hierarchy of loss has been reported in numerous studies, they have only considered a subset of questions across the (I)ADL spectrum; the age of the people who have been investigated are predominantly the younger old (65-80) and few include those who reside in institutions (Siu *et al.*, 1990; Travis and McAuley, 1990; Lazaridis *et al.*, 1994; Verbrugge and Jette, 1994; Kempen, 1995; Dunlop *et al.*, 1997; Ferrucci *et al.*, 1998a; Weiss *et al.*, 2007).

The majority of research that has been conducted has considered (I)ADLs as an aggregated measure and higher scores are assumed to reflect greater levels of disability. However, a study by Jagger *et al.* (2001) investigated the patterning of loss in ADLs for an older population aged 75 years and over and found that the capability to bathe, walk and transfer from the toilet were lost first these requiring lower extremity strength. Following loss in capability in these items a subsequent loss of capability was found in the ability to dress oneself and then the ability to eat; items that require upper extremity strength (Jagger *et al.*, 2001b). This patterning has also been found when both IADL and ADL items are considered as a single index (Spector *et al.*, 1987; Kempen and Suurmeijer, 1990) pointing toward loss of capability in (I)ADLs in terms of functional body domain and that the loss may occur in clusters that call on demand from that domain (Dunlop *et al.*, 1997; Ferrucci *et al.*, 1998a; Njegovan *et al.*, 2001; Weiss *et al.*, 2007). This 'patterning of loss' is an important concept in terms of elucidating the causal pathway leading to disability and as an initial stage in understanding its pathophysiology. Delineating the effect of disease, its impacted domain and subsequent disability may yield benefits in terms of preventing, delaying or decelerating the functional decline of older people. The importance of determining the ordering of loss in (I)ADLs in the very old is vitally important and is an area of scant research. Some studies may have included the very old as part of a greater sample that incorporate the younger old but often these are limited by sample size and tend to exclude those who reside in institutions. Chapter four of this thesis will investigate the ordering of loss across all (I)ADLs at baseline and will examine whether the ordering is gender specific. Additionally, the ordering of loss will be confirmed longitudinally.

2.3 Risk factors for disability

The loss of ability to perform (I)ADLs is not an event which occurs in isolation (or at random) and it is frequently related to diseases which impinge upon the body structure/area to which an activity relates. Thus any examination of the performance of (I)ADLs must consider the risk factors that affect their performance.

Risk factors that are associated with disability are largely modifiable, though there are some which are not, for example chronological age, gender and genetics are, in principal, immutable. On the contrary, modifiable risk factors generally originate from a prior chapter in one's life and are related to lifestyle factors such as sedentary behaviour and physical activity or lifestyle choices such as smoking, alcohol consumption and diet both of which can be a function of socioeconomic status (SES) (Parker *et al.*, 1994; Melzer *et al.*, 2000; Rautio *et al.*, 2001; Seeman and Crimmins, 2001). Furthermore, increasing age is accompanied by a greater risk of disease (this too can be a function of SES), and it plays a crucial role in the disablement process (Lawrence and Jette, 1996). Likewise, many studies have reported strong dose-response associations with SES and mortality, disability, disease and depression (Smith *et al.*, 1990; Adler *et al.*, 1993; Melzer *et al.*, 2000; Lorant *et al.*, 2003; Coppin *et al.*, 2006; Lynch, 2008; Taylor, 2010; Taylor, 2011).

2.3.1 Socio-economic status and disability

Socio-economic status (SES) and its relationship with health throughout life is an area of lively research. SES is often measured by education, income, or occupation, and is known as a strong predictor of health and mortality (Lynch, 2008). This has been particularly observed with increasing education and declines in disability prevalence (Taylor, 2011), suggesting there is a mechanism by which increased levels of education have the potential to reduce possible later life disability. This mechanism has been suggested to be related to intelligent behaviours that impact risk factor decision-making, mastery over one's life, and postponed gratification (Freedman and Martin, 1999), impacting exposure later in the life-course. Research exposing the association of socio-economic status with health and mortality suggests the two are not mutually exclusive and that the latter is intrinsically linked to the former (Link and Phelan, 1995).

Two complementary hypotheses exist that attempt to expound upon the mechanisms driving the impact of socio-economic status. The cumulative disadvantage hypothesis (O'Rand, 2002) posits that socio-economic disparities amplify across the life course, largely as a result of differential exposure to risk factors associated with low SES, for example smoking, alcohol consumption, occupation, education and physical exercise. The cumulative insult of negative health behaviours/situations associated with low SES then steer the health and mortality discrepancy. The alternative, age-as-leveller hypothesis (Lynch, 2008), proposes that SES in younger age groups may produce divergent health trajectories; however, as populations move into late-life (and those exposed to high SES risk factors become decedents), age-related biological forces move with greater strength to produce poor health and mortality trajectories. Thus, irrespective of exposure to high SES risk factors at an earlier age, it becomes insignificant in impact on divergent health trajectories, as age-related disease, disability, and frailty take hold.

In chapter six of this thesis, I will investigate trajectories of disability and, in so doing, will consider associations of the trajectories with life-course socioeconomic status.

2.3.2 Disease and disability

Proving a direct connection between disease and disability is problematic as many older people suffer from multiple diseases simultaneously and the task of disentangling direct effects is complicated, although some studies do provide evidence on the correlation between the two (Fields *et al.*, 1999; Hogan *et al.*, 1999; Stuck *et al.*, 1999; Brach and VanSwearingen, 2002). Others go further and provide evidence of the individual effects of diseases (Freedman and Martin, 2000; Jagger *et al.*, 2007; Puts *et al.*, 2008; WHO, 2008; Sousa *et al.*, 2009). However, given that the prevalence and incidence of diseases are likely to change as new therapies emerge and technology advances, recent and relevant studies are scarce. Furthermore, research has shown that those over the age of 70 are, on average, diagnosed with two or three chronic diseases and the impact is such that they account for 66% of total health care expenditure (Lorig *et al.*, 1999; Femia *et al.*, 2001b). Thus, understanding the disabling impact of diseases is important for health care policy and provision.

A comprehensive review was conducted to investigate risk factors for disability in 1999 by Stuck *et al* and the greatest and most consistent factors found were disease burden, cognitive impairment, depression, low physical activity, smoking, visual impairment and lower extremity functional limitation. Associations (but not as strong) were also found with low and high body mass index (BMI), poor self-rated health, infrequent social interaction and no alcohol consumption (contrasted with moderate consumption) (Stuck *et al.*, 1999). Where Stuck *et al* reported a consistent association with disease they did not focus on specific diseases and whether some were more deterministic of disability burden than others. However, a recent study by Klijs *et al.* (2011) considered the disabling impact of individual diseases and found that back pain, peripheral vascular disease, stroke, arthritis, lung disease (only for men), diabetes (only for women) and heart disease should be targeted by clinicians to reduce the burden of disability. The impact of these diseases were also shown to be more disabling in people over the age of 80 (Klijs *et al.*, 2011). While it has been shown that chronic diseases lie on the causal pathway to disability, it is also argued by some that they are the sequelae of prerequisite underlying pathology, e.g. hypertension (potential cardiovascular diseases), elevated circulating lipid and glucose levels (potential stroke and diabetes) and reduced bone density (potential osteoporosis) (Goldberg and Chavin, 1997; Wagner, 1997).

A strong and unconfounded relationship has been reported between disability and depression; the direction of the relationship being that disability is a dominant cause of onset of depression in later life (Prince *et al.*, 1998), however other sources of depression ally themselves with social isolation (and loneliness), deprivation (SES), and negative life events such as widowhood. While it has been shown that treatments for depression can have a positive impact on quality of life, it is postulated that this still goes largely undetected in the very old (Blazer, 2003).

Many factors have been discussed that impact disability prevalence and incidence, however at this point is important to introduce another concept that relates to disability, disease and mortality and how this is gender specifically expressed. This is known as the gender-disability survival paradox.

2.3.3 The gender-disability survival paradox

The gender-disability survival paradox refers to the phenomenon that women tend to live longer than men but, at the same time, have more disability and disease. It is an anomaly that has been observed for at least the past 100 years. This paradox is well researched and reported in studies that belong to the 20th century, in particular countries that are considered 'first world' (Oksuzyan *et al.*, 2008; Crimmins *et al.*, 2011; Thorslund *et al.*, 2013). However, as far back as the 18th century when the first constructed life tables were calculated, differential survival rates have shown that men have greater age-specific mortality than women. What lies at the heart of the mechanisms that drive the gender specific disparity is still debated. The areas of discussion, and the causal mechanisms, focus on a number of key areas. The first, and most popular area, is disease and gender specific disease patterning. Men tend to have fewer diseases, fewer limiting long standing limitations, be physically stronger and have less difficulty with (I)ADLs and yet their age-specific mortality rates are higher. Although they report fewer diseases, this conveys nothing of the type of diseases they are diagnosed with, which could be important in explaining this phenomenon. In fact, it has been reported that women are more likely to have a greater number of non-fatal chronic diseases (Gold *et al.*, 2002; Marengoni *et al.*, 2008; Marengoni *et al.*, 2009) compared to men. However, the task of untangling the impact of disease type and its influence on gender specific mortality is complicated by co-occurring disease patterns and high levels of multimorbidity in the very old (DuGoff *et al.*, 2014; Marventano *et al.*, 2014; Melis *et al.*, 2014; Lu *et al.*, 2015; Santoni *et al.*, 2015).

Intrinsic gender specific biology may also play its part is creating the paradox, especially the role of hormones. Some argue that the sex hormones of men (notably testosterone) play a crucial role. A study of Korean eunuchs showed that their average life span was around 70 years (±1.76), this being 14.4-19.1 years longer than their counterparts who remained 'intact' suggesting that testosterone plays a key role in the ageing of men (Min *et al.*, 2012). The causal mechanisms thought to be driving decreased mortality are associated with its effect on the immune system (Roberts *et al.*, 2004) and cardiovascular health (Nettleship *et al.*, 2009). Likewise, the sex hormones of women are reported to modulate circulating lipid levels, reducing cardiovascular risk and also affecting immune response (Gold *et al.*, 2002).

Other reasons that have been posited as mechanisms that may impact differential survival include gender differences in physician diagnostic patterns or the self-reporting of disease (Kriegsman *et al.*, 1996) and that progression to a disabled state is more severe and/or swift for women than for men (Mikhail, 2005).

It is important to understand the mechanisms that drive the gender specific disparity in disability as this has ramifications from an economic perspective and for the delivery of medical care packages. In addition, the use of appropriate statistical techniques are essential, especially those that account for mortality when examining co-occurring disease patterns and their temporal evolution, none more so than in the very old. As such, chapter five of this thesis will examine the impact of a collection a major diseases on transitions to disability and death, using appropriate statistical techniques.

2.3.4 Preclinical disability

All of the risk factors discussed so far have been related to exposure, whether in terms of disease or life-course exposures to risk factors. However, another school of thought is now beginning to think of disability in preclinical terms. Extending the understanding of the disability pathway in this fashion has the potential to identify high risk groups of people becoming disabled at a later date. Furthermore, extending knowledge of preclinical disability has the potential to identify those who may become disabled at an earlier stage in the disablement process and as such it could be easier to reverse when contrasted against those who are already disabled.

The ability to predict whether an individual will become disabled in the near future has huge benefits in terms of the identification of high risk groups and the ability to intervene before disability. However, research investigating biological parameters/molecules that have the capacity to detect and predict future disability is scant. Notwithstanding this lack of research, one mechanism proposed to underpin and predict initial declines in function is related to chronic inflammation (Taaffe *et al.*, 2000). Inflammation is generally defined as the reaction of an organism to instabilities in homeostatic equilibrium and is often a result of infections, injuries or chronic disease. The inflammatory response mechanism is characterised by the

release of cytokine molecules into the blood stream. Cytokines are biological molecules that are involved in the regulation of immune response, inflammation and the production of blood cells and platelets within bone marrow (Jue *et al.*, 1990). Cytokine biomarkers have been linked to the build-up of atherosclerotic plaques in the vascular system (Skoog *et al.*, 2002), multimorbidity and mortality in older people (Visser *et al.*, 2002). Additionally, in the presence of a chronically inflamed biological environment, the progression of diseases that are associated with disability may be accelerated, thus having a two-fold effect; first on disease progression itself and then on disability (Ferrucci *et al.*, 1999; Taaffe *et al.*, 2000). Research surrounding the impact of inflammatory markers has tended to focus on two main protagonists, interleukin-6 and C - reactive protein and this research is predominantly from younger populations.

Interleukin-6 is a cytokine released into the blood stream by T-cells and macrophages to rouse immune response and is typically a reaction to infections or damaged tissue. T-cells (or T-lymphocytes) and macrophages play an intrinsic role in immunity. It therefore forms a key pathway in managing a biological environment which is compromised by infection or chronic disease.

C-reactive protein is another of the cytokine molecules that has been investigated. This molecule is released by the liver hours after the detection of tissue damage, the beginnings of an infection or inflammation from another source.

Both of these molecules have shown associations with functional decline, frailty and physical activity (Ferrucci *et al.*, 1999; Ford, 2002; Leng *et al.*, 2002). However, there are other inflammatory markers that are under-researched, such as Tumour Necrosis Factor alpha. In addition, few people have examined whether markers of cellular ageing such as DNA damage and telomere length are associated with functional decline. Moreover, those studies that have looked at inflammatory markers and functional decline do not stratify by gender. Given the discussion surrounding the role of sex hormones on gender specific mortality, it is therefore important that this is taken into account.

In chapter six, where I examine trajectories of disability, I investigate how these markers associate with any detected trajectories.

2.4 Summary

The measurement of disability through (I)ADLs and the use of an aggregate score to gauge total individual burden still causes debate amongst researchers (Glass, 1998; Breithaupt and McDowell, 2001). Additionally, many studies have also shown a particular hierarchy to the order of loss but are limited by the number (I)ADL items used; the exclusion of the very old and/or those with dementia and often men and women are analysed together which can mask situational disability as opposed to true functional disability (Deeg, 1993; Department of Economic Social Affairs Population Division, 2002). Therefore, chapter four of this thesis aims to investigate the order in which (I)ADLs are lost by men and women separately and, in doing so, also examine the issue of dimensionality in the aggregate (I)ADL score.

The impact of diseases on the disability process in the younger old is well documented (Goldberg and Chavin, 1997; Wagner, 1997; Stuck *et al.*, 1999; Blazer, 2003; Klijs *et al.*, 2011). However, the majority of studies have only considered the younger old and do not take account where multiple diseases are frequent – a common finding in the very old (Lorig *et al.*, 1999; Femia *et al.*, 2001a). It has also been shown that women live longer than men and yet a woman's longer life is generally accompanied by more years with disability, both as a proportion of remaining life and in absolute terms (Bronnum-Hansen *et al.*, 2009). This apparent contradiction - that women live longer than men but with more disease or disability – is known as the 'disability-survival paradox' (Case and Paxson, 2005; Oksuzyan *et al.*, 2009). Chapter five of this thesis examines the impact of eight major disease categories on disability incidence and progression as well as their effect on mortality, whilst realising that for many of the participants, multimorbidity is common. Furthermore, we try to understand whether particular diseases are driving the gender disability-survival paradox.

The majority of research on disability has been focused on its incidence and progression and the examination of factors which influence this process.

Furthermore, most of this research has been focused on the younger old (Taylor, 2004; Chiu and Wray, 2011). There is, however, very limited information that examines disability from a trajectories perspective and even less so in the very old (Zimmer *et al.*, 2012; Gill *et al.*, 2013b; Han *et al.*, 2013). Even those investigations that do examine disability from a trajectories perspective, fewer still account for non-random subject attrition, whether this be through mortality or those lost-to-follow-up which is an important requirement when analysing trajectories to reduce bias (Wolinsky *et al.*, 2000). Chapter six aims to identify distinct trajectories of disability from ages 85 to 90 and accounts for non-random subject attrition, in particular mortality. In doing so, it also examines the impact of life-course socioeconomic status and affiliation with particular trajectories, alongside other general health measures, inflammatory biomarkers and markers of cellular ageing.

3 THE NEWCASTLE 85+ STUDY

3.1 Aims of the chapter

The aims of this chapter are to:

(i) Outline world-wide longitudinal studies that examine the health of the very old.

(ii) Outline the study which forms the basis of this thesis, including its rationale, recruitment and retention over the study period.

(iii) Describe in detail the data that have been collected as part of the study.

(iv) Describe the creation of composite variables that will be used in analyses that form this thesis.

(v) Detail the results of key health characteristics at baseline including associations with gender.

(vi) Describe the distribution of disease burden over all waves of the study.

The structure of this chapter will follow the above order.

3.2 Introduction

Diversity in the life course of the very old is a phenomenon which poses pragmatic challenges related to recruitment and retention to research programs. Some people age well, with only relatively modest decrements in performance, whereas others age in such a way that they have multiple health and social needs, including the need for daily personal care. Understanding why this heterogeneity exists is of profound importance if we are to understand the ageing process in the very old. Moreover, very few measures of health status have been systematically applied within the 85+ age group in the UK and no study has yet attempted a comprehensive in-depth assessment of biological, medical and social characteristics.

3.3 Creating composite variables

A number of key diseases were constructed from the GP record review and multi-dimensional health assessment data. The determination of some of the components of the key diseases was done in consultation with a senior clinical research fellow.

3.3.1 Incontinence

A measure of incontinence was constructed using the frequency and volume of incontinent episodes (Perry *et al.*, 2000). This was a multiplicative score whose maximum was 16. Participants were then classified as:

i) 0: Continent

ii) 1-2: Minimal incontinence

iii) 3-4: Moderate incontinence

iv) 5-6: Severe incontinence

v) 7-16: Profound incontinence

3.3.2 Renal impairment

Using serum creatinine from the collected blood samples, expected glomerular filtration rates (eGFR) were calculated using the Modification of Diet in Renal Disease formula (Manjunath *et al.*, 2001):

$$eGFR = 186 \times \left(\frac{creatinine}{88.4} \right)^{-1.154} \times (Age)^{-0.203} \times 0.742(if\ female) \times 1.210(if\ black)$$

Participants were then assigned categories according to the National Kidney Foundation classification (NKF-KDOQI) for kidney disease (National Kidney Foundation).

3.3.3 Cognitive impairment

The Standardised Mini-Mental State examination (SMMSE) was used (Molloy *et al.*, 1991; Molloy and Standish, 1997) and items were score one if correct and zero otherwise. Questions with missing items were scored zero.

SMMSE scores were categorised using the same scheme as the CFAS group in their paper focusing on the very old (Xie *et al.*, 2008).

i) 0-17: Severe cognitive impairment

ii) 18-21: Moderate cognitive impairment

iii) 22-25: Mild cognitive impairment

iv) 26-30: No cognitive impairment

3.3.4 Geriatric Depression

The 15 item Geriatric Depression Scale was chosen as a screening instrument for depression (Sheikh J. and Yesavage, 1986). This widely used scale retains 15 yes/no items from the original 30 item version, takes less time to complete and correlates well with the original version (Sheikh J. and Yesavage, 1986; Alden *et al.*, 1989). The scale was omitted in participants with a SMMSE score less than 15 as it is considered to be unreliable in this setting (Burke *et al.*, 1991).
Scoring the items and choosing cut-points of less than six, between 6 and 7 and greater than 8 has been used previously by the MRC Trial of Assessment and Management of Older People in the Community (Osborn *et al.*, 2002). This yields a three level likert scale of increasing depressive symptomatology.

3.3.5 Body Mass Index (BMI)

Both weight and demi-span (distance from middle of sternal notch to the tip of the middle finger) was collected. A standard formula was applied to the demi span measurement to calculate height. For women: $[(1.35 \times demi-span) + 60.1]$ and for men: $[(1.40 \times demi-span) + 57.8]$. BMI was calculated using the ratio of weight (Kg) to height squared (m). Participants were assigned to BMI categories using criteria published by the WHO (World Health Organisation, 2006).

3.3.6 Auditory & visual function

Information related to visual and auditory impairments was collected. If participants had difficulty recognising a friend across the road or reading ordinary newsprint they were deemed visually impaired. For auditory impairment, having difficulty hearing someone talking in a quiet room or following a conversation with background noise was judged impaired

3.3.7 Blood based biomarkers

Blood was collected between 07:00 and 10:30am from participants who agreed to this element of the assessment. It was intended that a morning collection will be after an overnight fast and that samples would be delivered to the laboratory within an hour of being drawn. Over 72 candidate biomarkers were profiled from the blood samples (Martin-Ruiz *et al.*, 2011). For the purposes of this thesis three markers related to inflammation will be used to investigate associations with disability:

i) Interleukin-6

ii) Tumour Necrosis Factors alpha

iii) C reactive protein

In addition, two makers of cellular ageing will also be considered:

i) DNA damage

ii) Telomere length

3.3.8 Disease count

A count of the major diseases was created as a measure of disease burden for which composite variables were included. The detail for the construction of each composite is shown in the table below and where a list of diseases appears in the second column, the 'OR' logical operator was used.

Disease Group	Included diseases and conditions
Arthritis*	Generalised Osteoarthritis, Hand, Hip and Knee Osteoarthritis Rheumatoid, Degenerative, Poly, Gouty, Septic, Peri, Lumbar Spondylosis, Cervical Spondylosis, Anklyosing Spondylitis and Psoriatic Arthropathy
Hypertension*	Hypertension
Cardiac disease*	Heart Failure, Ischaemic heart disease (Angina, Myocardial Infarction., Coronary Artery Bypass Graft, Coronary Angioplasty/Stent)
Respiratory disease*	Bronchiectasis, Pulmonary Fibrosis, Fibrosing Alveolitis, Asbestosis, Pneumoconiosis, Asthma, Chronic Bronchitis, Emphysema, COPD
Cerebrovascular disease*	Stroke, Transient Ischaemic Attack, Carotid Endarterectomy
Diabetes mellitus*	Type I, Type II and type unspecified
Cancer*	Any cancer diagnosis in past 5 years excluding non-melanoma skin cancer

Cognitive Impairment†	Standardised Mini-Mental State Examination (sMMSE) score of ≤21

* Data taken from GP record review
† Score calculated from multi-dimensional health assessment

3.4 Baseline findings from the Newcastle 85+ study

The following section will detail the representativeness of the study population, recruitment and retention of participants to the study, and baseline findings describing the spectrum of health across domains including sociodemography, geriatric conditions, impairments, self-rated health, disease and functional measures. Disability will be covered in chapter 4.

3.4.1 Comparison with the England and Wales census 2001

To ascertain how representative the full study population was of 85 year olds in Newcastle and North Tyneside and in England and Wales, comparisons were made on key socio-demographics with the Newcastle and North Tyneside Health Area and England and Wales data from the 2001 Census. This data is available on DVD from the Office for National Statistics (Office for National Statistics, 2003a). Where census data by single year of age (85) were unavailable, an average of the 80-84 and 85-89 age groups was taken. Comparisons were drawn on sex, those living in institutions, those living alone, marital status and ethnicity and are shown in table 3.2. These figures were contrasted against the 2001 National Census for Newcastle upon Tyne and North Tyneside and England and Wales. All were found to be broadly in-line with the census figures with the exception of ethnicity (99.3% white in study vs. 89.2% white from E&W census figures) (Office for National Statistics, 2003b).

3.4.2 Participant retention

The Strobe chart (figure 3.1) details participant retention across all four waves of the study. Attrition rates are broken down by those who withdraw and those who die. Between phase wave one and wave two and of those who consented to the full study (i.e. full responders), 223 (26%) people either withdrew (n=88) or died (n=135), therefore 631 maintained their involvement for wave two assessment (men = 234, women=397). Between wave two and three attrition rates dropped to 17% (of 849) with 39% (n=51) withdrawing and 61% (n=135) dying, leaving 484 (men=176, women=308) people eligible for involvement in wave 3. Attrition between wave three and wave four was 16%; made up of 19% (n=27) withdrawals and 81% (n=114) who died, as such 344 participants (men=118, women=225) took part in wave 4. Further details regarding retention strategies are discussed elsewhere where I have a looked at the reasons for withdrawal at each wave delineating the effects of withdrawal in

terms attrition for health and non-health reasons (Davies *et al.*, 2014). Longitudinally, none of the variables that have shown associations with attrition in longitudinal studies (Zunzunegui *et al.*, 2001; Deeg *et al.*, 2002; Jacomb *et al.*, 2002; Matthews *et al.*, 2004; Dapp *et al.*, 2012; Mein *et al.*, 2012) were shown to be significant predictors of attrition (or retention) within the 85+ cohort. This indicated that retention strategies employed (and detailed in the publication) were effective at maximising and maintaining participation.

3.4.3 Sociodemography

Associations with each of the sociodemographic variables and gender were examined. Where variables displayed a nominal structure, multinomial logistic regression was used; where they had ordinal structure, ordinal logistic regression and for raw scores (and where data were skewed – namely, deprivation index) a Mann-Whitney U test was implemented.

Of the 852 who consented at wave one to the face-to-face interviews 62.1% were women (n=529) and 37.9% were men (n=323) (table 3.2). Women were more likely to reside in an in sheltered accommodation (RR: 1.67, 95% CI: 1.08-2.59) and in an institution (RR: 2.10, 95% CI: 1.26-3.48) compared to men. In addition women were less likely to live with their spouse compared to women (RR: 0.16, 95% CI: 0.11-0.23) and therefore likely to be married (RR: 0.18, 95% CI: 0.12-0.25). Women were more likely to have worked in intermediate occupations during their working lives, compared to men (RR: 2.62, 95% CI: 1.59-4.33) however the level of deprivation (as measured through IMD) was not statistically significantly different between men and women.

3.4.4 Geriatric conditions, impairments and self-rated health

Twelve variables were selected from disorders related to geriatric conditions, impairments and self-rated health and these were assessed for gender associations. These variables were selected on the basis that they would be used as confounding variables or specifically as variables of interest in subsequent disability related analyses. Analyses used binary logistic regression and ordinal logistic regression depending the variable. Where ordinal logistic regression was used the proportionality assumption was checked through a Brant test.

Women were more likely to report problems with vision (OR: 1.5, 95% CI: 1.1-2.0); pain in the last month (OR: 1.4, 95% CI: 1.0-1.9) and take longer to complete timed-up-and-go (OR: 1.9, 95% CI: 1.4-2.6) in contrast to men (table 3.3). They were also more likely to report more severe symptoms of incontinence (OR: 2.1, 95% CI: 1.6-2.8) and depressive symptomatology (OR: 1.6, 95% CI: 1.1-2.3). In addition when asked to rate their health compared to others of a similar age, women were more likely to report their health in more negative terms (OR: 1.3, 95% CI: 1.0-1.7) compared to men (table 3.3)

3.4.5 Disease burden – cross sectionally and longitudinally

Epidemiological studies that compare the risk of disease through logistic regression are entirely correct, however, in some cases where the prevalence of a disease is high then the odds ratio can be inflated. On that basis, and given that the prevalence of some disease groups were composites of smaller, disease specific diagnoses, and their overall point prevalence was high (>50%), a generalised linear model was used with a log-link function to assess gender differences in the point prevalence.

Of the eight considered diseases, arthritis has the greatest prevalence for both men (60.4%) and women (71.8%) with a significant difference in favour of women (RR: 1.19, 95% CI: 1.07-1.32) i.e. women were 19% more likely to have diagnosis of arthritis (table 3.4). In addition women were also more likely to have diagnosis of hypertension (RR: 1.15, 95% CI: 1.01-1.30) which was also the second most prevalent diagnosis for both men and women. No statistical difference was found for the remaining diseases (in order of decreasing prevalence); cardiac disease (38.1%), respiratory disease (22.5%), cerebrovascular disease (21.1%), diabetes (13.3%), cognitive impairment (12.9%) and cancer (6.4%).

In terms of overall disease burden (a count of positive diagnoses in the eight disease groups) there was no difference between men (mean=2.4, sd=1.3) and women (mean=2.4, sd=1.3) (p=0.68). Additionally, the number of prescribed medications did not differ between men (median=6, IQR=4-8) and women (median=6, IQR=4-9) (p=0.09).

Figure 2 details the distribution of disease burden from wave one to wave four. Men and women carried the same burden of disease in terms of the median and inter-quartile rage (median=2, IQR=1-3) at wave one. Moving to wave two the amount of disease increased slightly for women (median=2.5, IQR=2-3) but remained the same for men. A similar picture was evident for those who participated in wave 3 (women: median=3, IQR=2-3; men: median=2, IQR=2-3). By wave four, the pattern reversed, men being diagnosed with more conditions, on average, than women (women: median=2, IQR=2-3; men: median=3, IQR=2-3). Although there was no gender difference in the overall disease burden it gives no information on gender specific patterns of disease in terms of whether chronic and fatal diseases cluster by gender – a potential avenue to explain some (or all) of the disability survival paradox (§2.3.3).

3.5 Summary

Recruitment of participants to the Newcastle 85+ study was high and strategies employed to preserve this participation secured excellent retention across all four waves of the study. We have shown elsewhere that predictors of retention were not strongly associated with health or non-health reasons. This was primarily down to the scrupulous administration of contact information and actively maintaining contact with the participants throughout the study period (Davies *et al.*, 2014). Furthermore, the study was truly inclusive insofar as not excluding those who lived in institutions or those cognitively impaired.

The most pertinent findings of the baseline results were:

i) Those who agreed to both interview and a review of their GP records formed the main sample. This comprised of 323 men (37.9%) and 529 women (62.1%) – this ratio is largely in line with the with the England and Wales 2001 census.

ii) Gender differences were found for housing status and NS-SEC from the sociodemographic data.

iii) Gender differences in health were found for visual impairment, timed up-and-go, incontinence, depression, and self-rated health; all showing women at a disadvantage.

iv) In terms of diseases, women were more likely to have diagnosis of arthritis and hypertension compared to men but have similar point prevalence's in the remaining six disease groups.

v) The burden of disease (a count of the 8 major categories) was similar for men and women, however, this did not account for the type of disease that was diagnosed.

This chapter has set out in detail the arrangement, recruitment and retention of participants to the Newcastle 85+ Study. It has shown clear gender differences in the prevalence's of some diseases, geriatric syndromes and impairments. This will have important implications for analyses in subsequent chapters.

In the next chapter the focus shifts to disability as the main outcome.

Table 3.1: Comparison of GP record review and interview participants

	Full Study			GPRR Only			
	Men	**Women**	**All**	**Men**	**Women**	**All**	**P-Value**
Cardiovascular % (n)	71.2 (233)	74.0 (390)	73.2 (623)	69.2 (36)	69.9 (95)	69.7 (131)	0.30
Respiratory % (n)	17.9 (58)	15.2 (80)	16.2 (138)	32.7 (17)	9.6 (13)	16.0 (30)	0.90
Cancer % (n)	29.3 (95)	20.7 (109)	24.0 (204)	36.5 (19)	15.4 (21)	21.3 (40)	0.64
Eye disease % (n)	34.6 (112)	48.6 (256)	43.2 (368)	42.3 (22)	42.7 (58)	42.6 (80)	0.63
Arthritis % (n)	54.3 (176)	65.1 (343)	60.1 (519)	46.2 (24)	55.2 (75)	52.7 (99)	0.02
Median number of consultations Median (IQR)*	8 (7)	7 (8)	7 (8)	7 (7.5)	6.5 (7)	7 (7)	N/A

* Consultation with GP (practice based or out of hours) or practice nurse

Table 3.2: Sociodemography of interview participants

	Men	Women	All	Magnitude of gender difference	Comparison with 2001 Census **
Gender					
Men	-	-	37.9 (323)	-	33.5
Women	-	-	62.1 (529)	-	66.5
Ethnic origin					
White	99.1 (321)	99.3 (526)	99.2 (847)	-	99.3
Other	0.6 (2)	0.2 (1)	0.4 (3)	-	0.7
North East Born	72.2 (234)	79.1 (419)	76.5 (653)	-	
Housing					
Standard	82.7 (268)	73.0 (387)	76.7 (655)	Referent*	
Sheltered	10.5 (34)	14.0 (74)	12.7 (108)	1.67 (1.08-2.59)	
Institution	6.8 (22)	12.8 (68)	10.5 (90)	2.10 (1.26-3.48)	12
Other	0 (0)	0.2 (1)	0.1 (1)	-	
Living arrangements					
Alone	42.2 (127)	73.3 (338)	61.0 (465)	Referent*	57
With spouse only	49.8 (150)	13.9 (64)	28.1 (214)	0.16 (0.11-0.23)	
With others	7.8 (24)	12.8 (59)	10.9 (83)	0.92 (0.55-1.54)	
Marital status					
Widowed	40.2 (129)	70.5 (371)	59.03 (500)	Referent*	62.3
Married	52.3 (168)	16.4 (86)	30.0 (254)	0.18 (0.12-0.25)	27
Never married	5.61 (18)	9.7 (51)	8.2 (69)	0.99 (0.56-1.74)	8
Divorced/separated	1.87 (6)	3.4 (18)	2.8 (24)	1.04 (0.41-2.68)	2.8

Education				
0-9	61.8 (196)	65.6 (339)	64.2 (535)	0.87 (0.65-1.15)†
10-11	24.9 (79)	21.9 (113)	23.0 (192)	
12+	13.3 (42)	12.6 (65)	12.87 (107)	
NS-SEC (3 group)				
Routine and manual occupations	53.5 (168)	51.0 (250)	52.0 (418)	Referent*
Intermediate occupations	7.3 (23)	18.4 (90)	14.1 (113)	2.62 (1.59-4.33)
Managerial / Professional	39.2 (123)	30.6 (150)	34.0 (273)	0.82 (0.60-1.12)
Deprivation (IMD) - Median (IQR)	26.1 (12.1-42.7)	29.0 (15.6-45.4)	28.8 (13.4 - 44.3)	-

All data taken from interview

* - Multinomial logistic regression - Relative risk (95% CI) - Women:Men

† - Ordinal Logistic Regression - Odds Ratio (95% CI) - Women:Men

** - Comparison with across gender on averages from the 85-89 age groups

Where numbers do not sum to 852, data are missing

Table 3.3: Geriatric conditions, impairments and self-rated health

	Men	Women	All	OR (95% CI)
Hearing impairment	63.9 (205)	56.9 (300)	59.6 (505)	0.8 (0.6-1.0)†
Visual impairment	31.6 (100)	40.7 (209)	37.2 (309)	1.5 (1.1-2.0) †
Pain in last month (lasting 1+days)	45.0 (140)	53.0 (262)	49.9 (402)	1.4 (1.0-1.9) †
Limiting longstanding illnesses (median (IQR))	2 (1-3)	2 (1-3)	2 (1-3)	-
Timed up-and-go				1.9 (1.4-2.6) †
≤ 12 seconds	43.5 (127)	28.5 (128)	34.4 (255)	
>12 seconds	56.5 (165)	71.5 (321)	65.6 (486)	
Falls in last 12 months				1.0 (0.7-1.3)‡
No falls	61.6 (191)	61.8 (312)	61.7 (503)	
1 fall	19.4 (60)	21.2 (107)	20.5 (167)	
2 falls	11.3 (35)	8.9 (45)	9.8 (80)	
3+ falls	7.7 (24)	8.1 (41)	8.0 (65)	
Incontinence				
Urinary				2.1 (1.6-2.8) ‡
None	67.7 (210)	49.9 (251)	56.7 (461)	
Minimal	9.7 (30)	11.3 (57)	10.7 (87)	
Moderate	8.7 (27)	10.9 (55)	10.1 (82)	
Severe or profound	12.6 (39)	26.6 (134)	21.3 (173)	
Catheterised for last 12 months	1.3 (4)	1.2 (6)	1.2 (10)	
Faecal Incontinence	7.4 (23)	9.3 (47)	8.6 (70)	1.3 (0.8-2.3) †

Table 3.3 cont.

Depression (GDS-15)				1.6 (1.1-2.3) ‡
No depression (GDS-15: 0-5)	83.3 (245)	76.4 (356)	79.1 (601)	
Mild/Moderate depression (GDS-15: 6-7)	9.5 (28)	14.2 (66)	12.4 (94)	
Severe depression (GDS-15: 8-15)	7.1 (21)	9.4 (44)	8.6 (65)	
Cognitive impairment (SMMSE)				1.1 (0.8-1.5) ‡
'Normal' (sMMSE: 26-30)	73.0 (230)	73.1 (372)	73.1 (602)	
Mild cognitive impairment (sMMSE: 22-25)	17.5 (55)	14.0 (71)	15.3 (126)	
Moderate cognitive impairment (sMMSE:18-21)	2.9 (9)	6.5 (33)	5.1 (42)	
Severe cognitive impairment (sMMSE: 0-17)	6.7 (21)	6.5 (33)	6.6 (54)	
Body Mass Index (BMI)				0.9 (0.7-1.2) ‡
Underweight	4.4 (13)	7.8 (35)	6.4 (48)	
Desirable weight	51.3 (153)	51.2 (230)	51.3 (383)	
Overweight	35.9 (107)	30.3 (136)	30.3 (136)	
Obese	8.4 (25)	10.2 (46)	10.2 (46)	
Morbidly Obese	0.00 (0)	0.45 (2)	0.5 (2)	
Self-rated health (compared to others of same age)				1.3 (1.0-1.7) ‡
Excellent	11.7 (37)	9.5 (49)	10.3 (86)	
Very Good	32.3 (102)	28.1 (145)	29.7 (247)	
Good	36.7 (116)	38.2 (197)	37.6 (313)	
Fair	16.8 (53)	20.2 (104)	18.9 (157)	
Poor	2.5 (8)	4.1 (21)	3.5 (29)	

Where numbers do not sum to 852 they are missing data
† - Logistic Regression - Women : men comparison
‡ - Ordinal Logistic Regression – Women : men comparison

Table 3.4: Disease prevalence at baseline

Disease**	Men	Women	All	P-Value	Gender difference
Arthritis	60.44 (194)	71.84 (375)	67.50 (569)	0.001	1.19 (1.07-1.32) †
Hypertension	52.34 (168)	59.96 (313)	57.06 (481)	0.034	1.15 (1.01-1.30) †
Cardiac disease	42.06 (135)	35.63 (186)	38.08 (321)	0.06	0.85 (0.71-1.01) †
Cerebrovascular disease	24.61 (79)	18.97 (99)	21.12 (178)	0.05	0.77 (0.59-1.00) †
Respiratory disease	22.43 (72)	22.61 (118)	22.54 (190)	0.953	1.01 (0.78-1.30) †
Diabetes mellitus	14.33 (46)	12.64 (66)	13.29 (112)	0.483	0.88 (0.62-1.25) †
Cognitive impairment	10.28 (33)	14.56 (76)	12.93 (109)	0.076	1.42 (0.96-2.08) †
Cancer	8.10 (26)	5.36 (28)	6.41 (54)	0.104	0.65 (0.39-1.09) †
Disease count (mean(sd))	2.4 (1.3)	2.4 (1.3)	2.4 (1.3)	0.68*	-
Number of prescribed medications	6 (4-8)	6 (4-9)	6 (4-9)	0.09‡	-

† - Generalised linear model - Women: Men

* - T-Test

‡ - Wilcoxon rank sum test

** - Composite disease groups

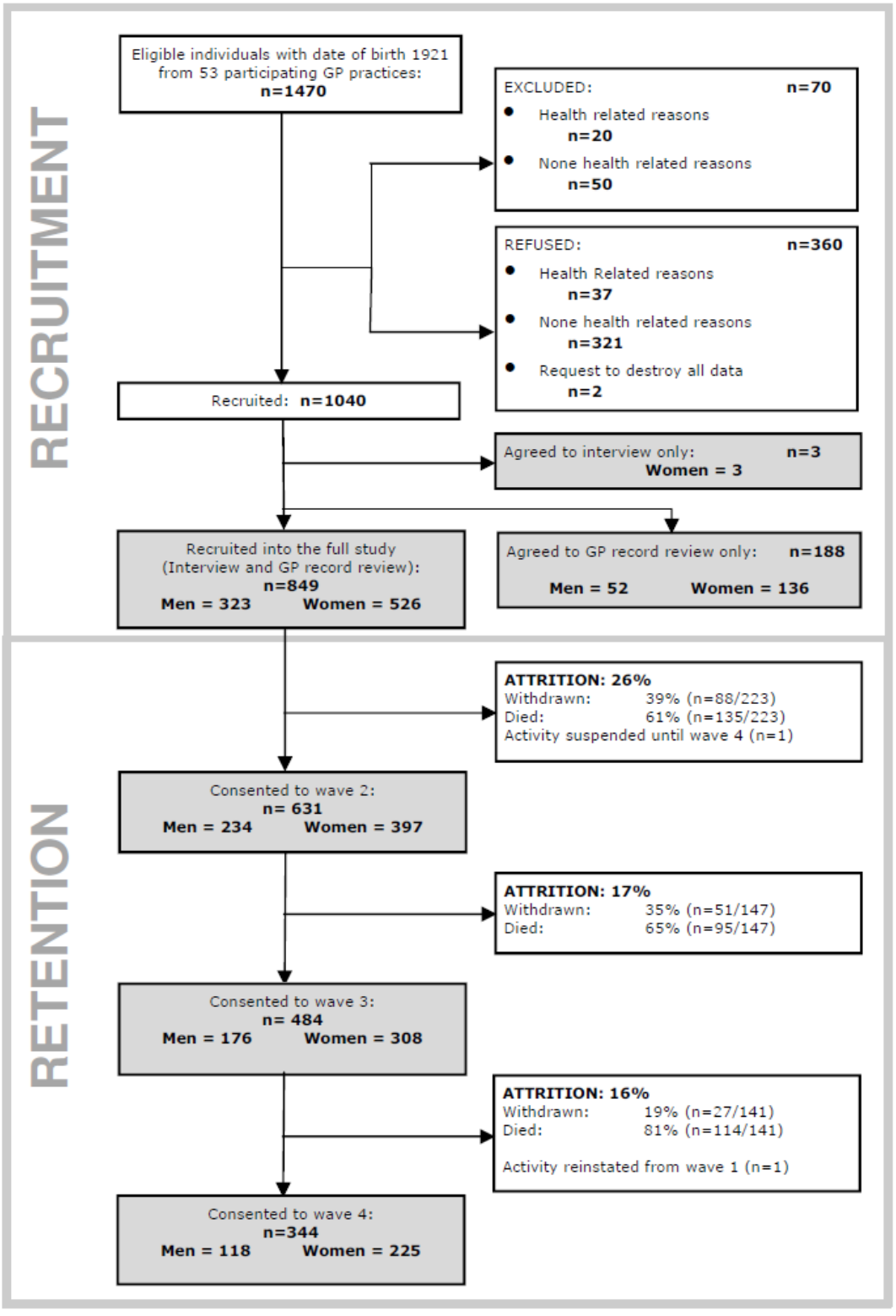


Figure 3.1: Recruitment and retention STROBE chart

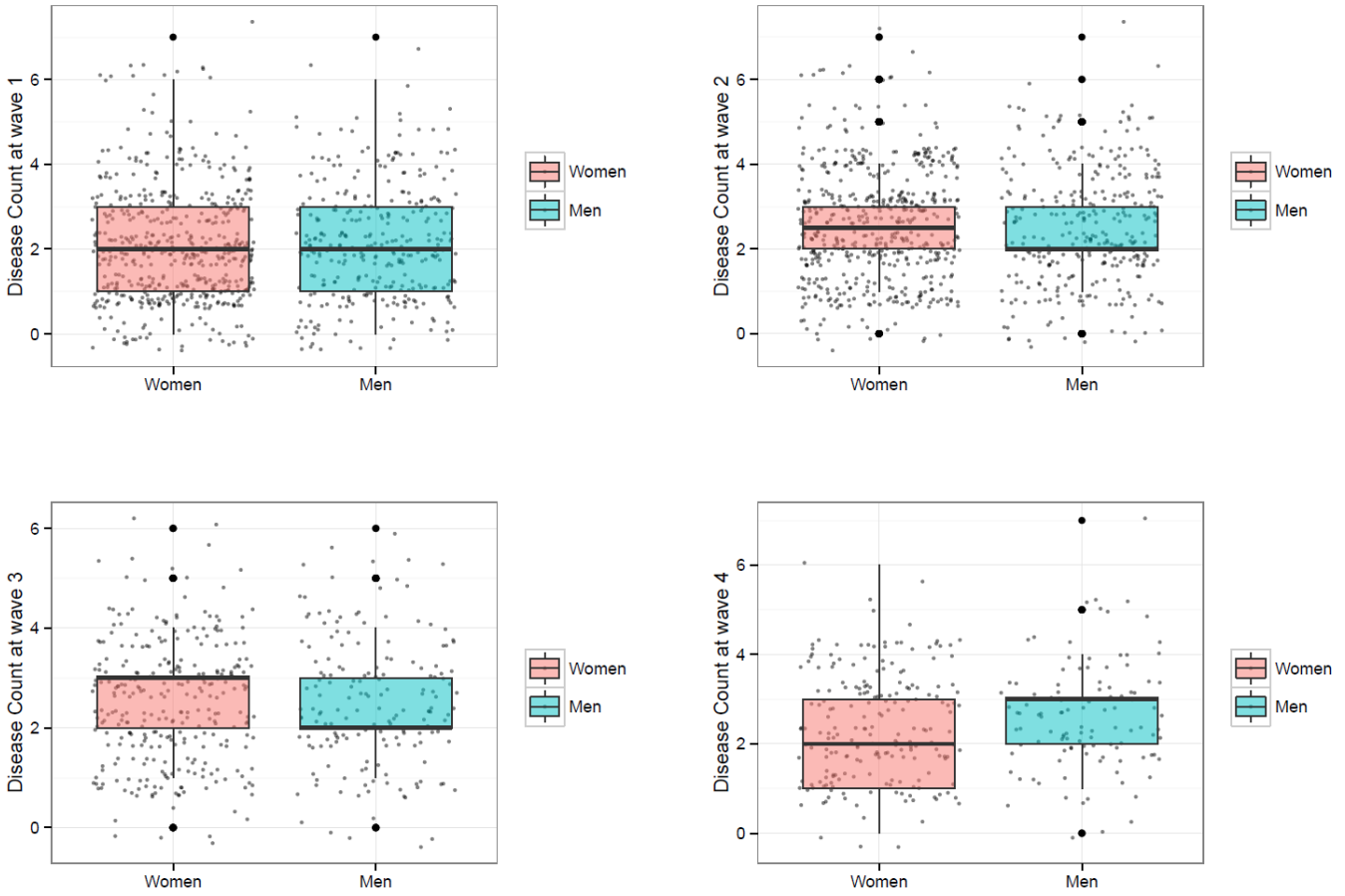


Figure 3.2: Distribution of disease burden from baseline to wave 4

4 DISABILITY IN THE NEWCASTLE 85+ STUDY

4.1 Introduction

In chapter 2, the concerns around the measurement of disability via (I)ADLs and mobility items were discussed. These were connected to the dimensional construct of (I)ADLs items and whether they measure a single latent variable (§2.2). In addition, there has been evidence to suggest that the items included in the measurement of disability contain additional properties which dictate the order in which the ability to perform (I)ADLs is lost i.e. a hierarchy of disability (§2.2.1). These issues have not been fully explored in the very old and so the main objectives of this chapter are three-fold. The first is to outline the structure of the disability data that have been collected as part of the Newcastle 85+ study and will:

i) Detail the prevalence of disability at baseline (wave 1) via a composite score and detailing the prevalence for individual items.

ii) Examine the composite scores from waves two to four.

iii) Examine the correlation between the composite scores at each wave with an objective measure of performance (timed up-and-go).

The second objective is to investigate the dimensional construct of the (I)ADLs and mobility items and determine whether they measure one or more dimensions to disability and, in so doing, explore whether they can be used as a single scale to measure disability burden. In addition, the methodological issues regarding the data type and the correct way of analysing it will be briefly discussed. Thirdly, an examination of the (I)ADL items to determine whether they exhibit a latent hierarchy (i.e. an order of loss) will be explored and key aspects of the methods used to assess the hierarchy outlined.

For each of the objectives gender differences will also be examined.

The structure of this chapter will follow the order of the objectives.

4.2 Disability data in the Newcastle 85+

Seventeen items were used in the Newcastle 85+ Study to collect data measuring level (or burden) of disability. These items were principally related to ADLs and IADLs with three additional measures assessing mobility. Using these items to measure disability was designed to allow comparison with the Groningen Activity Restriction Scale (GARS) (Kempen *et al.*, 1996) (§2.2) which was used in the Leiden 85+ Study and also to allow comparison with the OPCS Disability tool (Martin J. *et al.*, 1988). Fifteen of the original eighteen GARS items were selected and where there was overlap with OPCS items, the phrasing was changed to that of the OPCS question. Two additional items were added; managing medication and managing money. The items included activities of daily living (ADL), instrumental activities of daily living (IADL) and mobility items and are detailed below with their possible responses in figure 4.1.

ADL	Are you able to get in and out of bed?
	Are you able to get and out of a chair?
	Are you able to get on and off the toilet?
	Are you able to dress and undress yourself?
	Are you able to wash your face and hands?
	Are you able to wash yourself all over?
	Are you able to cut your own toenails?
	Are you able to feed yourself?
IADL	Are you able to cook a hot meal?
	Are you able to shop for your groceries?
	Are you able to do light housework?
	Are you able to do heavy housework?
	Are you able to manage money?
	Are you able to manage your medications?
MOBILITY	Are you able to up and down stairs/steps?
	Are you able to get around the house?
	Are you able to walk 400 yards

Figure 4.1: (I)ADL and Mobility questions

Response categories were in a ‘can do’ rather than ‘do-do’ framework, thus:

i) I have no difficulty doing this by myself
ii) I have some difficulty doing this by myself
iii) I can only do this by myself if I use an aid or appliance
iv) I am unable to do this by myself, I need someone else's help

Allowing responses in the ‘can do’ framework allows the capacity and ability of individuals to be accurately assessed and lessen the impact of situational responses as outlined in section 2.2.

The responses to the disability questions were manipulated into a binary format with the cut-point focused on difficulty:

i) Score of 1 = response categories 2-4
ii) Score of 0 = response category 1

Cutting at the level of difficulty allows for a more accurate level of true disability to be assessed rather than dependency (§2.2). Scores for individual items were then summed to give an overall disability score between 0 and 17. Participants were placed into categories of 0, 1-6, 7-12 and 13-17; a total score of zero would represent those fully independent, whilst a score of 17 would represent the completely dependent. Forming a scale using this routine will be then further assessed for its validity in section 4.4.4 of this chapter.

4.3 (I)ADL and mobility item dimensionality

Using a scale of (I)ADL items to measure disability assumes that the items relate to one underlying trait, and in this case, that items are measuring disability as single construct which is unidimensional. If a scale forms more than one dimension then ignoring this fact has serious consequences in terms of psychometric quality and meaning i.e. interpretation of results under this assumption would be invalid. Therefore, if a scale contains more than one dimension then items should be scored in a manner that reflects the multidimensionality. If a scale is shown to exhibit unidimensionality then it is also important to ensure that this property is maintained across subsets of the population e.g. gender.

Assessing dimensionality has often been implemented via Principal Component Analysis (PCA) (Aguilova *et al.*, 2014; Parsons *et al.*, 2015; Vernon and Lawson, 2015). This has frequently been applied in its traditional sense; by submitting matrix of Pearson's correlations to the PCA procedure. However, this technique is caveated by two key assumptions:

i) The data must have a distribution which is multivariate normal and linear.

ii) The observations must be independent.

Initial calculations involved in PCA involve the construction of a matrix of inter-item correlations which are then submitted to the PCA procedure. However, some studies ignore the fact that many psychometric scales are constructed in a Likert framework and calculate standard Pearson correlations to be used in the PCA process (Aguilova *et al.*, 2014; Parsons *et al.*, 2015; Vernon and Lawson, 2015). This has important implications for the first assumption, that the data must be multivariate normal and linear. Likert type scales do not exhibit either of these properties and so they violate the first assumption. As such, correlations between items which are from a Likert scale must be considered.

4.3.1 Correlations for discrete data

The disability data from the Newcastle 85+ Study form responses in a scale:

i) I have no difficulty doing this by myself.
ii) I have some difficulty doing this by myself.
iii) I can only do this by myself if I use an aid or appliance.
iv) I am unable to do this by myself, I need someone else's help.

As such, the correlations between the variables in the (I)ADL and mobility cannot be calculated in the traditional fashion using Pearson's correlations and furthermore, if they are, they violate the assumptions of multivariate normality and/or linearity and may under or over represent the true correlation. To subvert the violation of the assumption of PCA a number of approaches have been considered historically. In the development of a socioeconomic index The World Bank used categorical variables related to hygiene facilities, household rooms, household goods, and its construction materials. They created dummy variables for each level of the categorical variable, constructed a matrix of correlations and submitted this to the

PCA procedure. Using this method causes the loss of information contained within categorical variables, which could prove informative and, more importantly, it is statistically incorrect. Notwithstanding these criticisms, this approach was swiftly accepted for use by The World Bank .

An alternative method would be to use Spearman's Rank correlation coefficient (or Spearman's Rho), to account for non-normality of the data (but not ordinality or nominality) and use these correlations to form the correlation matrix. However, while this is an improvement on Pearson's correlations it still relies on continuous data and therefore doesn't satisfy the first assumption.

Around the time that Pearson's Correlation Coefficient was being developed (c1922), correlations between ordinal variables was also being developed by the same individual (Pearson and Pearson, 1922). This initially began by investigating the correlation between two binary variables, which has the potential to exhibit ordinal behaviour i.e. suffering from a disease is worse than not. These correlations were named tetrachoric correlations. Likewise, items which have more than two responses (whether nominal or ordinal) can have their correlation structure accurately assessed by extending the methodology for tetrachoric correlations; these correlations are known as polychoric (Pearson and Pearson, 1922). Maximum likelihood estimation (MLE) is used to calculate polychoric correlations (and indeed tetrachoric and polyserial (between categorical and continuous data) correlations too) using bespoke software written in the Stata statistical language by Stanislav Kolenikov (Kolenikov and Angeles, 2004), the methodology for which can be found in appendix E. Taking this approach provides more accurate and representative correlations which can then be used in the Principal Component Analysis.

4.3.2 Principal Component Analysis

Principal Components Analysis is often used for the assessment of dimensional structures within a dataset and can then be further utilised to reduce these dimensions. Its basic foundation lies in orthogonal transformations of the data-space from as set of correlated variables to one which is linearly uncorrelated (known as principal components). Transformation of the data in this way leads to a number of *principal components* (and this can be equal to the number of variables). The first

component captures the greatest variance of the responses and each principal component thereafter attempts to capture the remaining variance in descending order of size (constrained by its orthogonality).

PCA is used mainly as a tool for exploratory data analysis and, in so doing, has the capacity to highlight the main characteristics of a dataset via the captured variance of each component. There are two possible methods of calculating principal components:

i) **Eigenvalue decomposition** (sometimes referred to as spectral decomposition or diagonalisation) of a correlation matrix into canonical from i.e. a correlation matrix that is represented as a product of its eigenvalues and corresponding eigenvectors.

ii) **Single value decomposition** uses mean centring and normalisation of each variable yielding the same structure as eigenvalue decomposition i.e. a way of restructuring the correlated variables into a set which is uncorrelated that have the capacity to better expose relationships within datasets.

For the purpose of the analysis I used Eigenvalue decomposition, the methodology for which is detailed further in appendix E.

PCA is discussed in terms of 'loadings' and 'scores':

i) **Component loadings** are the correlation coefficients between variables represented in the rows of a matrix and the factors which are represented in the columns.

ii) **Component scores** are the scores for each row in each factor. This is a sum of the product of standardised score in each variable and the component loadings.

Often PCA is used to reduce the dimensional space of a dataset and so the number of retained components retained will be less than the number of variables under consideration. This implies that where retained components are less than the number of original variables some of the variation will inevitably be lost. As such, after PCA has been implemented it must be decided how many principal components

should be retained. Three key criteria have been suggested to aid this decision (Jolliffe, 2002a):

i) **The cumulative percentage of total variation**: this involves a subjective decision regarding what is acceptable in terms of the total variation that can be explained from the original variables that were entered into the procedure and is often determined by the nature of the variables and to what they refer.

ii) **Kaisers Rule** (Kaiser, 1960): this rule suggests that all components should be retained if they have an eigenvalue greater than one.

iii) **Scree Plot (or the broken stick model**) (Zhu and Ghodsi, 2006): this is a heuristic method (and therefore subjective) of determining the number retained components. This plot represents the eigenvalues plotted in descending order of size with their component number. This generally takes the shape of a steep curve to start which then flattens out (where the stick breaks) as the component number increases. Where the 'break' in the 'stick' occurs then all components after should be ignored and all preceding components retained.

After the determination of the retained components and a scale has been created, a further check is implemented to ensure that it is measuring the same general construct. In other words, what is the agreement between items that form the scale? This is a measure of internal consistency. To test for internal consistency the scalar Cronbach's Alpha is used (Bland and Altman, 1997) which is specific case of the Kuder-Richardson coefficient of equivalence (Cronbach, 1951). This yields values between zero and one and the internal consistency is interpreted as:

i)	$\alpha \geq 0.9$	Excellent internal consistency
ii)	$0.8 \leq \alpha < 0.9$	Good internal consistency
iii)	$0.7 \leq \alpha < 0.8$	Acceptable internal consistency
iv)	$0.6 \leq \alpha < 0.5$	Questionable internal consistency
v)	$0.5 \leq \alpha < 0.4$	Poor internal consistency
vi)	$\alpha \leq 0.4$	Unacceptable internal consistency

While PCA's greatest strength lies in its ability to test the dimensional structure and potentially reduce the data-space, for the purposes of this thesis it will be used to assess dimensionality only in the (I)ADL and mobility items.

4.3.3 Disability items – a hierarchy of loss

The third objective of this chapter was to investigate whether there is an order (or hierarchy) in terms of the loss of ability with (I)ADL and mobility items. Understanding the order in which the very old lose functional capacity has the potential to:

i) Assist in the selection of tasks that measure the whole disability spectrum.

ii) Reveal a fuller understanding of the order in which difficulty with (I)ADLs is encountered in the very old.

As the data from the Newcastle 85+ study are self-reported they come with some drawbacks. These drawbacks relate to weak sensitivity and reproducibility with ceiling and floor effects (Guralnik and Simonsick, 1993; Reuben *et al.*, 2004). The use of Item Response Theory (IRT) methods are recommended to lessen the impact of these drawbacks (McHorney *et al.*, 1997). It does this by avoiding some of these problems by examining the order via 'difficulty' with each (I)ADL item on a continuum using a stochastic framework. Mokken Scaling is the branch of IRT used to examine item hierarchy which also has the capability to self-determine construct unidimensionality and should, therefore, confirm of refute the conclusions that are drawn from the Polychoric Principal Component Analysis (PPCA).

4.3.4 The Mokken Scaling algorithm

Original scaling methods were deterministic in their approach to defining unidimensionality. This gave rise to problems for those who deviate from the scale. Researchers could not untangle whether these deviations arose because of true measurement error or whether the items were exhibiting multidimensionality (Louis, 1974) and so an alternative approach was proposed in 1987 (Gillespie *et al.*, 1987) and is known as Mokken Scaling.

Mokken scaling shifts from a deterministic to a stochastic relationship between scaling items and the latent variable being measured (in this case disability). Making this shift allows the examination of:

i) Whether the whole set of items are measuring one dimension i.e. disability.

ii) Whether a particular item should be included / excluded.

Mokken Scaling also has established methods of assessing the goodness-of-fit. The Mokken method is applied to dichotomised items whose positive response to the item represents the measurement of some underlying latent construct - in this case, disability. As such, it is therefore treated as a single construct and within this paradigm an individual is assigned two parameters.

i) Score scale (θ): this is taken from the number of items for which a person has a positive response

ii) Item difficulty (δ): this is estimated from the proportion of people who have positive responses.

The relationship between the item and the latent continuum being measured (the score scale and the item difficulty) is connected through the Item Characteristic Curve (ICC). The ICC describes the relationship between a latent variable (disability) and the probability of a positive response as you move from no difficulty to difficulty, and is bounded by two assumptions:

i) Single monotonicity: that items form at distinct loci on the latent continuum.
ii) Double monotonicity: that ICCs of items across the continuum do not intersect.

The Mokken scaling procedure examines the scalability of the item response data for each item under consideration and then as a whole over all items. So, each item has its own unique scalability coefficient as well as a scalability coefficient across the full spectrum. This coefficient is known the Loevinger Scalability Coefficient and allows the measurement of the quality of items that form a single and doubly monotonic scale. This Loevinger Scalability coefficient is calculated as follows:

Let *i* and *j* represent a pair of items in the scale, then the Loevinger Scalability Coefficient is defined as:

$$H_{ij} = 1 - \frac{Observed\ N_{ij}(1,0)}{Expected\ N_{ij}(1,0)} \qquad (1)$$

The null model is used for the calculation of the expected value; this being that the items are independent. If the number of errors that are observed is zero then $H_{ij} = 1$ (i.e. perfect scalability), however if the observed errors are as many as expected under independence then $H_{ij} = 0$. As such, the range of H is [0,1] and the interpretation of values within this range, in terms of the scalability of a set of items, is:

i)	$H_{ij} < 0.3$	Poor scalability
ii)	$0.3 \le H_{ij} \le 0.4$	Weak scalability
iii)	$0.4 \le H_{ij} \le 0.5$	Medium scalability
iv)	$H_{ij} \ge 0.5$	Good scalability

Therefore for each item, the Loevinger scalability coefficient is defined as all the pairwise errors and the Loevinger scalability over the entire scale is taken as all errors over all items. The assumption of single monotonicity is checked through the difficulty parameter (i.e. all items are measuring at different 'levels of difficulty') and the second assumption, that the scale is doubly monotonic. If a scale is doubly monotonely homogeneous then, in practice, this means that interpretation of the questionnaire (i.e. disability items) is similar across all individuals regardless of the severity of disability. Statistically, this means that for any two people *i* and *j*, where the level of the underlying trait (disability) is less for *i* than it is for *j* then the probability of a positive response for any item on the scale should be less for person *i* than person *j*. Traditionally, assessment of the assumptions of the Mokken Scaling algorithm can be done in two ways; either via the ICCs, or using the P++ matrix. The two methods are in fact one and the same – the ICCs being a graphical representation of the P++ matrix. In essence the P++ matrix is a numerical array showing increasing probabilities from the least to the most difficult items - therefore each column in P++ matrix should be in ascending order if double monotonicity holds.

Using Polychoric PCA and Mokken Scaling we use the Newcastle 85+ study to assess the dimensional structure of the (I)ADL and mobility items and determine whether distinct hierarchy exists in which a person is likely to have difficulty with the items.

4.3.5 Applying methods to the Newcastle 85+ disability data

The second and third objectives of this chapter are to assess the dimensional construct of the (I)ADL and mobility items and determine whether a hierarchy of loss is evident. As such, to resolve whether the items formed a single dimension, principal component analysis (PCA) using polychoric correlations across the whole ordinal scale was used. The number of retained components was determined using Kaiser's Criterion; including only eigenvalues greater than one (Jolliffe, 2002b). Items were then dichotomised using a cut point of no difficulty / some difficulty and Mokken Scaling was then implemented to verify the unidimensionality and to determine the hierarchy from the Loevinger Scalability Coefficient (H) (Diesfeldt, 2004) and the 'difficulty' parameter. As Mokken scaling uses multiple tests on the data a Bonferroni correction was implemented to reduce the type I error. A scoring system was then formed based on the highest item in the hierarchy with which the participant had difficulty (a score of 1 being low indicating difficulty with the first (most difficult) item in the hierarchy and a score of 17 being the highest indicating difficulty with the last (least difficult) item in the scale). Participants having no difficulty with all items in the scale were assigned a score of zero. Cronbach's alpha (Bland and Altman, 1997) was used to assess the internal consistency and the scale was validated by assessing its association with known predictors of disability (some of which were outlined in §2.4) (Stuck *et al.*, 1999). Goodness-of-fit was assessed via inspection of the Item Characteristic Curves and the P++ matrices.

Separate analyses were carried out for men and women and then all participants together.

4.4 Disability prevalence

At baseline (wave 1) a significant proportion of men (27.6%) and women (14.4%) reported no difficulty with any of the (I)ADLs. Of those who report difficulty with any of the (I)ADLs (men = 72.4% and women=85.6%) the gender difference was statistically significant ($p<0.001$), suggesting that women were likely to report having difficulty with more disability items than men (table 4.2). Turning attention to the individual items that constitute the overall score, the ability to cut one's own toenails was the most prevalent item for which difficulty was reported (men=58.9%, women=69.4%) and the item with the least difficulty was the ability to feed oneself (men = 3.1%, women = 7.3%). Overall, all other individual point prevalence's fell in the range [5.7% - 65.4%] (table 4.1). In all but the ability to transfer from a chair or to carry out light housework or to (un)dress or washing face and hands; women were more likely to report difficulty compared to men (table 4.1).

Follow up assessments of difficulty with the (I)ADL and mobility items showed similar results to that found at baseline. At wave two, 85.8% of men and 92.8% of women reported difficulty with at least one item. At wave 3 this increased to 89.7% for men and 95.7% for women and by wave four this had increased to 96.5% for women. However, by wave four the point-prevalence of difficulty with at least one item decreased to 85.4% for men (table 4.2).

Using the 'disability score' (summation of items reported with difficulty) to assess the distribution at each wave (figure 4.1) it is evident that that amount of disability increased at each wave and likewise suggested that women have a greater burden, in terms of difficulty, compared to the men. The shape of the distribution also indicated that its nature was one that showed both left and right censoring i.e. individuals tended to cluster at each end of the scale. This will have important implications if these data are to be modelled and will be discussed further in chapter 6.

For women, the categorised disability scores indicated that as time progressed, then the burden of disability increased from 85.6% at baseline to 96.5% by wave four (table 4.2). This pattern was also evident for men but only up to wave three (72.5% at baseline to 89.7% by wave 3), however this reduced to 88.4% wave four. At every

wave, except wave three, women were 90% more likely to report increased difficulty compared to men and at wave three it still remained significantly higher at 66% (table 4.2).

4.4.1 Disability and objective measures of performance

As the disability data are self-reported it is important that it is shown to be reporting an accurate level of disability by contrasting it against an objective measure of performance. The objective measure of performance chosen was the timed up-and-go test (TUAG). This was checked at every wave using both the categorised and continuous scores of disability and TUAG (and was stratified on gender) using a combination of Polyserial and Polychoric correlations (dependent on the data types being analysed). These correlations are shown in table 4.3 and indicate for men that all correlations were above 0.5 and statistically significant (p<0.001 for all). For men, the strongest correlation was found at wave four between the categorised disability score and the continuous version of TUAG ($\rho = 0.871$) and the weakest at wave two between categorised disability score and TUAG ($\rho = 0.529$). For women the strongest was found between the same correlates as for men ($\rho = 0.859$) and the weakest between continuous disability score and categorised TUAG ($\rho = 0.517$) at wave three. Irrespective of the differences between the minimum and maximum correlation they still remained strong and statistically significant at every wave, regardless of whether they were categorised or continuous.

4.4.2 Disability item correlations

All items yielded strong and statistically significant correlations (p<0.001) for men (table 4.5), women (table 4.6) and overall (table 4.4). The weakest correlation found when considering all items together was 0.52 (manage money vs. cutting toenails) but was still statistically significant (p<0.001) and the strongest correlation was between the ability to cut toenails and washing one's face and hands ($\rho = 0.981, p < 0.001$). The weakest correlation for women was for managing money vs. cutting toenails ($\rho = 0.456$, p<0.001) (table 4.6) and for men managing money vs. transferring from bed ($\rho = 0.442$, p<0.001) (table 4.5). The ability to wash face and hands was a common item that formed the strongest correlation for men, women and overall. For men the complementary correlated item was cooking and hot meal

($\rho = 0.996, p < 0.001$) and for women it was the ability to shop for groceries ($\rho = 0.980, p < 0.001$).

4.4.3 Testing unidimensionality

From the PCA of the (I)ADL and mobility items (table 4.7), 75.4% of the variance for men was captured by one component (eigenvalue = 12.8) with the second component (eigenvalue = 1.1) capturing a further 6.7%. Similar results were found for women, with the first component (eigenvalue = 11.0) capturing 71.8% of the variance and the second component (eigenvalue = 1.2) explaining a further 7.2%. Loadings on the first component were similar across all items for both men and women (table 4.7). Men and women considered together yielded similar results; component 1 accounted for 76.2% of variation (eigenvalue 11.9); component two explained 6.2% of the variation (eigenvalue = 1.1). Whether men and women were analysed together or separately, component one always produced a far greater eigenvalue than component two with approximate equal loading factors across all items for that component. This consistency was taken as evidence of unidimensionality for the items under consideration. The items related to cognition i.e. the ability to manage money or medications, did have higher loading factors when men and women were analysed together (in the second component) and also the ability to manage money loaded highly for women alone in the second component. This could be indicative that a dimension related to cognition was also present, separate from the functional measures of the (I)ADLs.

4.4.4 Mokken scaling

When considering all data together (i.e. no gender stratification) Mokken Scaling (table 4.8) indicated that a hierarchy was present within the data and confirmed the conclusions of the PCA, namely that the ADL, IADL and mobility items formed a single dimension. The item that was the most 'difficult' to carry out was cutting one's toenails (difficulty parameter=0.63) and the least difficult was the ability to wash face and hands (difficulty parameter=0.03). All items in between formed at either similar or levels of 'difficulty' as adjacent items in the scale and in order of increasing 'difficulty' on the latent continuum. As such, the scale satisfies the single monotone assumption suggesting that each item forms at distinct loci on a disability scale i.e. no items is measuring disability at *exactly* the same level. All items were statistically

significant, further suggesting that all ADL, IADL and mobility measures can be used to construct a disability scale. Double monotonicity was violated by two items (transfer from chair and cooking a hot meal), suggesting that their ICCs intersect. This was evident in the P++ matrix (table 4.8) where the ascending order in each column is interrupted (shown by a decrease in value to the preceding item) where the two items form in the scale. Although the structure of the disability questions are intended to account for situational responses, it could be that the cooking is still an artefact of a gender specific response or that the hierarchy itself is gender specific. For that reason, the hierarchy was assessed for men and women separately to examine this hypothesis.

Investigating the hierarchy for men showed a similar scale pattern to that when all participants were analysed together with some relocation of items in the scale in terms of 'difficulty'. The most difficult item was the ability to cut toenails (difficulty parameter = 0.589) and the least was feeding (difficulty parameter = 0.031) with all other items located within the difficulty range of the two extremes (table 4.10). All items yielded Loevinger-H coefficients ≥0.54 and were statistically significant ($p<0.001$ for all items) suggesting good scalability. The overall Loevinger-H coefficient was 0.68, again suggesting good scalability over all items. All items were found to form at distinct and increasingly difficult locations (unique 'difficulty' parameters) on the latent disability continuum and so the single monotone assumption was satisfied (table 4.10). Shifting attention to examine the doubly monotone assumption it was found that four items were in violation; these were managing money, cooking a hot meal, transfer from toilet and managing medications. These were identified via the corresponding P++ matrix from the Mokken procedure (table 4.11) by a violation in the ascending score within the columns for these four items.

An identical procedure was carried out for women and it was found that cutting toenails was the most difficult item to carry out (difficulty parameter = 0.6942) and washing face and hands the least (difficulty parameter = 0.0712) (table 4.12). All items formed at distinct locations on the latent disability continuum with none having exactly the same difficulty parameter. In addition, the Loevinger H coefficients, by items and overall, was greater than 0.656 suggesting good scalability. Although the

assumption of single monotonicity was satisfied, the second assumption, double monotonicity, failed on some items. These were: manage money, move around the home, transfer from toilet, manage medication and transfer from bed, and shown by interruptions in the numerically increasing values in the columns of its P++ matrix (table 4.13). A common theme of the items which violated double monotonicity (overall and gender specific) was that they either included the items manage money or manage medications or were very close to them in the latent continuum. Furthermore, as the PCA indicated a possible second dimension related to cognition, the Mokken procedure was repeated (overall and for men and women) with these items removed.

Considering all participants together, the removal of the cognition items increased the strength of the hierarchical scale (Loevinger Scalability Coefficient change from 0.68 to 0.71) and also removed any violation of the double monotonicity assumption. The same was true of men (increase of Loevinger H from 0.68 to 0.71) and of women (increase of Loevinger H from 0.72 to 0.68) (table 4.14). Although the strength of the scale was increased by removing the cognition items and it satisfied the underlying assumptions, the order of difficulty for the (I)ADLs was not identical for men and women. Cutting toenails was always the most difficulty item regardless of gender, however, the remaining order was slightly different and dependent on gender. The differences were at most a two-position shift within the hierarchy. For example, women experiencing difficulty shopping was number two in the hierarchy but for men it was the fourth and for men the second was walking 400 yards and the fourth, the use of steps. Although there was some gender specific shifting between the scales, they broadly followed a pattern of loss whereby IADLs were lost before ADLs. The full details of the ordering, overall and by gender can be found in table 4.14.

To graphically represent the hierarchy, the scaling algorithm attributes an arbitrary numerical value to each item relating to its ‘difficulty’ under the latent continuum, whereby the higher a score, the more difficulty it is (denoted the ‘difficulty parameter’ in tables). The difficulty parameter (per item) was plotted in descending order to better visualise the data and to indicate whether some items have a tendency to be clustered in terms of difficulty. Figure 4.2 shows there is evidence to suggest that use of steps, walking 400 yards and shopping cluster for men and using steps,

walking 400 yards and heavy housework cluster for women. The items cooking a hot meal, moving around the house, and transfer from chair, light housework, transfer from toilet, dressing and transfer from bed have close proximity in the difficulty parameter for men and women, as does washing hands and face and feeding (figure 4.2). This points to the loss of function related to functional domains as; complex manual dexterity and balance, long distance mobility and balance, upper limb control and standing balance and upper limb control in a seated position. These are denoted A-D respectively in figure 4.2.

4.4.5 Validating the hierarchic scale

Validating the scale is an important step in verifying whether it has any utility in practice. As such, this was undertaken by comparisons with known predictors of disability (Stuck *et al.*, 1999) (Table 4.15). The scale showed a strong and statistically significant association with living arrangements ($p<0.001$) suggesting that those who have greater scores (between 6 and 15) were more likely to reside in an institution. The same was true of MMSE ($p<0.001$) where those who were cognitively intact (MMSE>25) were likely to have a smaller score in the hierarchic scale. The number of limiting longstanding illnesses also showed that fewer illnesses were associated with a smaller score on the scale ($p<0.001$). The same was true for timed up-and-go i.e. a higher hierarchic score was associated with slower timed up-and-go ($p<0.001$). A higher score was also associated with increased prescription medications ($p<0.001$) and with a count of the number of diagnosed diseases ($p<0.001$). There was no association with the level of education a participant reported ($p=0.889$).

A scale was constructed corresponding to the highest hierarchical position with which an individual has difficulty. This scale was highly correlated with the more usual scale formed by summing the number of items (out of 15) with which the participant had difficulty (Spearman's $\rho = 0.940$). Furthermore, Cronbach's alpha was used to determine the internal consistency of the hierarchical scale. This yielded a value of 0.9371, suggesting very strong internal consistency.

A sensitivity analysis was carried out excluding those residing in institutions and was found have no effect on either the PCA or the Mokken Scaling procedure and

similarly assessing the responses to the (I)ADLs and mobility items using a cut point of needing help had no effect.

4.5 Summary

With respect to disability point-prevalence at baseline and follow-up waves, the most striking findings are:

i) A significant proportion of men (27.6%) and women (14.4%) reported no difficulty any (I)ADL or mobility item at baseline.

ii) At follow up waves the prevalence of disability for women increased from 85.6% at baseline to 96.5% by wave four with consistent increases at each wave.

iii) A similar picture was evident for men from baseline to wave 3 (72.4% - 89.7% prevalence in difficulty in at least one item). However, by wave four the prevalence decreased to 85.4%.

iv) At each wave women consistently report greater levels of disability compared to men.

v) The distribution of disability (as a summed score) showed clear ceiling and floor effects, the distribution being censored at both extremes.

vi) The disability score (summed) was strongly correlated with timed up-and-go at every wave. This was also true of gender specific correlations.

The dimensionality of the (I)ADL data (i.e. are they are measuring the same latent construct) was assessed using Polychoric PCA. Each item in the unidimensional scale had approximate equal loading factors and so we can conclude that (I)ADLs can be summed (via difficulty) to form a scale that represents the burden of disability.

We found a strong hierarchical ordering to loss of ability in a wide range of basic and instrumental activities of daily living and items measuring mobility in an unselected population aged 85 years. ‘Cutting toenails’ was the first item with which participants found difficulty and ‘washing hands and face’ and ‘feeding’ the last items. The ordering of the items in our hierarchic scale confirms previous studies using cross-

sectional (Kempen, 1995; Ferrucci *et al.*, 1998b; Njegovan *et al.*, 2001; Weiss *et al.*, 2007) and longitudinal (Dunlop, 1997; Jagger *et al.*, 2001a) data, which were based on more restricted sets of items and predominantly in the young old. Thus this chapter adds considerably to the evidence that the order of loss of activities does not vary with age. Sex differences were evident from our single birth year cohort; not only were women more likely to report difficulty with each activity than were men but we also found that the ordering of loss differed between men and women of the same age with women reporting more difficulty with activities requiring strength ('shopping' and 'heavy housework') whilst men were earlier in reporting difficulty walking. Moreover the ordering and our conclusions were unchanged if inability to perform was defined as requiring the help of another person rather than the more unbiased having difficulty performing alone.

The fact that (I)ADLs do form a hierarchy and a unidimensional construct gives confidence to use the data to form a scale (whether that be summed or hierarchical) and allow analyses from this perspective. In chapter two we discussed the risk factors for disability from a disease perspective (§2.3.2). The next chapter (chapter five) will assess the impact of disease on disability incidence and death. It will examine whether some diseases are more deterministic of disability incidence and/or death and, in doing so, will examine whether the gender-disability-disease paradox discussed in chapter two (§2.3.3) is still evident in those people aged 85. In addition, appropriate statistical methods that account for dual outcomes (disability and death) will be outlined.

Table 4.1: Cross-sectional prevalence of (I)ADL and mobility items

(I)ADL or Mobility Item	Men	Women	All	OR (95% CI) †
Cutting Toenails	58.9 (188)	69.4 (361)	65.4 (549)	1.6 (1.2, 2.1)*
Shopping	38.2 (122)	63.1 (328)	53.6 (450)	2.8 (2.0, 3.7)*
Use Steps	38.9 (124)	54.4 (283)	48.5 (407)	1.9 (1.4, 2.5)*
Walk 400 Yards	39.5 (126)	53.1 (276)	47.9 (402)	1.7 (1.3, 2.3)*
Heavy Housework	30.1 (96)	56.7 (295)	46.6 (391)	3.0 (2.2, 4.1)*
Full Wash	25.4 (81)	38.8 (202)	33.7 (283)	1.9 (1.4, 2.6)*
Manage Money	19.7 (63)	27.1 (141)	24.3 (204)	1.5 (1.1, 2.2)*
Move Around House	17.6 (56)	25.6 (133)	22.5 (189)	1.6 (1.1, 2.3)*
Cooking a Hot Meal	18.2 (58)	25.2 (131)	22.5 (189)	1.5 (1.1, 2.2)*
Transfer from Chair	20.4 (65)	22.1 (115)	21.5 (180)	1.1 (0.8, 1.6)
Light Housework	16.9 (54)	21.7 (113)	19.9 (167)	1.4 (0.9, 2.0)
Transfer from Toilet	14.4 (46)	20.6 (107)	18.2 (153)	1.5 (1.0, 2.3)*
Manage Medications	14.4 (46)	20.0 (104)	17.9 (150)	1.5 (1.0, 2.2)*
Dressing	15.7 (50)	18.8 (98)	17.6 (148)	1.2 (0.8, 1.9)
Transfer from Bed	11.9 (38)	18.1 (94)	15.7 (132)	1.6 (1.1, 2.5)*
Wash Face & Hands	4.4 (14)	7.1 (37)	6.1 (51)	1.7 (0.9, 3.4)
Feeding	3.1 (10)	7.3 (38)	5.7 (48)	2.4 (1.2, 5.6)*

***** Statistically significant gender difference at α=0.05

† - Odds ratio: Women: Men

Table 4.2: Levels of disability at baseline and follow-up

	Men	Women	All	Odds Ratio (95% CI) ‡
Baseline				1.92 (1.46-2.51)
None	27.6 (89)	14.4 (76)	19.4 (165)	
1-6	49.2 (159)	51.4 (271)	50.6 (430)	
7-12	14.9 (48)	22.6 (119)	16.7 (167)	
13-17	8.4 (27)	11.6 (61)	10.4 (88)	
Wave 2				1.90 (1.40-2.60)
None	14.2 (33)	7.3 (28)	9.9 (61)	
1-6	53.2 (124)	46.6 (180)	49.1 (304)	
7-12	23.6 (55)	27.5 (106)	26.0 (161)	
13-17	9.0 (21)	18.7 (72)	15.0 (93)	
Wave 3				1.66 (1.17-2.38)
None	10.3 (18)	4.3 (13)	6.5 (31)	
1-6	50.3 (88)	44.2 (134)	46.4 (222)	
7-12	24.0 (42)	31.4 (95)	28.7 (137)	
13-17	15.4 (27)	20.1 (61)	18.4 (88)	
Wave 4				1.91 (1.25-2.94)
None	14.5 (17)	3.6 (8)	7.3 (25)	
1-6	44.4 (52)	40.2 (90)	41.6 (142)	
7-12	24.8 (29)	37.1 (83)	32.8 (112)	
13-17	16.2 (19)	19.2 (43)	18.2 (62)	

‡ - Ordinal logistic regression - Women:Men

Table 4.3: Disability correlation with timed up-and-go

		Men		Women		All	
		Categorised TUAG	**Continuous TUAG**	**Categorised TUAG**	**Continuous TUAG**	**Categorised TUAG**	**Continuous TUAG**
Baseline disability	Categorised	0.6018	0.6508	0.5498	0.7130	0.5857	0.6976
	Raw Score	0.5498	0.5876	0.5601	0.5927	0.5629	0.5955
Wave 2 disability	Categorised	**0.5285**	0.6788	0.5238	0.6502	**0.5414**	0.6814
	Raw Score	0.7209	0.6536	0.6888	0.5718	0.6998	0.5997
Wave 3 disability	Categorised	0.6051	0.7118	0.6687	0.7992	0.6498	0.7662
	Raw Score	0.7283	0.5964	**0.5167**	0.5484	0.5789	0.5704
Wave 4 disability	Categorised	0.7637	**0.8711**	0.7491	**0.8589**	0.7636	**0.8592**
	Raw Score	0.7018	0.7180	0.6123	0.6824	0.6439	0.6954

Table 4.4: Polychoric correlations - men and women together

(I)ADL and mobility item	Transfer from bed	Transfer from chair	Transfer from toilet	Dressing	Wash face and hands	Full wash	Cut toenails	Feeding	Cook a hot meal	Shopping	Light housework	Heavy housework	Manage medications	Manage Money	Move around house	Use steps	Walk 400 Yards
Transfer from bed	1.00																
Transfer from chair	0.90	1.00															
Transfer from toilet	0.91	0.89	1.00														
Dressing	0.87	0.80	0.87	1.00													
Wash face and hands	0.86	0.78	0.88	0.94	1.00												
Full wash	0.78	0.70	0.77	0.85	0.91	1.00											
Cut toenails	0.66	0.58	0.69	0.70	0.98	0.65	1.00										
Feeding	0.83	0.77	0.83	0.89	0.92	0.80	0.98	1.00									
Cook a hot meal	0.76	0.69	0.75	0.86	0.91	0.83	0.63	0.86	1.00								
Shopping	0.68	0.60	0.72	0.78	0.98	0.73	0.64	0.80	0.85	1.00							
Light housework	0.79	0.76	0.81	0.87	0.89	0.85	0.68	0.81	0.91	0.86	1.00						
Heavy housework	0.74	0.64	0.75	0.81	0.81	0.76	0.68	0.85	0.85	0.86	0.92	1.00					
Manage medications	0.64	0.57	0.65	0.79	0.83	0.76	0.56	0.74	0.88	0.75	0.81	0.74	1.00				
Manage Money	0.63	0.55	0.63	0.77	0.81	0.70	0.52	0.72	0.87	0.76	0.81	0.69	0.90	1.00			
Move around house	0.85	0.84	0.87	0.84	0.82	0.83	0.71	0.81	0.82	0.85	0.87	0.82	0.71	0.69	1.00		
Use steps	0.79	0.77	0.84	0.80	0.79	0.76	0.62	0.82	0.73	0.80	0.82	0.81	0.61	0.60	0.90	1.00	
Walk 400 Yards	0.72	0.72	0.76	0.73	0.69	0.71	0.65	0.68	0.67	0.79	0.78	0.78	0.57	0.57	0.88	0.85	1.00

Table 4.5: Polychoric correlations for men

(I)ADL and mobility item	Transfer from bed	Transfer from chair	Transfer from toilet	Dressing	Wash face and hands	Full wash	Cut toenails	Feeding	Cook a hot meal	Shopping	Light housework	Heavy housework	Manage medications	Manage Money	Move around house	Use steps	Walk 400 Yards
Transfer from bed	1.00																
Transfer from chair	0.88	1.00															
Transfer from toilet	0.91	0.90	1.00														
Dressing	0.87	0.78	0.89	1.00													
Wash face and hands	0.79	0.67	0.84	0.91	1.00												
Full wash	0.83	0.70	0.85	0.88	0.89	1.00											
Cut toenails	0.67	0.58	0.74	0.73	0.84	0.74	1.00										
Feeding	0.76	0.67	0.75	0.83	0.88	0.72	0.75	1.00									
Cook a hot meal	0.80	0.67	0.81	0.88	1.00	0.84	0.68	0.83	1.00								
Shopping	0.77	0.61	0.79	0.81	0.87	0.78	0.70	0.80	0.91	1.00							
Light housework	0.80	0.69	0.83	0.91	0.85	0.85	0.71	0.88	0.94	0.92	1.00						
Heavy housework	0.77	0.60	0.80	0.82	0.99	0.77	0.66	0.80	0.89	0.90	0.96	1.00					
Manage medications	0.68	0.58	0.73	0.84	0.89	0.76	0.70	0.79	0.91	0.76	0.86	0.79	1.00				
Manage Money	0.56	0.44	0.65	0.81	0.88	0.74	0.63	0.70	0.92	0.78	0.88	0.78	0.93	1.00			
Move around house	0.83	0.83	0.88	0.85	0.81	0.86	0.68	0.76	0.83	0.87	0.87	0.82	0.74	0.69	1.00		
Use steps	0.79	0.78	0.87	0.78	0.79	0.81	0.58	0.70	0.78	0.82	0.84	0.82	0.63	0.65	0.92	1.00	
Walk 400 Yards	0.75	0.71	0.85	0.76	0.73	0.74	0.66	0.66	0.71	0.80	0.78	0.75	0.66	0.61	0.89	0.85	1.00

Table 4.6: Polychoric correlations - women

(I)ADL and mobility item	Transfer from bed	Transfer from chair	Transfer from toilet	Dressing	Wash face and hands	Full wash	Cut toenails	Feeding	Cook a hot meal	Shopping	Light housework	Heavy housework	Manage medications	Manage Money	Move around house	Use steps	Walk 400 Yards
Transfer from bed	1.00																
Transfer from chair	0.91	1.00															
Transfer from toilet	0.90	0.89	1.00														
Dressing	0.88	0.81	0.86	1.00													
Wash face and hands	0.89	0.82	0.90	0.95	1.00												
Full wash	0.75	0.70	0.72	0.83	0.94	1.00											
Cut toenails	0.64	0.58	0.64	0.67	0.98	0.58	1.00										
Feeding	0.84	0.80	0.86	0.90	0.94	0.82	0.65	1.00									
Cook a hot meal	0.75	0.70	0.71	0.86	0.90	0.83	0.59	0.87	1.00								
Shopping	0.62	0.62	0.67	0.79	0.98	0.69	0.58	0.76	0.81	1.00							
Light housework	0.78	0.80	0.79	0.85	0.88	0.85	0.66	0.80	0.90	0.81	1.00						
Heavy housework	0.72	0.70	0.73	0.85	0.80	0.75	0.66	0.81	0.84	0.81	0.91	1.00					
Manage medications	0.62	0.57	0.60	0.76	0.81	0.75	0.47	0.73	0.87	0.75	0.78	0.72	1.00				
Manage Money	0.65	0.60	0.61	0.74	0.77	0.67	0.45	0.73	0.84	0.76	0.77	0.64	0.89	1.00			
Move around house	0.86	0.84	0.87	0.84	0.83	0.81	0.71	0.82	0.81	0.83	0.87	0.83	0.69	0.69	1.00		
Use steps	0.79	0.78	0.81	0.82	0.78	0.73	0.62	0.86	0.71	0.77	0.82	0.79	0.59	0.57	0.88	1.00	
Walk 400 Yards	0.70	0.73	0.71	0.72	0.66	0.69	0.63	0.68	0.64	0.77	0.78	0.78	0.52	0.54	0.87	0.84	1.00

Table 4.7: Polychoric PCA overall and by gender

(I)ADL and mobility	All		Men		Women	
	Component 1	Component 2	Component 1	Component 2	Component 1	Component 2
Transfer from Bed	0.247	0.260	0.257	0.201	0.248	0.252
Transfer from Chair	0.231	0.363	0.248	0.172	0.224	0.413
Transfer from Toilet	0.250	0.276	0.255	0.182	0.259	0.231
Dressing	0.261	-0.005	0.269	0.055	0.265	-0.010
Wash Face & Hands	0.258	-0.081	0.209	0.563	0.231	-0.338
Full Wash	0.247	-0.037	0.252	0.061	0.253	0.027
Cutting Toenails	0.188	0.177	0.186	0.275	0.192	0.290
Feeding	0.225	-0.120	0.237	-0.064	0.210	0.131
Cooking a Hot Meal	0.256	-0.280	0.259	-0.090	0.264	-0.233
Shopping	0.247	-0.152	0.220	-0.506	0.253	-0.109
Light Housework	0.262	-0.095	0.269	-0.057	0.268	-0.163
Heavy Housework	0.250	-0.084	0.225	-0.428	0.218	-0.231
Manage Medications	0.230	-0.437	0.231	-0.144	0.243	-0.283
Manage Money	0.225	-0.453	0.228	-0.135	0.233	-0.427
Move Around House	0.260	0.178	0.271	0.001	0.261	0.161
Use Steps	0.246	0.236	0.253	0.003	0.248	0.154
Walk 400 Yards	0.230	0.265	0.236	-0.064	0.239	0.197
Eigenvalue	**11.9**	**1.1**	**12.8**	**1.1**	**11.0**	**1.2**
Captured variance	**76.2%**	**6.2%**	**75.4%**	**6.7%**	**71.8%**	**7.2%**

Table 4.8: Mokken scaling overall

Hierarchy order	Difficulty Parameter	Loevinger H Coefficient	Hierarchy Position	Z Statistic	P-value
Cut Toenails	0.63	0.66	1	32.98	<0.001
Shopping	0.51	0.72	2	44.98	<0.001
Use Steps	0.46	0.68	3	45.11	<0.001
Walk 400 Yards	0.46	0.67	4	44.39	<0.001
Heavy House Work	0.44	0.70	5	47.04	<0.001
Wash Fully	0.31	0.63	6	44.33	<0.001
Manage Money	0.21	0.52	7	38.78	<0.001
Move Around Home	0.20	0.68	8	50.58	<0.001
Transfer from Chair *	0.19	0.54	9	40.66	<0.001
Cook a Hot Meal *	0.19	0.64	10	47.54	<0.001
Light Housework	0.16	0.69	11	49.89	<0.001
Transfer from Toilet	0.16	0.62	12	44.81	<0.001
Administer Own Medication	0.15	0.52	13	37.09	<0.001
Dressing	0.14	0.67	14	46.78	<0.001
Transfer from Bed	0.13	0.61	15	41.09	<0.001
Feeding	0.03	0.82	16	29.70	<0.001
Wash Face and Hands	0.03	0.91	17	32.39	<0.001
Overall H		0.68		63.33	<0.001

*** Violates Double Monotonicity**

Table 4.9: Mokken P++ matrix - overall

	Feeding	Wash face and hands	Transfer from bed	Dress	Manage medications	Transfer from toilet	Light housework	Transfer from chair	Cook a hot meal	Move around home	Manage money	Full wash	Heavy housework	Walk 400 yards	Use steps	Shopping	Cut toenails
Feeding																	
Wash face and hands	0.04																
Transfer from bed	0.05	0.05															
Dress	0.05	0.05	0.06														
Manage medications	0.05	0.06	0.08	0.11													
Transfer from toilet	0.05	0.06	0.10	0.12	0.08												
Light housework	0.05	0.06	0.11	0.13	0.12	0.12											
Transfer from chair*	**0.05**	**0.05**	**0.12**	**0.11**	**0.08**	**0.14**	**0.12**										
Cook a hot meal*	**0.06**	**0.06**	**0.11**	**0.14**	**0.14**	**0.11**	**0.16**	**0.12**									
Move around home	0.05	0.06	0.12	0.13	0.11	0.14	0.16	0.14	0.15								
Manage money	0.05	0.06	0.12	0.14	0.15	0.14	0.16	0.14	0.17	0.14							
Full wash	0.06	0.06	0.13	0.15	0.15	0.15	0.17	0.15	0.18	0.19	0.17						
Heavy housework	0.06	0.06	0.15	0.17	0.16	0.17	0.17	0.17	0.21	0.21	0.20	0.27					
Walk 400 yards	0.06	0.06	0.15	0.17	0.16	0.17	0.18	0.19	0.21	0.22	0.20	0.28	0.36				
Use steps	0.06	0.06	0.15	0.17	0.16	0.17	0.18	0.20	0.21	0.22	0.21	0.28	0.37	0.40			
Shopping	0.06	0.06	0.15	0.17	0.17	0.17	0.18	0.20	0.22	0.22	0.22	0.29	0.41	0.41	0.40		
Cut toenails	0.06	0.06	0.15	0.17	0.17	0.18	0.19	0.20	0.22	0.22	0.22	0.30	0.41	0.42	0.41	0.45	

*** - Violates double monotonicity**

Table 4.10: Mokken scaling - men

Hierarchy order	**Difficulty Parameter**	**Loevinger H Coefficient**	**Hierarchy Position**	**Z Statistic**	**P-value**
Cutting Toenails	0.589	0.73	1	21.74	<0.001
Walk 400 Yards	0.395	0.69	2	29.53	<0.001
Use Steps	0.389	0.73	3	31.29	<0.001
Shopping	0.382	0.74	4	31.89	<0.001
Heavy Housework	0.301	0.70	5	31.78	<0.001
Full Wash	0.254	0.68	6	31.23	<0.001
Transfer from Chair	0.204	0.55	7	25.46	<0.001
Manage Money*	0.198	0.54	8	23.15	<0.001
Cooking a Hot Meal*	0.182	0.70	9	32.33	<0.001
Move Around House	0.176	0.72	10	33.27	<0.001
Light Housework	0.169	0.74	11	34.26	<0.001
Dressing	0.157	0.73	12	32.79	<0.001
Transfer from Toilet*	0.144	0.75	13	32.60	<0.001
Manage medications*	0.134	0.64	14	30.10	<0.001
Transfer from Bed	0.119	0.72	15	28.71	<0.001
Wash Face & Hands	0.044	0.90	16	23.02	<0.001
Feeding	0.031	0.86	17	18.81	<0.001
Overall H		**0.68**		**79.39**	**<0.001**

*** - Violates double monotonicity**

Table 4.11: Mokken P++ matrix - men

	Feeding	Wash face and hands	Transfer from bed	Manage medications	Transfer from toilet	Dressing	Light housework	Move around house	Cook a hot meal	Manage money	Transfer from chair	Full wash	Heavy housework	Shopping	Use steps	Walk 400 yards	Cut toenails
Feeding																	
Wash face and hands	0.02																
Transfer from bed	0.02	0.03															
Manage medications*	**0.01**	**0.02**	**0.06**														
Transfer from toilet*	**0.03**	**0.03**	**0.08**	**0.07**													
Dressing	0.03	0.04	0.08	0.09	0.11												
Light housework	0.03	0.04	0.08	0.10	0.10	0.12											
Move around house	0.03	0.04	0.08	0.10	0.11	0.11	0.12										
Cook a hot meal*	**0.02**	**0.04**	**0.08**	**0.07**	**0.09**	**0.10**	**0.08**	**0.11**									
Manage money*	**0.03**	**0.02**	**0.06**	**0.08**	**0.08**	**0.10**	**0.09**	**0.10**	**0.14**								
Transfer from chair	0.03	0.04	0.09	0.10	0.11	0.12	0.10	0.11	0.09	0.07							
Full wash	0.03	0.04	0.10	0.10	0.12	0.13	0.13	0.14	0.14	0.13	0.12						
Heavy housework	0.03	0.04	0.10	0.12	0.12	0.13	0.17	0.14	0.16	0.15	0.12	0.17					
Shopping	0.03	0.04	0.11	0.13	0.13	0.14	0.17	0.17	0.16	0.17	0.15	0.20	0.25				
Use steps	0.03	0.04	0.11	0.14	0.14	0.14	0.15	0.17	0.17	0.17	0.18	0.21	0.26	0.29			
Walk 400 yards	0.03	0.04	0.11	0.14	0.14	0.14	0.15	0.17	0.18	0.18	0.19	0.22	0.26	0.29	0.31		
Cut toenails	0.03	0.04	0.11	0.14	0.14	0.15	0.16	0.18	0.18	0.18	0.19	0.23	0.26	0.33	0.31	0.34	

*** - Violates double monotonicity**

Table 4.12: Mokken scaling - women

	Difficulty Parameter	Loevinger H Coefficient	Hierarchy Position	Z Statistic	P-value
Cutting Toenails	0.6942	0.66278	1	27.2463	<0.001
Shopping	0.6308	0.72097	2	33.4487	<0.001
Heavy Housework	0.5673	0.75086	3	37.9297	<0.001
Use Steps	0.5442	0.72571	4	37.4131	<0.001
Walk 400 Yards	0.5308	0.70085	5	36.3235	<0.001
Full Wash	0.3885	0.68836	6	36.7399	<0.001
Manage money*	**0.2897**	**0.70152**	**7**	**34.1542**	**<0.001**
Move Around House*	**0.2558**	**0.76817**	**8**	**43.3019**	**<0.001**
Cooking a Hot Meal	0.2519	0.67234	9	37.9499	<0.001
Transfer from Chair	0.2212	0.65614	10	36.9227	<0.001
Light Housework	0.2173	0.73944	11	41.5213	<0.001
Transfer from Toilet*	**0.2058**	**0.68725**	**12**	**38.0941**	**<0.001**
Manage medications*	**0.1975**	**0.71254**	**13**	**27.4512**	**<0.001**
Dressing	0.1885	0.73752	14	39.6909	<0.001
Transfer from Bed*	**0.1808**	**0.70321**	**15**	**37.1619**	**<0.001**
Feeding	0.0731	0.86296	16	30.4507	<0.001
Wash Face & Hands	0.0712	0.87457	17	30.4928	<0.001
Overall H		**0.68**		**98.71**	**<0.001**

* - Violates double monotonicity

Table 4.13: Mokken P++ matrix - women

	Wash face and hands	Feeding	Transfer from bed	Dress	Manage medications	Transfer from toilet	Light housework	Transfer from chair	Cook a hot meal	Move around house	Manage money	Full wash	Walk 400 yards	Use steps	Heavy housework	Shopping	Cut toenails
Wash face and hands																	
Feeding	0.05																
Transfer from bed*	**0.06**	**0.06**															
Dress	0.07	0.07	0.13														
Manage medications*	**0.06**	**0.06**	**0.08**	**0.12**													
Transfer from toilet*	**0.07**	**0.07**	**0.13**	**0.13**	**0.09**												
Light housework	0.07	0.07	0.13	0.14	0.13	0.13											
Transfer from chair	0.07	0.07	0.14	0.14	0.14	0.15	0.14										
Cook a hot meal	0.07	0.07	0.14	0.15	0.16	0.13	0.18	0.13									
Move around house*	**0.07**	**0.07**	**0.14**	**0.15**	**0.13**	**0.16**	**0.18**	**0.15**	**0.18**								
Manage money*	**0.06**	**0.06**	**0.12**	**0.13**	**0.17**	**0.12**	**0.16**	**0.13**	**0.19**	**0.16**							
Full wash	0.07	0.07	0.15	0.17	0.16	0.16	0.20	0.17	0.21	0.22	0.19						
Walk 400 yards	0.07	0.07	0.16	0.17	0.16	0.18	0.20	0.20	0.21	0.24	0.20	0.31					
Use steps	0.07	0.08	0.17	0.18	0.16	0.19	0.20	0.21	0.21	0.24	0.20	0.32	0.46				
Heavy housework	0.07	0.08	0.17	0.18	0.19	0.19	0.22	0.21	0.24	0.25	0.23	0.34	0.44	0.45			
Shopping	0.07	0.08	0.17	0.18	0.20	0.20	0.22	0.21	0.25	0.25	0.24	0.34	0.46	0.47	0.50		
Cut toenails	0.07	0.08	0.18	0.19	0.20	0.20	0.22	0.21	0.25	0.25	0.24	0.34	0.46	0.47	0.50	0.52	

*** - Violates double monotonicity**

Table 4.14: Hierarchy position men, women and overall

Hierarchy Position	All	Men	Women
1 – Most ‘difficult’ (lost first)	Cutting Toenails	Cutting Toenails	Cutting Toenails
2	Shopping	Walk 400 Yards	Shopping
3	Use Steps / Stairs	Use Steps / Stairs	Heavy Housework
4	Walk 400 Yards	Shopping	Use Steps / Stairs
5	Heavy Housework	Heavy Housework	Walk 400 Yards
6	Wash all over	Full Wash	Full Wash
7	Manage Money	Transfer from Chair	Manage Money*
8	Cook a Hot Meal	Manage Money*	Move Around House*
9	Move Around House*	Cook a Hot Meal*	Cook a Hot Meal
10	Transfer from Chair*	Move Around House	Transfer from Chair
11	Light Housework	Light Housework	Light Housework
12	Transfer from Toilet*	Dressing	Transfer from Toilet*
13	Manage Medication*	Transfer from Toilet*	Manage Medication*
14	Dressing	Manage Medication*	Dressing
15	Transfer from Bed	Transfer from Bed	Transfer from Bed*
16	Wash Face & Hands	Wash Face & Hands	Feeding
17 – Least ‘difficult’ (lost last)	Feeding	Feeding	Wash Face & Hands
Loevinger Scalability Coefficient	0.68	0.68	0.68
Loevinger Scalability Coefficient (with cognition items removed)	0.72	0.71	0.72

Table 4.15: Association of hierarchical scale with known disability predictors

	Hierarchic Scale				
	None	**1-5**	**6-10**	**11-15**	**p-value**
Living arrangements - %(n)					
Community	98.8 (168)	99.6 (264)	89.4 (160)	72.0 (162)	p<0.001
Institutions	1.2 (2)	0.4 (1)	10.6 (19)	28.0 (63)	
Years of education - %(n)					
<=9	61.8 (105)	63.8 (169)	62.0 (111)	64.0 (144)	p=0.8886
10-11	17.7 (30)	26.4 (70)	24.6 (44)	19.1 (43)	
>11	20.6 (35)	9.8 (26)	13.4 (24)	16.9 (38)	
MMSE - %(n)					
0-17	87.1 (148)	81.5 (216)	66.5 (119)	51.8 (114)	
18-21	11.2 (19)	14.0 (37)	17.9 (32)	20.9 (46)	p<0.001
22-25	1.8 (3)	4.2 (11)	7.8 (14)	7.7 (17)	
26-30	0.0 (0)	0.4 (1)	7.8 (14)	19.6 (43)	
No of longstanding illnesses - %(n)					
None	40.6 (69)	18.6 (49)	15.3 (27)	9.3 (20)	p<0.001
1	36.5 (62)	34.1 (90)	21.0 (37)	27.3 (59)	
2	15.9 (27)	23.9 (63)	34.1 (60)	24.1 (52)	
3+	7.1 (12)	23.5 (62)	29.6 (52)	39.4 (85)	
Timed up and go test - %(n)					
≤ 12 seconds	66.7 (112)	39.2 (100)	17.5 (28)	9.5 (15)	p<0.001
>12 seconds	33.3 (56)	60.8 (155)	82.5 (132)	90.5 (143)	
Number of prescribed medications (median(IQR))	4 (2-7)	5 (3-8)	7 (5-10)	7 (5-10)	p<0.001
Simple disease count (median(IQR))	4 (3-5)	4 (4-6)	5 (4-6)	5 (4-6)	p<0.001

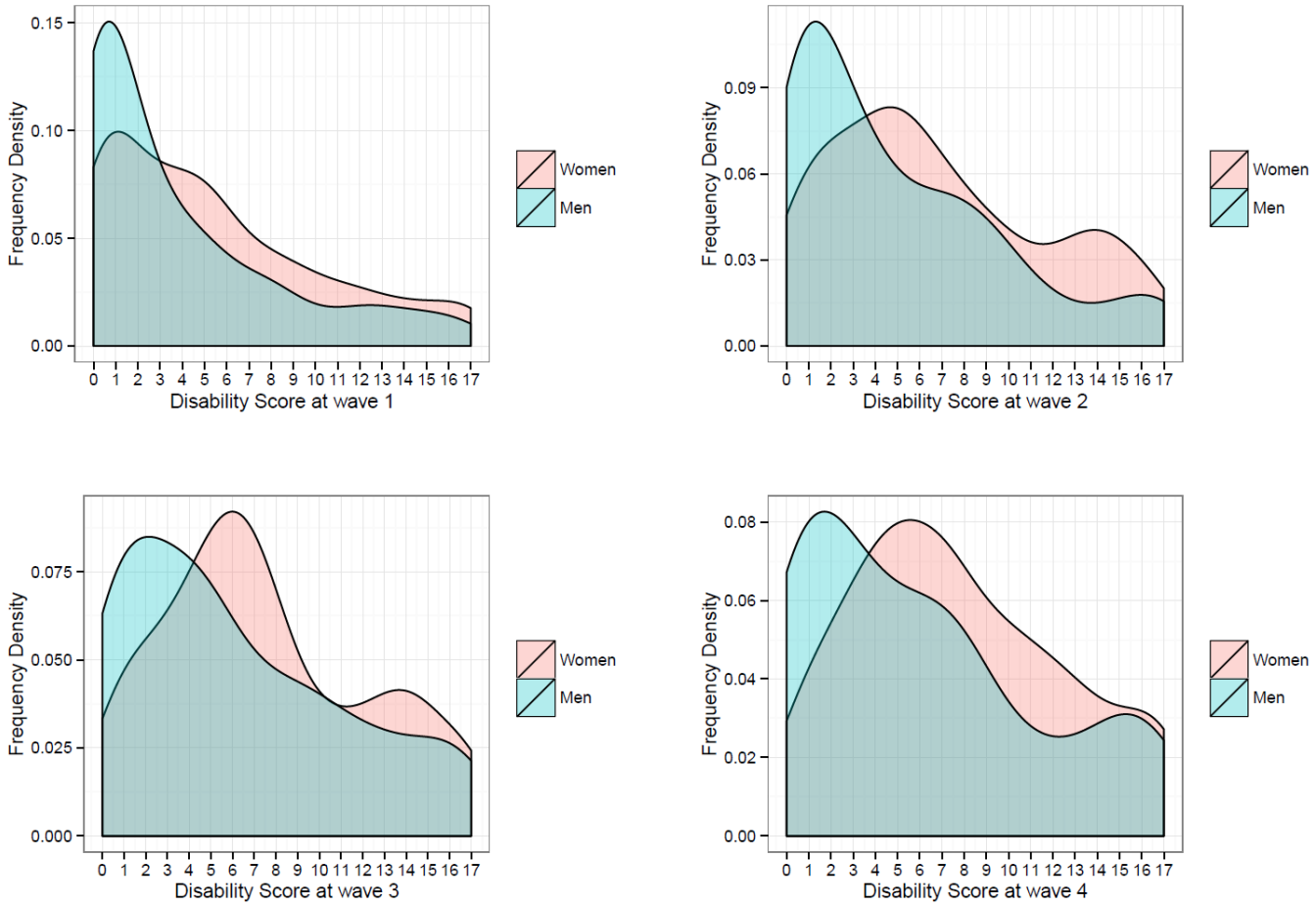


Figure 4.2: Distribution of disability at baseline and follow-up waves

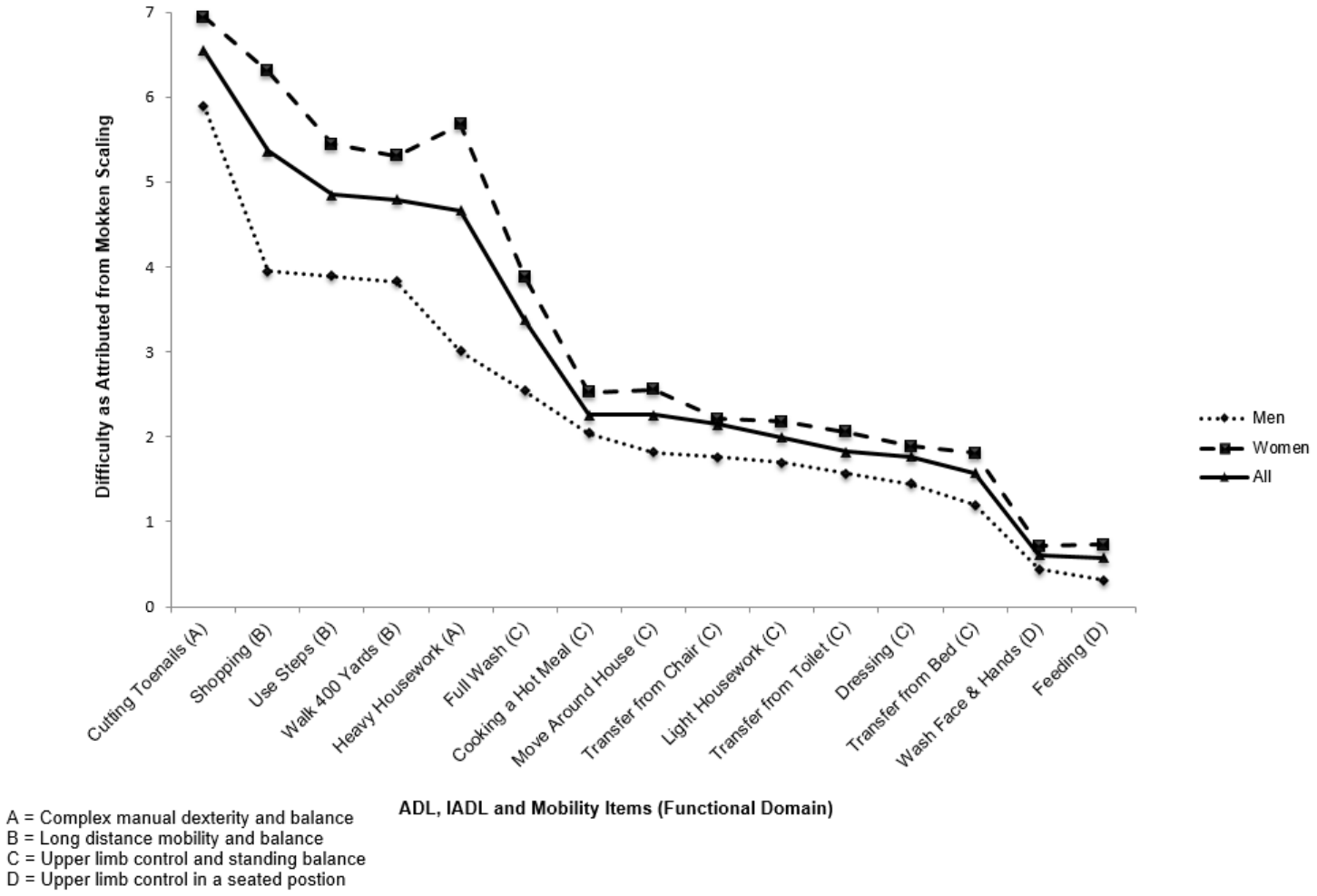


Figure 4.3: Hierarchical ordering for men, women and all participants

5 TRANSITIONS TO DISABILITY IN THE VERY OLD

5.1 Aims of chapter five

Explanations for the gender disability-survival paradox - that woman live longer than men but with more disability - include sex differences in diseases and their impact on disability and death. Further details of this paradox and possible causal mechanisms are discussed in chapter two (§2.3.3). Whether the paradox translates to people who are very old is still undetermined. In light of this gap in knowledge the objectives of this chapter are to:

i) Examine gender differences in survival from age 85.

ii) To examine sex differences in disability incidence and mortality in the presence of eight major disease groups and in so doing:

   a) Discuss the methodological implications of analysing longitudinal data in continuous time.

   b) Detail how a Markovian based model can be applied to the Newcastle 85+ data.

iii) To investigate whether the gender disability-survival paradox in very late life can be explained by the presence/absence of diseases.

The organisation of this chapter will broadly follow the aims outlined.

5.2 Modelling health transitions

Investigating the natural development of many health indicators can involve individuals moving into various health states (often defined in terms of declining health) before a final stage is encountered; frequently a stage from which one cannot return e.g. death. These types of data are longitudinal insofar as measurements are often made repeatedly in continuous time. Modelling an outcome of interest under this process can often be done via the use of multistate models. Multistate models are defined in a stochastic framework whereby individuals can visit any one of the pre-defined discrete states (which can be mutually exclusive) often finishing in a state from which they cannot return and is regularly defined as death. These states are defined by the health condition under investigation and are frequently described as healthy, diseased, disabled or infected; dependent upon what is being investigated.

A person's journey through possible states is described as a transition, event or incident. Multistate models have been used extensively within scientific literature and come in many forms, often dictated by the research question as well as the nature/type of the data to be analysed. With this in mind, it is possible to visualise a number of possible state structures that an individual can follow dependent upon the phenomena under investigation. The simplest of all models to consider is one with two states, in which a person is alive in one and dead in the second, as outlined in figure 5.1, which is in essence, a survival model.

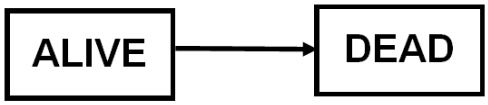


Figure 5.1: Two-state Markov model

This type of state structure has been used extensively within the literature to investigate the impact of covariate effects on mortality. Covariate variables generally come in two different forms. *Time-constant covariates* are variables that do not vary with the passage of time, for example, sex and genetics are, by and large, fixed in time (or study course). *Time-varying covariates* are factors that do change with time and reflect the fact they have the capacity to be linked with time itself (e.g. age or growth) or just vary with time (but not linked to with its passing) e.g. BMI, disease diagnoses, blood pressure. In addition, the type and nature of the data can also be modelled in terms of parametric distributions (Weibull, log-log, log-normal, exponential models) and non/semi-parametric distributions (Cox Proportional Hazards model) therefore giving it lots of flexibility dependent upon data types. Consequently, using the model in figure 5.1, an analyst is able to examine the effects of various covariates (time constant, varying and dependent) on mortality may be examined.

The two-state model can be extended to included further states that are visited over time, eventually ending in a state from which one cannot return, this is represented in figure 5.2.

Figure 5.2: Extension of survival model to 3 states

This model allows the investigation of risk factors which take an individual from a healthy state to and unhealthy one and then death. The risk factors are afforded the flexibility to have different effects upon 'unhealthy' incidence and mortality. An example when this structure would be useful is analysing the impact of variables on stroke incidence and death (Struijs *et al.*, 2005), where one assumes that once an individual has suffered a stroke, they are unable to recover.

The modelling structure can be extended to cover other health scenarios. These are discussed briefly in appendix F. The rest of this chapter focuses on models with three possible states.

The three state model can be augmented to allow the recovery of individuals from an unhealthy state and include death from a healthy state, as shown in figure 5.3.

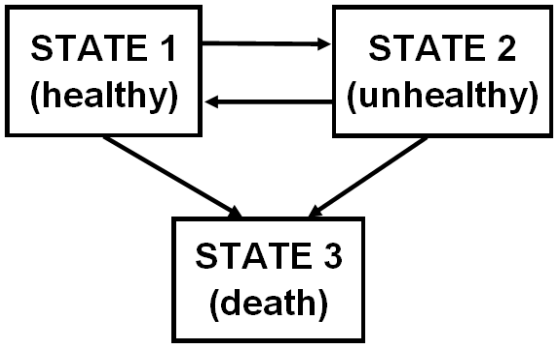


Figure 5.3: 3-state illness-death model

This has important implications as it allows differential mortality probabilities dependent upon the state from which state people travel from. In other words, the probability of death from state 1 can differ to the probability of death from state 2. Not allowing for this difference has the potential to yield a biased estimation of the age-specific incidence of a condition under examination (Joly *et al.*, 2002). In addition to the potential to evaluate state-specific mortality, these models also allow individuals to recover from the unhealthy state. This feature is established with an

arrow which highlights a transition from state 2 to state 1. The model outlined in figure 5.3 would suggest that those people who recover from the unhealthy state (state 2) have the same risk of travelling through to state 2 again as those who remained healthy. Similarly, this also suggests that those people who recover from state 2 also have the same probability of death as those people who are also in state 1 but have never visited state 2 i.e. someone who has been healthy all their life. This assumption can be examined for validity by modifying the model to include a further state called 'recovered', thus:

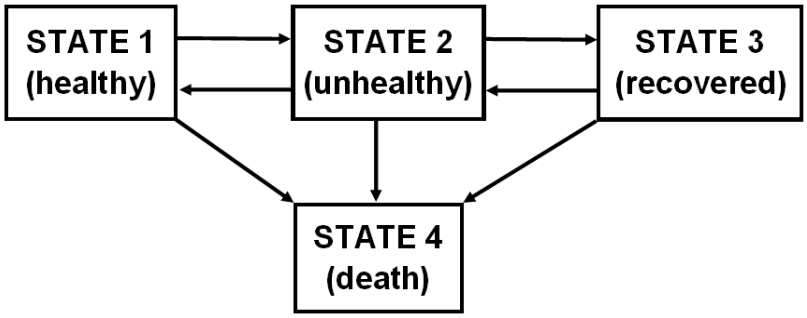


Figure 5.4: Multi-state model including a recovered state

Using the model in figure 5.4 is certainly an improvement on the standard three state model, however, as the number of states increases then the data must contain enough information on transitions between the various states to examine the impact of covariates. If enough transitions are not recorded then an alternative would be to include, as a covariate, previous episodes of ill-health and examine their impact on further transitions and revert to the three state model. The assumption for recovered persons, that their risk of death or further ill-health is the same as for those who have never experienced ill health, arises because of the Markov property. The Markov assumption means that an individual can only occupy one of fixed number of states at any point in time and that future progression only relies on the state currently occupied, and not influenced by states visited previously (i.e. the process is memoryless). Therefore, progress through this model is *only* dependent upon the state currently occupied.

The mathematical framework for the use of illness-death multi-state models has been developed over many years, often within a medical context (de Castro *et al.*, 2015; Ieva *et al.*, 2015; Jepsen *et al.*, 2015). Two seminal papers initially developed its

application to medicine; one investigated the influence of a cancer related biomarker and its impact on disease progression and mortality (Kay, 1986) and the other used a multi-state Markov model to investigate the distribution of the incubation period of Acquired Immunodeficiency Virus Syndrome (AIDS) (Longini *et al.*, 1989). Since the publication of these studies, others have since applied the same methodology to analyse a range of medical phenomena (Guihenneuc-Jouyaux *et al.*, 2000; Jackson and Sharples, 2002; Jackson *et al.*, 2003). The use of multi-state Markov models, within a particular medical context, must first define the outcome variable of interest and the possible transitions within the state space.

5.2.1 Multi-state Markov model for disability

Applying multi-state model methodology to the Newcastle 85+ Study data we define an illness-death model (where illness is disability) as:

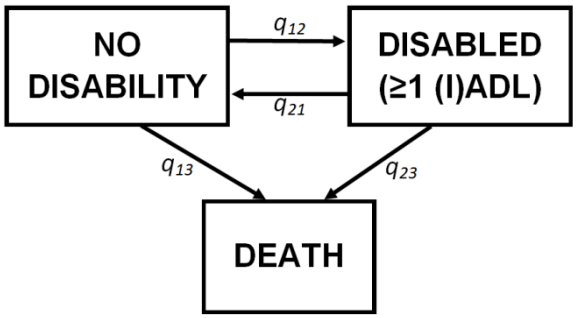


Figure 5.5: Disability-death model for the Newcastle 85+ Study

To assess the contribution of specific diseases on the transitions to and from disability and to death over five years, models were fitted in continuous time with three states: no disability, disability (≥1 (I)ADL), and death (absorbing state). This model was used to estimate the instantaneous rate of transition between the states (presented as hazard rates with 95% confidence intervals and mean time in the state). Models were fitted with each disease individually and then adjusted for the residual disease count, IMD and education. Models are parametrised in a log-linear framework, thus:

$$\log\{q_{xy}(\text{age})\} = \gamma_{xy.0} + \gamma_{xy.1}(age) + \gamma_{xy.2}(disease) + \gamma_{xy.3}(residual\ disease) + \gamma_{xy.4}(\text{education}) + \gamma_{xy.5}(\text{deprivation}) \quad (2)$$

The movement of individuals within the state space is directed by transition intensities, which are dependent on time *t,* and covariates related to the outcome under investigation. Transition intensities represent the instantaneous risk of an individual moving from one state to another. If, at time *t*, an individual is in state *x,* then the instantaneous risk of transition to state *y*, is defined as:

$$q_{xy}[t, r(t)] = \lim_{\delta t \to 0} \frac{P(S(t+\delta t) = y \mid S(t) = x)}{\delta t} \qquad \text{for } x \neq y \qquad (3)$$

Here, *r(t)* allows covariates (time constant, varying and dependent) to influence the how an individual moves through the state space. The transition intensities can be represented in 3-square matrix, where summation across any row equals zero, thus:

$$Q = \begin{pmatrix} q_{11} & q_{12} & q_{13} \\ q_{21} & q_{22} & q_{23} \\ q_{31} & q_{32} & q_{33} \end{pmatrix} \qquad (4)$$

Within this modelling structure, time is measured over a continuum and the risk of becoming disabled over a specified period is fixed i.e. the hazard of transition is constant in time - known as time-homogeneous models. A visit to a particular state and the time spent in that state (also known as the sojourn time) follows an exponential distribution specified by $-q_{xx}$ for state *x.* It follows that the probability of moving to the next state (*y*) can be calculated as: $-q_{xy} \div q_{xx}$. The basic structure of the likelihood function that describes the calculation of transition intensities within multi-state models has been described previously and can be found in a formative paper by Kalbfleisch and Lawless (Kalbfleisch and Lawless, 1985) but will be discussed further in the next section in terms of the 3-state illness-death model.

Given a three state, illness-death model (where illness is defined as disabled) model we assume that the exact death time is known but that the transition to disabled states are not i.e. data are interval censored. The parameters that dictate the shape of the likelihood function and how the transitions within the model are established has been described in detail elsewhere (van den Hout and Matthews, 2009) but will be outlined briefly below, following the same methodology. Let *t* represent the time since study entry. Then at any point $t \geq 0$ an individual is able to occupy any one of the given states, *x,* such that $x_t \in \{1,2,3\}$ where 1, 2 and 3 are states non-disabled,

disabled and dead respectively. It follows, under this model, that at time *t=0* then $x_{t=0} \neq 3$ i.e. all participants are alive to begin and can only become decedents thereafter. This model framework is outlined in figure 5.5 and individuals are able to transition through the states highlighted i.e. non-disabled to disabled, disabled to non-disabled (recovery), disabled to death and non-disabled to death. We define the intensity of moving from state *x* to state *y* as q_{xy} and that $q_{xy} \geq 0$ under the state space transitions defined as $(x, y) \in \{(1,2), (1,3), (2,1), (2,3)\}$. As death is a state from which one cannot return (known as an absorbing state) this places constraints on the dynamism of the model thus: $q_{xy} = 0$ *iff* $(x, y) \in \{(3,1), (3,2)\}$. Therefore, the instantaneous risk of movement within this model can be described by the 3-square matrix shown in equation 5.

$$Q = \begin{pmatrix} -(q_{12} + q_{13}) & q_{12} & q_{13} \\ q_{21} & -(q_{21} + q_{23}) & q_{23} \\ 0 & 0 & 0 \end{pmatrix} \qquad (5)$$

By their intrinsic properties, each row of matrix sums to zero (Kalbfleisch and Lawless, 1985) and diagonal elements of the zero-sum rows are also defined as:

$$q_{xx} = -\sum_{x \neq y} q_{xy} \qquad (6)$$

Inter and intra observation schedules are allowed to vary by individuals and we know that an individual may transition from one state to another over the time frame $(t_1, t_2]$ but the exact time of transition is unknown.

From the transition intensity matrix we can calculate the transition probabilities over a time interval $(t_1, t_2]$ thus: $P(t_1, t_2) = \exp[(t_1 - t_2)Q]$ where the entries are governed by $p_{xy}(t_1, t_2) = P(X_{t2} = y \mid X_{t1} = x) : x, y \in \{1,2,3\}$. The relationship between the transition probabilities and the transition intensities represented in *Q* are associated by the Kolmogorov forward and backward equations (Ross, 1996). Full details of how the likelihood function is defined and then maximised can be found in appendix G.

Intensities not restricted to zero (the states from which one cannot return i.e. death in this case) can be granted the flexibility to vary as a function of covariates that may

influence the magnitude (and sometimes direction) of the transition intensities themselves and are defined in the log-linear model in equation two.
In section 5.2 we discussed one of the assumptions of Markovian models; that the risk of transition is fixed over time i.e. time-homogeneous, and so using the framework outlined in equation 2 we can begin to mitigate some of the effects of this assumption. If we allow *r(t)* (the covariate function) to include a time dependent vector, age say, then the risk of transition will be influenced by the change in age over time and we can then examine the effects of this variable itself on the outcome of interest. However, with increasing age, risk for particular health outcomes can also increase and so, when and why individuals are assessed is an important consideration as sources of bias tied to inter and intra observation schedules.

Although the flexibility of this modelling process allows for variation in inter and intra observation schedules, the timing and reason for the observation of individuals can be influenced by how a person 'presents' to the assessor. This issue is similar to that of missing data; in whether they are missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR) and the impact this can have on analyses. For data where the observation schedules vary within and between individuals, there are a number of possible 'encounter scenarios' that can arise, which have the potential to yield biased results. Four possible observation schedules can be identified *(Jackson, 2011)* and the central concern is whether they actually provide information regarding the health condition under investigation itself. A *fixed* schedule is that which is determined in advance and assessments are carried out at predetermined intervals. A *random* schedule is one in which a person is assessed completely randomly and the assessments are not linked to the health condition. The third type of schedule relates to the people who are assessed because an aspect of their health determines they require more intense observation (and are often *determined by the health practitioner*) therefore the next observation point will be tied to the health condition under investigation. The fourth refers to a *self-determined* observation, whereby an individual presents as a consequence of the health condition, often when it changes or becomes worse.

Whether these four possible observation schedules are informative or uninformative, and whether this should be modelled alongside parameter estimation is an important

consideration for meaningful analyses. Gruger *et al.* discussed and investigated stochastic processes regarding this issue (including Markovian based models) and concluded that fixed, random and, in this case, health practitioner determined assessment points, give unbiased results for the estimation of transition intensities. However, self-determined observation schedules are not, and information not taken into account from this schedule during the modelling process can introduce bias in parameter estimation (Gruger *et al.*, 1991). On that basis it can be concluded that the observation schedules from the Newcastle 85+ data should yield unbiased results.

Analysing the data in a multi-state model framework was done via the `msm` package in R (Jackson, 2011). Disability data from the Newcastle 85+ study was used to fit gender stratified models that examined the impact of age initially, to mitigate some of the effects of the model being time-inhomogeneous. Subsequently, to explore the effect of the eight disease groups (defined in §3.4.8) models were fitted using the disease of interest alongside residual disease count (i.e. disease count minus the diseases of interest), education, deprivation and age. In total, 18 multistate models were built. In addition, the mean time in state was also calculated for each disease model to examine how it may influence length of stay in the states.

5.3 Disease, disability and mortality in the Newcastle 85+ Study

Exact date and cause of death was reported to the study from the Health and Social Care Information Centre and for the purposes of this thesis, only all-cause mortality will be considered.

Figure 5.1 shows the Kaplan Meier survival curve of participants from study inception to 70 months, stratified by gender. From the outset, the probability of survival in men was smaller than that for women, however the difference did not reach statistical significance until around 20 months into the study (log rank test: $p<0.035$). Thereafter, the survival curves for men and women further diverged; suggesting that the mortality rate is greater for men than women even at age 85. Indeed, by 65 months into the study 50% of the men had died, contrasted against approximately 30% of women. This is an interesting outcome given that we know that women show

greater levels of disability (§4.5) at every wave of the study and yet it does not follow that their mortality is higher.

At each of the 18, 36 and 60 month follow-ups, over 70% of participants remained in the study and higher levels of disability found in women at baseline were also clear at subsequent follow-up waves (table 5.2). This pattern was unlikely to result from men being less likely to report difficulty in performance than women, as the relationship between reported performance on mobility items and the objectively measured TUAG test were similar in men and women, at baseline and subsequent waves (§4.5.1). Compared to men, women had significantly higher levels of disability in the interview prior to dropout, whether dropout was due to death or withdrawal (table 5.2).

In chapter three (section 5.8) it was shown that women were more likely to have a diagnosis of arthritis (RR=1.2, 95% CI=1.1-1.3) or hypertension (RR=1.2, 95% CI=1.0-1.3) and less likely to have a diagnosis of cerebrovascular disease (CVD) (RR=0.8, 95% CI=0.6-1.0). However, there was no evidence of any sex difference in the total number of diseases (p=0.68). As there were gender differences in the prevalence of some diseases (arthritis, hypertension and cerebrovascular disease) we cross-checked the date of diagnosis in the GP records and calculated the disease duration (months) as a proxy for severity. No evidence of a difference in diagnosis time for any of the disease groups by gender was evident (table 5.1).

Sex differences in the baseline disability score, between participants with and without specific diseases at baseline, demonstrated that broadly the same diseases were significantly disabling for men and women (table 5.2). For both sexes, cognitive impairment (MMSE≤21) conferred the greatest difference in disability, by approximately 7 points (Men: difference=7.85, 95% CI=6.14-9.56; women: difference=6.28, 95% CI=5.15-7.40) compared to those cognitively intact followed by CVD with a difference in the disability score of 3 points (Men: difference=2.15, 95% CI=0.75-3.56), women: difference=3.10, 95% CI=2.01-4.20). Compared to men, women had a significantly greater disability score at baseline for all diseases except cognitive impairment and cancer where no difference was detected (table 5.2). Where disease was not present levels of disability remained higher for women than

men across all disease groups even after adjustment for potential confounders (deprivation, education and residual disease count).

These results offer some evidence to suggest that the gender-disability paradox is still apparent at age 85 but whether this is actually related to gender specific disease patterns is still unknown. As such, the next section assesses this hypothesis through multistate models, looking first at gender differences in disability incidence, recovery and death.

5.3.1 Transitions over 60 months

Table 5.3 details the number of transitions that have taken place between the states over the six year period from age 85 to 90. Over this duration there were 60 transitions to a disabled state for men and 79 for women. The vast majority of transitions were static i.e. 382 transitions remained in the disabled state for men and 777 for women. Little recovery was evident; only 12 transitions for men and 22 for women showed movement from a disabled state to non-disabled. Over the six year period 191 men and 239 women died. All those remaining were censored at the six year point for the multistate modelling analysis.

Multistate modelling generated eight parameters for men and eight for women which govern the transition intensities detailed in table 5.4, and show the effect of age on disability incidence, progression and death. With increasing age both men and women increase their likelihood of becoming disabled (men: $\gamma_{12.1}$=0.184, se=0.062; women: $\gamma_{12.1}$=0.215, se=0.104), however the magnitude of this effect was more pronounced in women. This was also true of those who die from a non-disabled state (men: $\gamma_{13.1}$=0.102, se=0.035; women: $\gamma_{13.1}$=0.094, se=0.034), however, in this case the effect was more pronounced in men. Once a person enters a disabled state then the chance of dying from that state was significantly increased with age for both men and women (men: $\gamma_{23.1}$=0.091, se=0.032; women: $\gamma_{23.1}$=0.120, se=0.041) but this was greater for women (approximately 32%). The chances of recovery from disability decreased with age for both men (men: $\gamma_{21.1}$=-0.031, se=0.012 and women: $\gamma_{21.1}$=-0.035, se=0.018).

5.3.2 The impact of disease on disability transitions

Fitting models for each disease resulted in those with diabetes conferring the highest risk of incident disability in men (HR=3.0, 95% CI=2.4-3.8) and women (HR=1.7, 95% CI=1.3-2.2) (table 5.5). Despite the prevalence of arthritis being highest in women, there is a suggestion that its impact on incident disability was greater for men (HR=1.7, 95% CI=1.2-2.5) than women (HR=1.2, 95% CI=1.0-1.5) but arthritis conferred a significantly increased risk of becoming disabled in both sexes. Both men (HR=1.6, 95% CI=1.3-1.9) and women (HR=2.4, 95% CI=1.9-3.0) with cardiac disease had significantly greater risk of incident disability but the risk was higher for women (p=0.003). A greater risk of incident disability was also evident for cognitive impairment (men HR=1.3, 95% CI=1.1-1.6; women HR=1.7, 95% CI=1.0-2.9). On the other hand CVD (HR=2.6, 95% CI=2.1-3.4) and respiratory disease (HR=2.0, 95% CI=1.4-3.0) increased the risk of incident disability for women only.

Significant gender differences in the risk of death for those without disability were observed only for cancer (men HR=4.1, 95% CI=2.4-7.1; women HR=1.1, 95% CI= 0.7-1.9) and respiratory disease (men HR=2.2, 95% CI=1.7-2.8; women HR=1.0, 95% CI=0.5-2.0) with men being at increased risk compared to women (Table 5.5). Men with cardiac disease (HR=1.4, 95% CI=1.2-1.8) or CVD (HR=1.3, 95% CI=1.1-1.6) were at increased risk of death from a non-disabled state but this did not differ significantly from the women. The risk of death from a non-disabled state was significantly increased for both men and women with cognitive impairment (men HR=1.7, 95% CI=1.4-2.0; women HR=1.4, 95% CI=1.0-1.9).

Recovery from disability was rare and lowest for participants with cognitive impairment though similarly for men (HR=0.2, 95% CI=0.1-0.3) and women (HR=0.2, 95% CI=0.03-0.9) and in both cases significantly less likely compared to participants without cognitive impairment (Table 5.5).

Hazard ratios for the risk of death once disabled were of similar magnitude for those with cognitive impairment (men HR=2.5, 95% CI=1.8-3.5; women HR=2.6, 95% CI=1.8-3.8) and cardiac disease (men HR=1.5, 95% CI=1.2-1.8; women HR=1.4, 95% CI=1.1-1.8). CVD increased the risk of death once disabled for women only

(HR=1.4, 95% CI=1.0-1.8) as did respiratory disease (HR=1.4, 95% CI=1.1-1.9) and cancer (HR=1.5, 95% CI=1.1-2.1).

The different ways in which different diseases impact on transitions to and from disability and to death for men and women is illustrated in figure 7 for two diseases: cognitive impairment and respiratory disease. Cognitive impairment confers a very high risk of disability with little chance of recovery from disability and a high risk of death, but little difference exists between men and women. Respiratory disease on the other hand is significantly disabling only in women and has a higher risk of death for men initially disability free and women initially disabled.

5.3.3 Mean time with and without disability

Overall, and regardless of disease status, more years are spent after age 85 with disability than without for both men and women, with women spending 2.2 years more on average with disability and 0.5 years less without disability than men (table 5.7).

Compared to those without the disease, men and women with hypertension spent an average of 0.7 years more with disability and for arthritis 0.5 years. Women with arthritis spent an additional year with disability (table 5.6) reflecting the low fatality but disabling effects of these conditions. This was additionally true for women with diabetes. For any of the diseases examined, women with the disease spent fewer years without disability compared to women without the disease. This was also broadly similar for men although men with hypertension spent more years (0.4 years) disability-free than men without hypertension and men with cognitive impairment spent 1.3 years longer disability-free than men without cognitive impairment.

5.4 Summary

The goal of this chapter was to determine potential reasons for the gender disability survival paradox in the very old, in particular the role of specific diseases on disability and mortality. I approached the investigation with a single question in mind: was the mortality and disability difference between men and women primarily driven by gender differences in the type and impact of diseases even in the very old?

The most pertinent findings of this chapter are:

Cross-sectionally:

By 85 women have a greater levels of disability compared to men and this was true for every wave of the study. In addition, women had a greater prevalence of disability at the point before death/withdrawal.

Women with a diagnosis of arthritis, hypertension, cardiac disease, CVD, respiratory disease and diabetes still showed higher levels of disability compared to men with the same diagnosis. Arthritis, CVD and cognitive impairment were associated with higher disability levels for both men and women whilst cardiac disease was associated with greater disability for women only. .

Longitudinally:

Women were more likely than men to become disabled ($p=0.041$) but death from a non-disabled state, disability recovery and death from a disabled state were not gender dependent.

Arthritis, cardiac disease, diabetes and cognitive impairment increased the risk of becoming disabled and, in addition, this was true for CVD and respiratory disease for women.

Men with cardiac disease CVD, respiratory disease and cancer were more likely to die from a non-disabled state and this was not true of women. Cognitive impairment was equally detrimental for moving from a non-disabled state for both men and women and the same was true for mortality.

Disability recovery was only evident in those people who were not cognitively impaired.

Men and women with a diagnosis of cardiac disease or cognitive impairment were more likely to die from a disabled state compared to those without a diagnosis. Additionally, CVD, respiratory disease and cancer were detrimental for survival from a disabled state for women only.

This chapter has considered transitions to disability, recovery from and death from both a non-disabled and disabled state. How this might go some way to explain the disability-survival paradox will be expanded upon in the discussion. The next chapter will shift the focus to examine whether trajectories of disability are detectable in the very old.

Table 5.1: Disease duration by gender (months)

	Men	Women	All	Sex difference p-value*
Arthritis	16 (8-25)	16 (8-25)	16 (8-25)	0.789
Hypertension	10 (5-18)	9 (5-15)	9 (5-16)	0.274
Cardiac Disease	12 (8-19)	10.5 (6-16)	11 (6-18)	0.135
Cerebrovascular Disease	7 (4-12)	6.5 (3-12)	7 (3.5-12)	0.515
Respiratory disease	13 (5-20)	12 (6-20)	12 (6-20)	0.786
Diabetes	7 (4-12)	8.5 (5-15)	8 (4.5-13.5)	0.372
Cognitive Impairment†	-	-	-	-
Cancer	1 (1-3)	1 (1-3)	1 (1-3)	0.503

*Mann-Whitney U Test for gender difference in disease duration
†Assessed at baseline therefore no duration

Table 5.2: Levels of disability at follow-up waves by gender and attrition

	Disability Score at interview			Disability Score at previous interview		
	Median (IQR)			Median (IQR)		
	Men	Women	Sex difference†	Men	Women	Sex difference†
Baseline	0 (1-5)	3 (1-7)	1.97 (1.21,2.72)	-	-	-
18 months (Wave 2)						
Participant	2 (1-6)	4.5 (2-9)	1.90 (1.11-2.70)	1 (0-4)	3 (1-5.5)	1.79 (1.01-2.58)
Died before W2	-	-	-	6 (1-12)	9 (4-14)	3.53 (0.29 - 7.35)
Withdrawn before W2	-	-	-	2 (1-6)	5 (2-9)	2.54 (0.85-4.24)
36 months (Wave 3)						
Participant	4 (1-8)	5 (3-9)	1.33 (0.41-2.26)	2 (1-6)	4 (2-7)	1.76 (0.91-2.61)
Died before W3	-	-	-	5 (2-8)	11 (3-14)	4.23 (1.06-7.40)
Withdrawn before W3	-	-	-	3 (1-8)	7 (4-12)	2.29 (0.20-4.39)
60 months (Wave 4)						
Participant	4 (1-7)	5 (3-9)	1.74 (0.60-2.87)	3 (1-7)	4 (3-7)	1.04 (0.55-2.02)
Died before W4	-	-	-	5 (1-10)	11 (5-13)	2.98 (0.51-5.44)
Withdrawn before W4	-	-	-	5 (1.5-10.5)	7 (3-11)	2.20 (-0.95-5.35)

† - Tobit regression – actual difference in score. Women compared to men.

Table 5.3: Disability score by disease and gender at baseline

	Men			Women			Sex difference in disability score†	
	With disease	Without disease	Disability score difference (95% CI)†*	With disease	Without disease	Disability score difference (95% CI) †	With disease	Without disease
Arthritis	2 (1-5)	1 (0-4)	1.55 (0.27,2.83)	3(1-7)	2(0-5)	1.68 (0.68,2.67)	1.82 (0.94,2.70)	1.78 (0.32,3.23)
Hypertension	1 (0-4)	2 (0-6)	-0.92 (-2.16,0.32)	3(1-7)	3(1-7)	0.01 (-0.90,0.92)	2.37 (1.39,3.35)	1.51 (0.34,2.69)
Cardiac Disease	2 (0-5)	1 (0-5)	-0.17 (-1.43,1.09)	4(2-8)	3(1-6)	1.26 (0.34,2.18)	2.80 (1.69,3.90)	1.46 (0.45,2.48)
CVD	2 (1-6)	1 (0-4)	2.15 (0.75,3.56)	6(3-11)	3(1-6)	3.10 (2.01,4.20)	2.99 (1.28,4.69)	1.86 (1.05,2.67)
Respiratory disease	2 (0-5)	1 (0-4)	0.69 (-0.79,2.17)	4(2-8)	3(1-6)	0.94 (-0.11,2.00)	2.12 (0.68,3.56)	1.92 (1.05,2.80)
Diabetes	2.5 (0-6)	1 (0-4)	0.64 (-1.12,2.41)	4(3-7)	3(1-7)	1.18 (-0.14,2.51)	2.37 (0.53,4.21)	1.91 (1.09,2.73)
Cognitive Impairment	11 (6-13)	1 (0-3)	7.85 (6.14,9.56)	9(5.5-13.5)	3(1-5)	6.28 (5.15,7.40)	0.37 (-2.00,2.74)	1.79 (1.11,2.46)
Cancer	2 (1-3)	1 (0-5)	0.72 (-1.46,2.90)	2.5(1-7)	3(1-7)	-0.23 (-2.22,1.76)	1.19 (-1.39,3.77)	2.12 (1.33,2.90)

† - Tobit regression adjusted for education deprivation and residual disease count. Actual difference in score.

Table 5.4: State-table showing participant transitions over 6 years

			To			
			No Disability	Disabled	Death	Censored
From	MEN	No disability	73	60	27	26
		Disabled	12	382	164	104
	WOMEN	No disability	36	79	6	22
		Disabled	22	777	233	261

Table 5.5: Maximum Likelihood Parameters for the multistate model for age by gender

	Incident disability (q_{12})		Death from no disability (q_{13})		Disability recovery (q_{21})		Death from disability (q_{23})	
Men								
Intercept	$\gamma_{12.0}$	-4.280 (1.250)	$\gamma_{13.0}$	-4.214 (1.184)	$\gamma_{21.0}$	-3.514 (1.314)	$\gamma_{23.0}$	-3.142 (1.015)
Age	$\gamma_{12.1}$	0.184 (0.062)	$\gamma_{13.1}$	0.102 (0.035)	$\gamma_{21.1}$	-0.031 (0.012)	$\gamma_{23.1}$	0.091 (0.032)
Women								
Intercept	$\gamma_{12.0}$	-4.315 (1.021)	$\gamma_{13.0}$	-4.124 (1.845)	$\gamma_{21.0}$	-3.325 (1.415)	$\gamma_{23.0}$	-3.214 (1.564)
Age	$\gamma_{12.1}$	0.215 (0.104)	$\gamma_{13.1}$	0.094 (0.034)	$\gamma_{21.1}$	-0.035 (0.018)	$\gamma_{23.1}$	0.120 (0.041)

Table 5.6: Hazard ratios for disability incidence, recovery and death

	Men	Women	Sex Difference *p*-value
Incident Disability	Referent*	1.26 (1.12-1.41)	0.041
Arthritis	1.72 (1.19-2.48)	1.23(1.02-1.49)	0.942
Hypertension	0.87 (0.48-1.58)	1.09(0.56-2.12)	0.315
Cardiac Disease	1.60 (1.32-1.93)	2.39(1.92-2.97)	0.003
Cerebrovascular Disease	1.11 (0.76-1.63)	2.63(2.06-3.35)	0.000
Respiratory disease	0.98 (0.74-1.29)	2.02(1.35-3.01)	0.002
Diabetes	3.03 (2.43-3.79)	1.67(1.26-2.22)	0.001
Cognitive Impairment	1.31 (1.06-1.62)	1.71 (1.02-2.86)	0.174
Cancer	0.84 (0.29-2.42)	1.85(0.71-4.80)	0.139
Death from no disability	Referent*	0.89(0.73-1.08)	0.216
Arthritis	0.70 (0.33-1.50)	0.99(0.47-2.13)	0.260
Hypertension	0.62 (0.28-1.34)	1.01(0.44-2.31)	0.200
Cardiac Disease	1.42 (1.17-1.73)	1.48 (0.97-2.26)	0.569
Cerebrovascular Disease	1.31 (1.09-1.57)	1.00(0.59-1.70)	0.173
Respiratory disease	2.16 (1.67-2.79)	1.00(0.49-2.04)	0.046
Diabetes	1.20 (0.88-1.62)	1.01(0.24-4.17)	0.592
Cognitive Impairment	1.68 (1.41-2.01)	1.38(1.01-1.89)	0.857
Cancer	4.10 (2.35-7.13)	1.10(0.65-1.86)	0.001
Disability recovery	Referent*	0.96 (0.80-1.15)	0.328
Arthritis	0.73 (0.42-1.28)	0.96(0.72-1.27)	0.196
Hypertension	1.63 (0.94-2.81)	0.79(0.30-2.08)	0.899
Cardiac Disease	0.94 (0.57-1.56)	0.96(0.49-1.88)	0.481
Cerebrovascular Disease	1.63 (0.50-5.38)	0.41(0.03-5.03)	0.837
Respiratory disease	1.07 (0.58-1.97)	0.82(0.26-2.66)	0.651
Diabetes	0.85 (0.28-2.57)	0.89(0.54-1.47)	0.470
Cognitive Impairment	0.17 (0.09-0.31)	0.17(0.03-0.88)	0.500
Cancer	0.94 (0.67-1.33)	0.90(0.53-1.54)	0.547
Death from disabled	Referent*	0.84 (0.72-0.98)	0.042
Arthritis	0.84 (0.61-1.17)	0.92(0.51-1.66)	0.403
Hypertension	0.81 (0.59-1.10)	1.08(0.76-1.52)	0.111
Cardiac Disease	1.46 (1.21-1.77)	1.40(1.11-1.78)	0.601
Cerebrovascular Disease	1.09 (0.62-1.92)	1.36(1.03-1.80)	0.244
Respiratory disease	1.39 (0.82-2.35)	1.42(1.05-1.92)	0.474
Diabetes	1.27 (0.87-1.87)	1.11(0.76-1.63)	0.693
Cognitive Impairment	2.49 (1.76-3.54)	2.62(1.81-3.78)	0.428
Cancer	1.43 (0.92-2.22)	1.51(1.10-2.08)	0.416

Table 5.7: Mean times in state (years) by disease group

	Without disability		With Disability	
	Without disease	**With disease**	**Without disease**	**With disease**
		Women		
Overall	1.31		6.44	
Arthritis	1.47	1.20	6.12	6.51
Hypertension	1.37	1.26	5.97	6.70
Cardiac Disease	1.53	0.64	6.95	5.29
CVD	1.38	0.53	6.61	5.67
Respiratory disease	1.46	0.72	6.86	5.26
Diabetes	3.46	2.07	4.36	5.20
Cognitive Impairment	3.58	2.23	4.64	3.04
Cancer	1.36	0.73	6.58	4.67
		Men		
Overall	1.82		4.20	
Arthritis	2.52	1.60	4.09	5.11
Hypertension	1.87	2.22	4.34	5.00
Cardiac Disease	2.46	1.57	5.44	3.88
CVD	2.12	1.92	4.85	4.25
Respiratory disease	2.15	1.56	4.74	3.89
Diabetes	2.28	0.81	4.86	3.97
Cognitive Impairment	2.04	3.36	5.21	2.41
Cancer	2.04	1.81	4.79	3.43

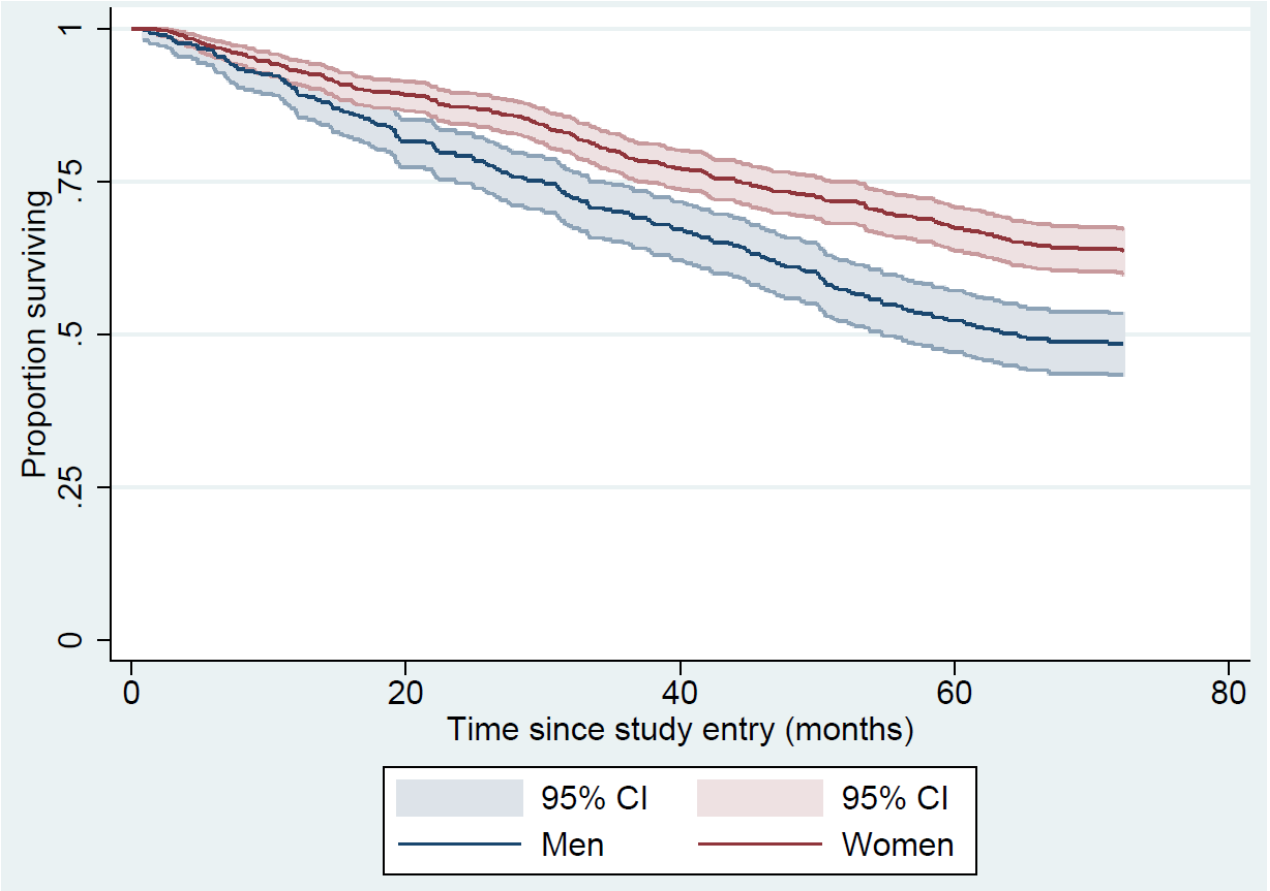


Figure 5.6: Kaplan Meier survival curve by gender

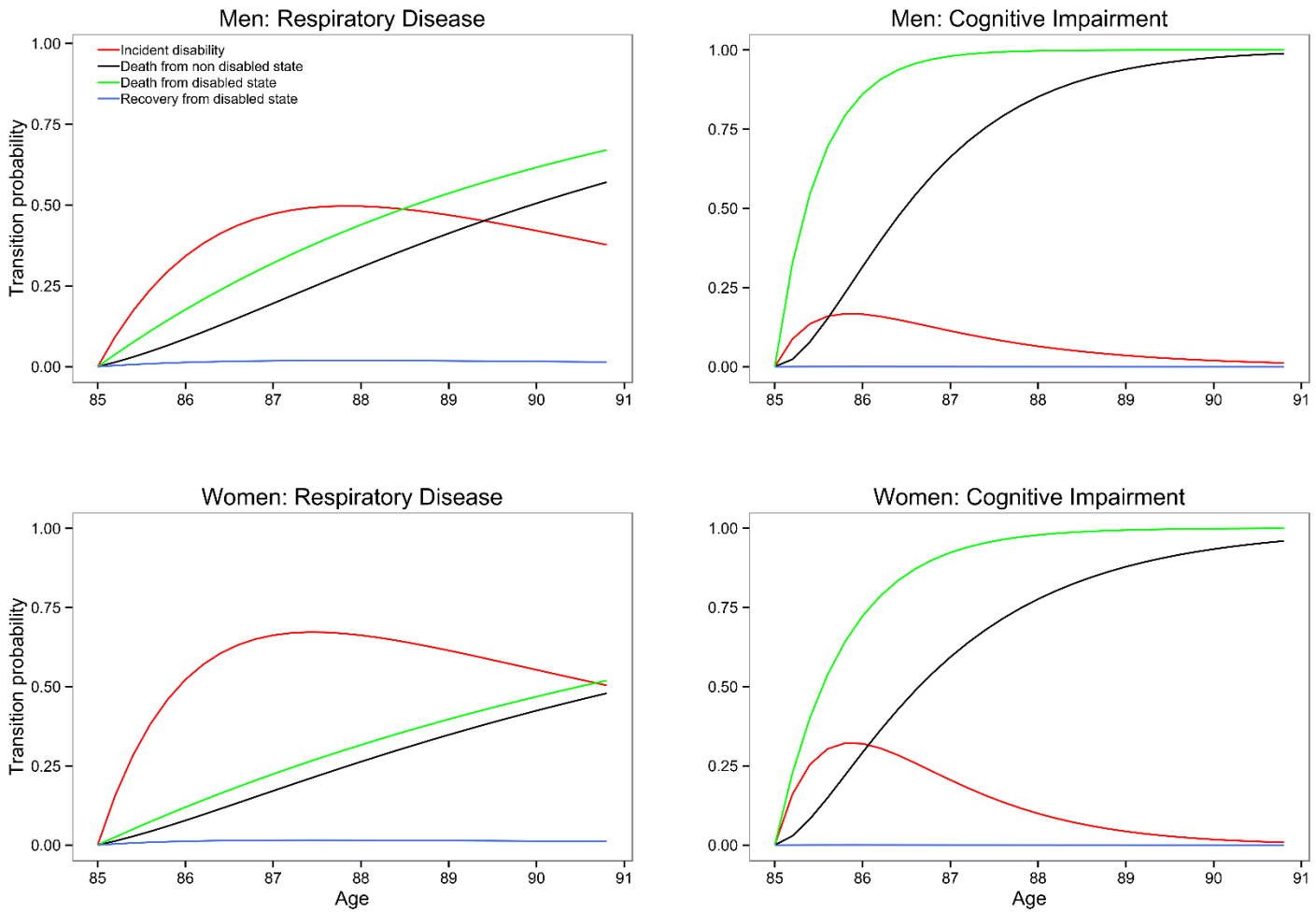


Figure 5.7: Predicted probability of moving into specified states over a six year period

6 TRAJECTORIES OF DISABILITY

6.1 Aims of chapter six

The objectives of the research presented in this chapter are to identify gender specific trajectories of disability accounting for non-random subject attrition. In addition to the exposition of disability trajectories, a secondary objective aims to identify the mortality profile of participants who are affiliated with particular trajectories. A final objective is to examine whether the trajectories are associated with a selection of inflammatory biomarkers and markers of cellular aging.

The organisation of chapter six will be as follows. Section 6.2 will introduce trajectory modelling and discuss the benefits of this analysis versus other readily available statistical techniques and will briefly detail the statistical methodology underpinning its use. The results of the analysis will be presented in two subsections within section 6.3. The first will detail the results of the trajectory modelling procedure accounting for non-random subject attrition (in particular mortality). Specifically this will outline the model parameters for both the disability trajectories and the mortality profiles thereof. It will also cover the proportion of people who are affiliated with the trajectories and present them graphically (alongside mortality profiles). The second results subsection will detail the health profile of participants between trajectories and associations with a selection of biomarkers.

6.2 Group Based Trajectory Modelling (GBTM)

The progress of heath over time is one of the most basic and empirically important research questions that an epidemiologist can ask. Tracking the course of disease or disability allows the researcher to analyse its evolution, and data of this nature is often found in epidemiological datasets whose fundamental basis lies in the temporality of repeated observations across the same individuals. The analysis of these types of data is frequently anchored in variation about a trend in the population mean. However, this detracts from, what is often, an important question in analysing the natural history of disease or health: are there meaningful subgroups of individuals within a population whose developmental trajectory (by whatever measure of health) is unlikely to be identified ex-ante by a given set of predictor variables?

There is a dearth of analytical techniques available to an investigator to identify unique developmental trajectories. Some of which are a hybrid of theoretical groupings and standard statistical methods. However, this inevitably leads to subjective results; primarily caused by a-priori decisions regarding the number and shape of potential trajectories and the possibility of identify groups that represent random variation within the data. As a result, this can have the unwanted effect of failing to identify important and clinically meaningful health trajectories.

Two popular alternatives to GBTM are growth curve analysis and subjective pathway classification. These two techniques, along with GBTM have a fundamental structure that allows the exploration of differences in observations between individuals in terms of their future trajectories. However, the technicalities of each of the methods are different in terms of the underlying assumptions on which they are based, specifically surrounding the distribution of trajectories within the population. For growth curve analysis (focusing specifically on repeated measures (hierarchical modelling) and latent curve analysis) the common underlying assumption is that the distribution of trajectories is continuous throughout the population and multivariate normal. As such that main goal of this type of analysis is the estimation of the mean and its variance (or the covariance structure) of the distribution of trajectory parameters; the former describing the average growth of the population over time and the latter used to adjust the variation in growth. One or more explanatory variables may also be included in the modelling process. It is at this juncture that GBTM diverges from growth curve analysis. GBTM does not assume that the distribution of trajectories varies continuously within the population. Instead it attempts to detect clusters of individuals that may be a function of distinctive developmental trajectories, with the potential to identify explanatory factors for membership to particular trajectories. Using this methodology allows the exploration of heterogeneity at the individual level expressed as a function of trajectory differences rather than using the standard growth curve model and explaining it through a distribution function. It is important to emphasise that it is not a cluster analysis but a particular application of finite mixture modelling. The foundation of the technique lies in the calculation of maximum likelihood and as such it retains many of the desirable aspects of parameter estimates in terms of consistency, asymptotic normality and stability. Furthermore, this method can be adapted to various data distributions and in the case of the

disability data, a censored normal distribution. The formulation of the maximum likelihood and how this is adapted for a censored normal distribution can be found in appendix G.

6.2.1 Attrition

The most common source of attrition in studies of the very old is mortality, but this mortality can be related to the health measure itself, insofar as ill health is frequently at its peak at the point before death. Sources of attrition in the Newcastle 85+ Study have been examined in detail and can be summarised in three broad categories; those who withdraw for health reasons, those who withdraw for non-health reasons and those who die (Davies *et al.*, 2014). The impact of attrition can have lasting effects upon analyses that seek to investigate trajectories in health if they are not accounted for. Using GBTM allows for data to be missing at various assessment schedules and assumes that although the data are missing, they do exist but are not observed and just missing at random. As such the probability of trajectory membership and the source of attrition are independent. However, this is not always a reasonable assumption as often the reason for missing data is related to the outcome itself. Extending the model to allow for missing data that are not missing completely at random allows the investigation of trajectories and attrition. This increases the scope of the analysis, not only look for distinct developmental trajectories in health, but also to explore attrition by allowing the probability to be estimated (as a function of the health outcome being measured) and by allowing it to fluctuate. The estimation of parameters that describe non-random participant attrition (in particular due to mortality) is anticipated to be of significant interest when the source of attrition is related to the health measure itself.

The GBTM procedure has since been generalised to relax the assumptions that data which are missing are missing at random. One primary source of attrition in the Newcastle 85+ study is mortality and allowing this information to be included yields probabilities around mortality itself. These, however, are not age-specific probabilities of dying but rather the probability of death prior to the next assessment schedule. As these probabilities are afforded the flexibility to vary by trajectory then the mortality trajectories and the health trajectories are no longer independent.

The combination of the GBTM procedure and the flexibility to investigate sources of attrition allows one to examine distinct trajectories of disability in the Newcastle 85+ dataset together with dependent attrition (sources being mortality and/or drop-out) profiles.

6.2.2 Statistical methods as applied to the Newcastle 85+ dataset

To explore patterns of individual trajectories of disability we used the method outlined in the previous section (GBTM) (Nagin, 2005). Firstly the number of distinct trajectories was determined via polynomial functions in time using a censored normal distribution. Non-random subject attrition, in particular due to mortality, was accounted for by a group-specific function linked to the probability of death by age (Haviland *et al.*, 2011). A number of trajectory models were explored with the best fitting determined by the Bayesian Information Criterion (BIC) and the fit further assessed by ensuring the posterior probability of group membership for all participants exceeded 70%. All participants satisfied this condition in the final model (Nagin, 2005). The effect of SES measures on the disability trajectories were assessed by multinomial logistic regression, first fitting SES measures singly, then with adjustment for confounders, and finally with all SES measures together. As we have previously shown in this cohort that women are at a disadvantage in terms of disability (Kingston *et al.*, 2012; Kingston *et al.*, 2014), we fitted trajectory models separately for men and women. Sensitivity analyses were undertaken to determine the effects of combining both mortality and participants lost to follow-up into one category. Models were adjusted for the major factors associated with both disability and SES: disease burden, Body Mass Index (BMI); and depressive symptomatology.

To validate the detected trajectories, they were analysed for their association with sociodemographic variables and geriatric syndromes outlined in chapter 3 (§3.4).

In chapter two (§3.4) the concept of preclinical disease was introduced in terms of its utility in identifying, ex-ante, those people who could go on to become disabled before active pathology presents itself. This was discussed in terms of inflammatory biomarkers [particularly C reactive protein (CRP) and interleukin 6 (IL-6)]. Trajectories identified were contrasted against five biomarkers in total. Firstly CRP and IL-6 as discussed previously (§2.3.4). In addition a further inflammatory

biomarker was examined – Tumour Necrosis Factor alpha (TNF-α). TNF-α is another inflammatory biomarker that is released by the body in reaction to a biological environment compromised by injury, trauma or infection and is a chief molecule in regulating inflammatory response (Esposito and Cuzzocrea, 2009). In addition, two other biomarkers linked to cellular aging were also examined; these being DNA damage and telomere length. DNA damage is a measure of how much cellular DNA has been damaged or how much the structure of DNA has been altered. Causes of DNA damage are diverse and can be related to metabolic process (endogenous) or detrimental exposures throughout the life course (exogenous) e.g. smoking, alcohol, asbestos or other agents. Telomeres are located at the end of chromosomes and are 'caps' that protect the DNA stands. An important property of telomeres, that may provide some utility in measuring biological age, is that with each cell division they shorten and so it is expected that those who have greater biological age will have shorter telomeres.

Assessing the markers of inflammation with the trajectories, it is hypothesised that those with greater disability would, in theory, show greater levels of inflammation. In addition, the same principle would apply to the markers of cellular ageing. Those people who identified with the most disabled categories may show greater levels of cellular ageing. Assessing the association of the trajectories with these biomarkers marks the beginning of an investigation to understand whether they have utility for further examination in their ability to identify individuals before they become disabled.

Analyses were carried out in Stata 12.1 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.) and the SAS® Trajectory Procedure (Jones *et al.*, 2001) on the SAS® platform (v9.2).

6.3 Disability trajectories

Four distinct trajectories of disability were evident for both men and women. The parameters that determine these trajectories are outlined in table 6.1. For ease of reference they are denoted MT1-MT4 for men and FT1-FT4 for women; each representing increasing levels of disability, both at baseline and over time (or with increasing age) with the exception of one group of men. Parsimonious models were constructed via the use of the Bayesian Information Criterion (BIC) and the attribution

of people to specific trajectories was checked to confirm that the posterior probability of trajectory membership exceeded 70%.

The first male trajectory (MT1) showed no disability at baseline and remained free of disability to age 90 with 9% of the male sample attributed to this trajectory. MT2 described men who had very mild disability at age 85, experiencing difficulty with around one or two (I)ADL, of which 44.3% of the male sample were attributed. Their future trajectory involved gradual increases in disability over time to age 90 and was described by a negative quadratic in age (quadratic parameter: β_2= -0·113 (SE=0·052)) suggesting that the rate of increase in the level of disability slowed over time. MT3 describes men with began with mild disability (difficulty with around 4 items) and progressed rapidly over time to moderate/severe disability (difficulty with around 11 items) by age 90. The course of disability was described only by a linear parameter in age and 29.7% of men were attributed to this trajectory. The final trajectory, MT4, consisted of the remaining 17% of the sample and represented those men with severe persistent disability. This was also best described by a linear parameter in age.

Women who belonged to FT1 consisted of 21.8% of the sample and reflected slight to mild levels of disability. It characterised those women who had difficulty with around one IADL item increasing in a linear fashion to age 90 with difficulty in approximately four items. FT2 consisted of 43.6% of the sample and represented those women beginning with mild disability (difficulty in around four items) and increasing linearly to difficulty with around nine items by aged 90. FT3 comprised 21.9% of the sample and was characteristic of those beginning with moderate disability (difficulty with approximately eight items) graduating to severe disability at age 90 and reporting difficulty with around 14 items. This trajectory was characterised by a deceleration of increasing disability over time (i.e. a negative quadratic in age - quadratic parameter: β_2= -0·232 (SE=0·069)). The final women's trajectory, FT4, comprised of the remaining 12.7% of the sample and described those who had severe, persistent disability. At age 85 these women reported difficulty with around 14 IADL items. This progressed to difficulty with nearly all items by age 90 having increased linearly with age.

Gender specific trajectories are displayed graphically in figure 6.1, where the black lines denote the course of disability over time; the coloured bands the 95% confidence interval around the model estimates, and the solid points the actually (mean) disability score at the respective wave. It shows that gender specific trajectories are all statistically different (in terms of the level of disability) from one another. A notable exception to this is those men who belong to either MT1 or MT2 at age 85. For these men, there was no statistically significant difference in their level of disability at 85 (p=0.321), however, as time progressed these trajectories diverged to identify those men whose disability increases from those who remain disability free.

6.3.1 Mortality profiles

Figure 6.2 represents the mortality profiles of the trajectories of men and women respectively and table 6.1 contains the parameters that describe the profiles which represent the probability of dying prior to the next assessment phase. For men who belong to trajectory MT1, the probability of dying did not increase over the course of the study and remained static at around 23%. Given that these men report no disability in any (I)ADL items then this could be an expected result. Men who belonged to the second trajectory, MT2, showed a linear increase in the chances of dying before the next round of assessments. The chance of dying prior to the next wave was 21% at wave 2 and this increased to 29% by wave four and was in line with their increasing disability. MT3 also developed in similar fashion to those who belonged to MT2 with the probably of dying prior to the next assessment phase starting at 22% at wave one and increasing to 32% by wave four. MT4 displayed the greatest chance of dying prior to the next phase compared to any other male trajectory. At phase one, men who belonged to the most disabled trajectory had a 43% chance of dying prior to the next assessment and this increased to 57% by wave four. All trajectories suggested that as disability increased then so did the chances of dying prior to the next phase, the functional form of which described by linear parameters for all.

For those women who belonged to the FT1 (the least disabled) their probability of dying prior to the next wave remained fairly static at around 12% over the study period. Women who belonged to trajectory two (FT2) had a similar profile but the

chances of dying prior to the next wave increased to around 21%. The probability of dying prior to the next wave for those women who belonged to FT3 started at approximately the same point as those who belonged to FT2 (~21%), but by wave three this increased to 35% and by wave four it increased further to 41%. Those women who were in the most disabled category (FT4) had the greatest probability of dying prior to the next wave. At wave two this was around 61%, by wave three it reduced to 59% and by wave four it was further reduced to 56%. This decrease in the probability of dying prior to the next wave for those women in FT4 was found not to be statistically significant (p=0.128).

6.3.2 Validation of trajectory affiliation

Four trajectories of disability have been shown to describe the course of disability for men and women aged 85 and over. The following section will describe associations with key baseline variables focusing specifically on sociodemography, geriatric syndromes (including a count of major diseases) and inflammatory biomarkers.

Sociodemography

Table 6.2 shows the distribution of housing status, living arrangements, marital status, smoking status and self-rated health by trajectory. Significant associations were found between and housing status and self-rated health only. Men who belonged to the most disabled trajectory (MT4) were more likely to reside in an institution ($p<0.001$) compared to their less disabled counterparts. Similarly, those men who were more disabled (MT2-MT4) were more likely to report their health as worse that those men who belonged to the least (non-disabled) trajectory MT1 ($p<0.001$).

Table 6.3 shows that, similar to men, women who belonged to the more disabled trajectories were more likely to reside in an institution ($p<0.001$) and rate their health more poorly ($p<0.001$) compared to their less disabled counterparts. No associations were found in the remaining sociodemographic variables.

Geriatric syndromes

Table 6.4 details associations of the male trajectories with key geriatric syndromes. Men who belonged to the most disabled trajectories were more likely to report

difficulties with vision (p<0.001), reported more falls (p=0.001), experience increased levels of incontinence or faecal incontinence (p<0.001 for both), report that they have symptoms of depression (p<0.001, display symptoms of reduced cognition (p<0.001) and have a greater number of diseases (p<0.001). Associations were not found with BMI, hearing impairment or reported pain the previous month.

Similar associations were found for the female trajectories, with a couple of notable exceptions (table 6.5). Visual impairment (p<0.001), urinary and faecal incontinence (p<0.001 for both), depression (p<0.001), reduced cognitive ability (p<0.001) and disease count (p<0.001) all showed associations with the disability trajectories. The direction of the association indicated that with each increasing disability trajectory there was a negative impact on each variable under consideration. In addition to these variables, associations were also detected for hearing impairment (p<0.002), pain in the last month (p=0.001) and a borderline association with BMI (p=0.0542); the direction of the association suggesting that increasing disability negatively impacts the health variable under consideration. These additional associations were not detected when analysing the male trajectories. The female trajectories showed no association with the number of falls in the previous year (p=0.476), which is opposite to what was discovered for men.

6.3.3 Inflammatory biomarkers and cellular ageing

Three inflammatory biomarkers were selected: interleukin 6 (IL-6), tumour necrosis factor alpha (TNF α) and C - reactive protein (CRP) and alongside these, two markers of cellular ageing were also assessed for an association with the disability trajectories (DNA damage (%) and telomere length (mean base pairs - mpb)).As these markers are largely skewed in their distribution; table 6.7 details the median and interquartile range by trajectory for men. Kruskal-Wallis tests were used to compare biomarkers across the trajectories. None of the biomarkers of inflammation or cellular ageing were associated with male trajectories. This was not the case for women, however, associations with the female trajectories was detected for TNF-α (p=0.0368) and IL6, although the association was borderline significant (p=0.0728) (table 6.8). However, there was a strong significant relationship between increasing disability and levels of CRP (p=0.001). The direction of the association for those markers that are statistically associated with the trajectories is proportional the

circulating levels of each. As was found in men, the two markers of cellular ageing were not associated with the disability trajectories in women.

Further examination, through ordinal logistical regression, allowed quantification of the level of biomarkers (in quartiles due to data skewness) and the disability trajectories. This analysis confirmed that none of the biomarkers were associated with the disability trajectories for men. However, it confirmed previous findings (table 6.9). Those women who had levels of IL-6 in the 25^{th}-50^{th} centile, 50^{th}-75^{th} centile and 75^{th}-100^{th} centile were 74%, 92% and 86% more likely to belong to trajectories FT2, FT3 and FT4 respectively compared to FT1. The same was true of TNF-α with a 70%, 71% and 85% increased likelihood of belonging to the more disabled trajectories respectively compared to the least disabled. The relationship with CRP was slightly different but still significant. Only when CRP levels were found to be in the 75-100^{th} centile was a relationship detected. This suggested that those women with (relatively) very high levels of CRP were 209% more likely to belong to the more disabled trajectories compared to the least. Again, no relationship with either of the makers of cellular aging was detected in women.

6.3.4 Life course socioeconomic status and disability trajectories

Socioeconomic status (SES) across the life course and its affiliation with the disability trajectories was examined via multinomial logistic regression and adjusted for multiple confounders. Three variables were selected that were chosen to reflect an individual's SES at various points in the life-course. For early life SES, the number of formal years' education was used; for mid-life a person's SES was assessed via the use of the National Statistic Socioeconomic Classification (NS-SEC). This classification is used as a primary social classification in the UK and rates individuals according to their occupation – we used the three category version which is described by higher occupations (professional and managerial), intermediate occupations (clerical, sales, service) and lower occupations (routine occupations and those who have never worked including the long terms unemployed). Late-life SES was assessed via the index of multiple deprivation which is a metric that assesses and individuals SES at the small area level and is based on a participants post-code and is a relative score reflecting income, employment, health, education, crime and the living environment.

Three models were fitted using multinomial logistic regression. The first analysed the impact of individual life-course SES variables alone, not taking into account other SES variables. The second model constructed analysed the impact of all SES variables together, all adjusted for each other. The final model built upon the second and included adjustment for potential confounding factors including BMI, disease burden and depressive symptomatology.

Table 6.9 details the first model where each SES variable is considered alone. Men and women with more education were less likely to belong to the more disabled trajectories with a stronger education gradient in women than men. Those with 12 or more years of education were less likely to belong to the most disabled trajectory compared to the least (Men: OR=0.69, 95% CI 0.51 to 0.93; women: OR=0.54, 95% CI 0.30 to 0.96) and women with the least education (0-9 years) were more likely to be in the most disabled (FT4) than the least disabled (FT1) trajectory (OR=1.21, 95% CI 1.01 to 1.45). With regard to mid-life SES, identical patterns prevailed. Men and women who had been in managerial occupations were less likely to belong to the most disabled trajectory (Men: OR=0.33, 95% CI 0.15 to 0.71; women: OR=0.33, 95% CI 0.21 to 0.51) and women from manual occupations were more likely to be in the most disabled (FT4) than the least disabled (FT1) trajectory (OR=1.35, 95% CI 1.05 to 1.74). Late-life socio-economic status (IMD) only impacted men, with those in the least deprived quartile of IMD being less likely to be in the most disabled trajectory (MT4) compared to the least disabled (MT1) (OR=0.42, 95% CI 0.31 to 0.57).

When all socio-economic status indicators (i.e. early, mid and late life) were included in the model (table 6.10) only the effect of education remained significant and this effect persisted, though attenuated, after adjustment for potential confounders (disease burden, BMI, depressive symptomatology) (table 6.11). Thus men and women with the most education remained less likely to be in the greatest, compared to the least, disabled trajectory (men: OR=0.80, 95% CI 0.65 to 0.98; women: OR=0.59, 95% CI 0.42 to 0.83).

6.4 Summary

Group-based trajectory modelling which accounted for non-random subject attrition (mortality) was used to investigate whether distinct disability trajectories were present for very old men and women, whilst also examining the effect of life course SES. For both men and women, four distinct disability trajectories were found though these were different between men and women. In men only, a group comprising 9% of the sample, remained disability free from aged 85 to 90. Despite the disability free trajectory being absent in women, there were similarities in the initial level and progression of the remaining trajectories between the sexes.

Although the effects of SES in mid-life (occupationally based) and late-life (area deprivation) on trajectory membership were attenuated after adjustment for potential confounders, the effect of early-life SES (education) remained, with men and women with the more education (12+ years) being significantly less likely to be in the most disabled trajectories.

As well as associations with SES, the disability trajectories were also found to vary with sociodemographic factors although these relationships were not identical for men and women. The same was true of geriatric syndromes. All markers of inflammation (IL6 TNF-α, CRP) were found to associate strongly with the trajectories for women, but not for men, whilst markers of cellular ageing (DNA damage and telomere length) did not vary by the trajectories for either men or women.

The next chapter of this thesis will aim to bring together the results from the previous four chapters and discuss them in light of existing literature, forming an overall conclusion about the course of disability in the very old.

Table 6.1: GBTM Trajectory Parameters

	TRAJECTORY 1	TRAJECTORY 2	TRAJECTORY 3	TRAJECTORY 4
MEN	**Disability free (MT1)**	**Slight-mild disability (MT2)**	**Mild disability progressing rapidly (MT3)**	**Severe persistent disability (MT4)**
Parameters for disability trajectory				
Intercept	-3·620 (1·307)	3·121 (0·290)	8·565 (0·347)	15·772 (0·526)
Linear age (centred)		0·487 (0·115)	1·390 (0·131)	1·105 (0·215)
Quadratic age (centred)		-0·113 (0·052)		
Parameters for mortality trajectory				
Intercept	-1·485 (0·460)	-1·652 (0·300)	-1·674 (0·760)	-2·011 (1·037)
Linear centred age at previous wave	1·610 (1·049)	0·209 (0·080)	0·095 (0·079)	0·143 (0·073)
BIC	-2532·22			
WOMEN	**Slight-mild disability (FT1)**	**Mild-moderate disability (FT2)**	**Moderate to severe disability (FT3)**	**Severe persistent disability (FT4)**
Parameters for disability trajectory				
Intercept	2·234 (0·265)	6·901 (0·247)	13·420 (0·377)	16·26 (0·837)
Linear age (centred)	0·699 (0·100)	0·957 (0·077)	1·031 (0·165)	1·115 (0·271)
Quadratic age (centred)			-0·232 (0·069)	
Parameters for mortality trajectory				
Intercept	-2·155 (0·365)	-1·470 (0·326)	-2·797 (0·837)	1·789 (2·012)
Linear centred age at previous wave	0·087 (0·153)	0·033 (0·052)	0·179 (0·064)	-0·093 (0·128)
BIC	-4427·65			

Table 6.2: Trajectory affiliations with Sociodemography - MEN

	Men				
	MT1	**MT2**	**MT3**	**MT4**	**p-value**
Housing					
Standard	100.00 (24)	88.89 (136)	86.52 (77)	55.56 (30)	<0.001
Sheltered	0.00 (0)	11.11 (17)	12.36 (11)	9.26 (5)	
Institution	0.00 (0)	0.00 (0)	1.12 (1)	35.19 (19)	
Other	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	
Living Arrangements					
Alone	58.33 (14)	39.87 (61)	43.18 (38)	37.14 (13)	0.7006
With spouse only	37.50 (9)	52.29 (80)	48.86 (43)	51.43 (18)	
With others	4.17 (1)	7.84 (12)	7.95 (7)	11.43 (4)	
Marital Status					
Widowed	54.17 (13)	39.22 (60)	38.20 (34)	36.54 (19)	0.5566
Married	41.67 (10)	53.59 (82)	56.18 (50)	50.00 (26)	
Never Married	4.17 (1)	4.58 (7)	5.62 (5)	9.62 (5)	
Divorced/Separated	0.00 (0)	2.61 (4)	0.00 (0)	3.85 (2)	
Smoking status					
Never smoker	29.17 (7)	24.18 (37)	31.82 (28)	19.23 (10)	0.3978
Current smoker	4.17 (1)	2.61 (4)	6.82 (6)	7.69 (4)	
Former regular smoker	62.50 (15)	68.63 (105)	57.95 (51)	73.08 (38)	
Former occasional smoker	4.17 (1)	4.58 (7)	3.41 (3)	0.00 (0)	
Self-rated health (compared to others of the same age)					
Excellent	26.09 (6)	12.50 (19)	10.11 (9)	4.26 (2)	<0.001
Very Good	52.17 (12)	37.50 (57)	22.47 (20)	25.53 (12)	
Good	21.74 (5)	34.87 (53)	41.57 (37)	40.43 (19)	
Fair	0.00 (0)	13.82 (21)	23.60 (21)	21.28 (10)	
Poor	0.00 (0)	1.32 (2)	2.25 (2)	8.51 (4)	

Table 6.3: Trajectory affiliations with Sociodemography - WOMEN

	Women				
	FT1	**FT2**	**FT3**	**FT4**	**p-value**
Housing					
Standard	89.42 (93)	83.54 (198)	61.26 (68)	27.94 (19)	<0.001
Sheltered	8.65 (9)	14.35 (34)	20.72 (23)	16.18 (11)	
Institution	0.96 (1)	2.11 (5)	18.02 (20)	55.88 (38)	
Other	0.96 (1)	0.00 (0)	0.00 (0)	0.00 (0)	
Living Arrangements					
Alone	76.70 (79)	73.16 (169)	68.89 (62)	73.33 (22)	0.5223
With spouse only	12.62 (13)	15.58 (36)	14.44 (13)	6.67 (2)	
With others	10.68 (11)	11.26 (26)	16.67 (15)	20.00 (6)	
Marital Status					
Widowed	73.08 (76)	67.93 (161)	70.00 (77)	74.63 (50)	0.6146
Married	13.46 (14)	19.83 (47)	12.73 (14)	16.42 (11)	
Never Married	11.54 (12)	8.86 (21)	12.73 (14)	5.97 (4)	
Divorced/Separated	1.92 (2)	3.38 (8)	4.55 (5)	2.99 (2)	
Smoking status					
Never smoker	43.27 (45)	37.13 (88)	44.55 (49)	52.24 (35)	0.3767
Current smoker	4.81 (5)	8.02 (19)	7.27 (8)	2.99 (2)	
Former regular smoker	46.15 (48)	47.26 (112)	45.45 (50)	38.81 (26)	
Former occasional smoker	5.77 (6)	7.59 (18)	2.73 (3)	5.97 (4)	
Self-rated health (compared to others of the same age)					
Excellent	20.75 (22)	8.30 (19)	4.31 (5)	3.92 (2)	<0.001
Very Good	42.45 (45)	27.51 (63)	21.55 (25)	17.65 (9)	
Good	32.08 (34)	41.05 (94)	38.79 (45)	39.22 (20)	
Fair	4.72 (5)	20.52 (47)	30.17 (35)	25.49 (13)	
Poor	0.00 (0)	2.62 (6)	5.17 (6)	13.73 (7)	

Table 6.4: Trajectory affiliations with Geriatric Syndromes - MEN

	Men				
	MT1	**MT2**	**MT3**	**MT4**	**p-value**
Hearing impairment	54.17 (13)	62.34 (96)	67.78 (61)	67.31 (35)	0.536
Visual impairment	12.50 (3)	26.14 (40)	35.56 (32)	51.02 (25)	<0.001
Pain in past month (lasting ≥ 1 days)	33.33 (8)	43.62 (65)	48.86 (43)	47.92 (23)	0.529
Falls in the past year:					
None	66.67 (16)	69.59 (103)	60.23 (53)	38.78 (19)	0.001
1	25.00 (6)	16.89 (25)	19.32 (17)	24.49 (12)	
2	4.17 (1)	8.78 (13)	13.64 (12)	18.37 (9)	
3+	4.17 (1)	4.73 (7)	6.82 (6)	18.37 (9)	
Urinary Incontinence					
None	86.96 (20)	75.17 (112)	67.82 (59)	34.69 (17)	<0.001
Minimal	13.04 (3)	11.41 (17)	9.20 (8)	4.08 (2)	
Moderate	0.00 (0)	7.38 (11)	6.90 (6)	20.41 (10)	
Severe or Profound	0.00 (0)	5.37 (8)	14.94 (13)	36.73 (18)	
Catheterised for past year	0.00 (0)	0.67 (1)	1.15 (1)	4.08 (2)	
Faecal Incontinence	4.17 (1)	3.36 (5)	3.41 (3)	28.57 (14)	<0.001
Depression (GDS-15 score):					
None (0-5)	100.00 (24)	90.73 (137)	77.65 (66)	55.56 (20)	<0.001
Mild or Moderate (6-7)	0.00 (0)	4.64 (7)	11.76 (10)	30.56 (11)	
Severe (8-15)	0.00 (0)	4.64 (7)	10.59 (9)	13.89 (5)	
Cognitive Impairment (SMMSE score):					
Normal (26-30)	95.83 (23)	81.82 (126)	71.11 (64)	33.33 (17)	<0.001
Mild (22-25)	4.17 (1)	15.58 (24)	22.22 (20)	25.49 (13)	
Moderate (18-21)	0.00 (0)	2.60 (4)	4.44 (4)	3.92 (2)	
Severe (0-17)	0.00 (0)	0.00 (0)	2.22 (2)	37.25 (19)	
Body mass index (kg/m^2):					
Underweight (<18.50)	0.00 (0)	3.38 (5)	5.75 (5)	7.89 (3)	0.3592
Normal range (18.50-24.99)	45.83 (11)	55.41 (82)	47.13 (41)	47.37 (18)	
Pre-obese (25.00-29.99)	41.67 (10)	35.81 (53)	33.33 (29)	39.47 (15)	
Obese (30.00-39.99)	12.50 (3)	5.41 (8)	13.79 (12)	5.26 (2)	
Morbidly obese (≥40.00)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	
Disease Count (median (IQR))	1(0-2)	2(1-3)	2(1-3)	3(2-4)	<0.001

Table 6.5: Trajectory affiliations with Geriatric Syndromes - WOMEN

	Women				
	FT1	**FT2**	**FT3**	**FT4**	**p-value**
Hearing impairment	43.40 (46)	60.83 (73)	57.39 (132)	70.49 (43)	0.002
Visual impairment	25.47 (27)	41.53 (49)	45.22 (104)	46.00 (23)	0.001
Pain in past month (lasting ≥ 1 days)	35.24 (37)	62.61 (72)	56.82 (125)	54.35 (25)	<0.001
Falls in the past year:					
None	65.71 (69)	56.90 (66)	63.18 (139)	58.18 (32)	0.4755
1	20.95 (22)	25.86 (30)	20.91 (46)	10.91 (6)	
2	7.62 (8)	7.76 (9)	9.09 (20)	14.55 (8)	
3+	5.71 (6)	9.48 (11)	6.82 (15)	16.36 (9)	
Urinary Incontinence					
None	60.95 (64)	52.51 (115)	43.97 (51)	25.93 (14)	<0.001
Minimal	20.95 (22)	10.50 (23)	8.62 (10)	3.70 (2)	
Moderate	9.52 (10)	13.24 (29)	5.17 (6)	18.52 (10)	
Severe or Profound	8.57 (9)	22.83 (50)	42.24 (49)	46.30 (25)	
Catheterised for past year	0.00 (0)	0.91 (2)	0.00 (0)	5.56 (3)	
Faecal Incontinence	2.86 (3)	11.21 (13)	5.00 (11)	35.19 (19)	<0.001
Depression (GDS-15 score):					
None (0-5)	93.40 (99)	55.45 (171)	32.73 (72)	50.00 (16)	<0.001
Mild or Moderate (6-7)	4.72 (5)	27.27 (30)	10.91 (24)	28.13 (9)	
Severe (8-15)	1.89 (2)	17.27 (19)	6.36 (14)	21.88 (7)	
Cognitive Impairment (SMMSE score):					
Normal (26-30)	90.57 (96)	81.74 (188)	55.00 (66)	30.00 (18)	<0.001
Mild (22-25)	7.55 (8)	14.78 (34)	17.50 (21)	21.67 (13)	
Moderate (18-21)	1.89 (2)	3.04 (7)	17.50 (21)	8.33 (5)	
Severe (0-17)	0.00 (0)	0.43 (1)	10.00 (12)	40.00 (24)	
Body mass index (kg/m^2):					
Underweight (<18.50)	8.91 (9)	7.80 (17)	7.00 (7)	8.33 (2)	0.0542
Normal range (18.50-24.99)	61.39 (62)	50.92 (111)	43.00 (43)	37.50 (9)	
Pre-obese (25.00-29.99)	26.73 (27)	28.90 (63)	36.00 (36)	37.50 (9)	
Obese (30.00-39.99)	2.97 (3)	12.39 (27)	12.00 (12)	16.67 (4)	
Morbidly obese (≥40.00)	0.00 (0)	0.00 (0)	2.00 (2)	0.00 (0)	
Disease Count (median (IQR))	1(1-2)	2(1-3)	2(2-3)	3(2-4)	<0.001

Table 6.6: Biomarker associations with trajectories - MEN

	MEN				
	MT1	MT2	MT3	MT4	p-value
Interleukin 6 (IL6)	25669.92 (14972.83 - 35776.15)	23939.80 (14159.75 - 32648.08)	24145.58 (12442.38 - 33217.52)	21681.20 (11825.72 - 28772.02)	0.7824
Tumour Necrosis Factor alpha (TNF alpha)	584.05 (319.97 - 1072.34)	508.96 (230.13 - 942.57)	619.01 (270.48 - 1333.82)	520.16 (340.72 - 745.01)	0.4877
C-reactive protein (CRP)	2.05 (0.90 - 3.45)	2.70 (1.20 - 6.00)	3.10 (1.80 - 7.20)	3.70 (1.10 - 9.50)	0.1254
DNA damage (%)	41.31 (26.83 - 68.84)	40.27 (19.65 - 63.95)	43.94 (22.93 - 61.41)	41.07 (26.88 - 72.39)	0.3926
Telomere Length (mpb)	3798.54 (3537.96 - 4346.97)	3842.61 (3362.67 - 4497.64)	3978.04 (3630.68 - 4558.12)	3914.72 (3279.87 - 4303.92)	0.2702

Table 6.7: Biomarker associations with trajectories - WOMEN

	WOMEN				
	FT1	FT2	FT3	FT4	p-value
Interleukin 6 (IL6)	17258.61 (6506.94 - 27776.37)	21009.62 (10247.95 - 31017.00)	22605.85 (11776.94 - 32407.01)	21764.77 (13153.22 - 31534.00)	0.0728
Tumour Necrosis Factor alpha (TNF alpha)	391.03 (174.56 - 827.94)	440.07 (195.16 - 878.91)	576.73 (272.98 - 1055.65)	449.15 (269.91 - 857.59)	0.0368
C-reactive protein (CRP)	1.90 (0.90 - 2.80)	2.50 (1.25 - 5.70)	2.70 (1.30 - 7.30)	5.60 (2.20 - 15.10)	0.0001
DNA damage (%)	48.00 (27.79 - 67.94)	45.89 (25.63 - 64.56)	41.05 (24.02 - 65.11)	38.34 (25.24 - 56.06)	0.7142
Telomere Length (mbp)	3752.85 (3330.47 - 4068.17)	3783.30 (3396.10 - 4249.52)	3707.54 (3327.80 - 4142.60)	3532.43 (3104.43 - 4135.04)	0.1303

Table 6.8: Association of trajectories with biomarkers

Outcome: Trajectory membership	Quartile	Men	Women
IL6	0-25	Referent	
	25-50	0.92 (0.49-1.73)	1.74 (1.06-2.85)
	50-75	1.02 (0.54-1.92)	1.92 (1.18-3.12)
	75-100	0.82 (0.44-1.55)	1.86 (1.14-3.04)
TNF - α	0-25	Referent	
	25-50	1.44 (0.77-2.71)	1.70 (1.04-2.76)
	50-75	1.42 (0.75-2.68)	1.71 (1.05-2.80)
	75-100	1.20 (0.65-2.21)	1.85 (1.13-3.02)
CRP	0-25	Referent	
	25-50	1.41 (0.76-2.61)	0.84 (0.52-1.34)
	50-75	1.22 (0.67-2.23)	1.36 (0.83-2.21)
	75-100	2.01 (1.12-3.62)	3.09 (1.91-5.01)
Telomere Length	0-25	Referent	
	25-50	1.60 (0.88-2.91)	1.29 (0.79-2.12)
	50-75	1.30 (0.72-2.34)	0.94 (0.58-1.52)
	75-100	1.39 (0.77-2.52)	0.92 (0.56-1.51)
DNA damage	0-25	Referent	
	25-50	0.66 (0.33-1.29)	1.04 (0.65-1.66)
	50-75	1.26 (0.68-2.33)	0.58 (0.35-0.94)
	75-100	1.07 (0.59-1.93)	1.06 (0.64-1.75)

Table 6.9: Model 1 - Non adjusted model assessing trajectory affiliation with SES

	MEN			WOMEN		
	MT2 vs. MT1	MT3 vs. MT1	MT4 vs. MT1	FT2 vs. FT1	FT3 vs. FT1	FT4 vs. FT1
Education (no. of years)						
0-9	1.02 (0.82-1.27)	1.21 (0.32-4.58)	1.23 (0.26-5.82)	0.98 (0.38-2.53)	1.01 (0.52-1.96)	1.21 (1.01-1.45)*
10-11		Referent			Referent	
12+	0.92 (0.54-1.57)	0.99 (0.21-4.67)	0.69 (0.51-0.93)*	0.93 (0.31-2.79)	0.73 (0.54-0.98)*	0.54 (0.30-0.96)*
Occupational class						
Routine and manual	0.88 (0.39-1.99)	1.03 (0.41-2.59)	1.01 (0.38-2.68)	1.00 (0.45-2.22)	1.02 (0.68-1.53)	1.35 (1.05-1.74)*
Intermediate		Referent			Referent	
Managerial	1.21 (0.45-3.25)	0.84 (0.21-3.36)	0.33 (0.15-0.71)*	0.96 (0.21-4.39)	0.82 (0.34-1.98)	0.33 (0.21-0.51)*
Deprivation (IMD)						
> 75th centile	0.84 (0.21-3.36)	0.98 (0.51-1.88)	1.19 (0.87-1.63)	1.05 (0.81-1.36)	1.06 (0.72-1.56)	1.15 (0.81-1.63)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	0.87 (0.11-6.88)	0.99 (0.51-1.92)	0.42 (0.31-0.57)*	1.02 (0.79-1.32)	0.84 (0.51-1.38)	0.82 (0.56-1.20)

Table 6.10: Model 2 - Model assessing trajectory affiliation adjusted for other SES covariates

	MEN			WOMEN		
	MT2 vs. MT1	MT3 vs. MT1	MT4 vs. MT1	FT2 vs. FT1	FT3 vs. FT1	FT4 vs. FT1
Education (no. of years)						
0-9	0.99 (0.51-1.92)	0.99 (0.48-2.04)	1.09 (0.84-1.41)	1.04 (0.41-2.64)	1.03 (0.46-2.31)	1.12 (0.81-1.55)
10-11		Referent			Referent	
12+	0.92 (0.73-1.16)	0.88 (0.62-1.25)	0.71 (0.55-0.92)*	1.02 (0.51-2.04)	0.62 (0.32-1.20)	0.55 (0.41-0.74)*
Occupational class						
Routine and manual	0.98 (0.42-2.29)	1.12 (0.64-1.96)	1.14 (0.79-1.65)	1.05 (0.59-1.87)	1.03 (0.51-2.08)	1.11 (0.63-1.96)
Intermediate		Referent			Referent	
Managerial	0.91 (0.31-2.67)	0.90 (0.42-1.93)	0.82 (0.29-2.32)	0.85 (0.21-3.44)	0.89 (0.45-1.76)	0.74 (0.39-1.40)
Deprivation (IMD)						
> 75th centile	1.05 (0.52-2.12)	1.06 (0.68-1.65)	1.06 (0.78-1.44)	1.01 (0.42-2.43)	1.05 (0.11-10.02)	1.06 (0.41-2.74)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	1.03 (0.42-2.53)	0.92 (0.52-1.63)	0.86 (0.62-1.19)	1.11 (0.35-3.49)	0.97 (0.59-1.59)	0.91 (0.61-1.36)

Table 6.11: Model 3 - Each covariate adjusted for other SES covariates plus BMI, disease burden and depressive symptomatology :

	MEN			WOMEN		
	MT2 vs. MT1	MT3 vs. MT1	MT4 vs. MT1	FT2 vs. FT1	FT3 vs. FT1	FT4 vs. FT1
Education (no. of years)						
0-9	1.00 (0.53-1.89)	0.99 (0.69-1.42)	1.12 (0.57-2.20)	0.97 (0.35-2.69)	1.01 (0.42-2.43)	1.09 (0.63-1.89)
10-11		Referent			Referent	
12+	0.87 (0.21-3.60)	0.82 (0.54-1.25)	0.80 (0.65-0.98)*	0.93 (0.49-1.77)	0.86 (0.54-1.37)	0.59 (0.42-0.83)*
Occupational class						
Routine and manual	1.15 (0.32-4.13)	1.08 (0.41-2.84)	1.18 (0.39-3.57)	1.06 (0.88-1.28)	1.10 (0.72-1.68)	1.09 (0.76-1.56)
Intermediate		Referent			Referent	
Managerial	1.09 (0.49-2.42)	0.93 (0.42-2.06)	0.87 (0.56-1.35)	0.90 (0.51-1.59)	0.87 (0.67-1.13)	0.86 (0.64-1.16)
Deprivation (IMD)						
> 75th centile	1.03 (0.47-2.26)	1.02 (0.52-2.00)	1.05 (0.43-2.56)	1.00 (0.21-4.76)	1.02 (0.35-2.97)	1.15 (0.87-1.52)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	0.98 (0.35-2.74)	0.98 (0.46-2.09)	0.93 (0.67-1.29)	0.93 (0.19-4.55)	0.93 (0.16-5.41)	0.89 (0.28-2.83)

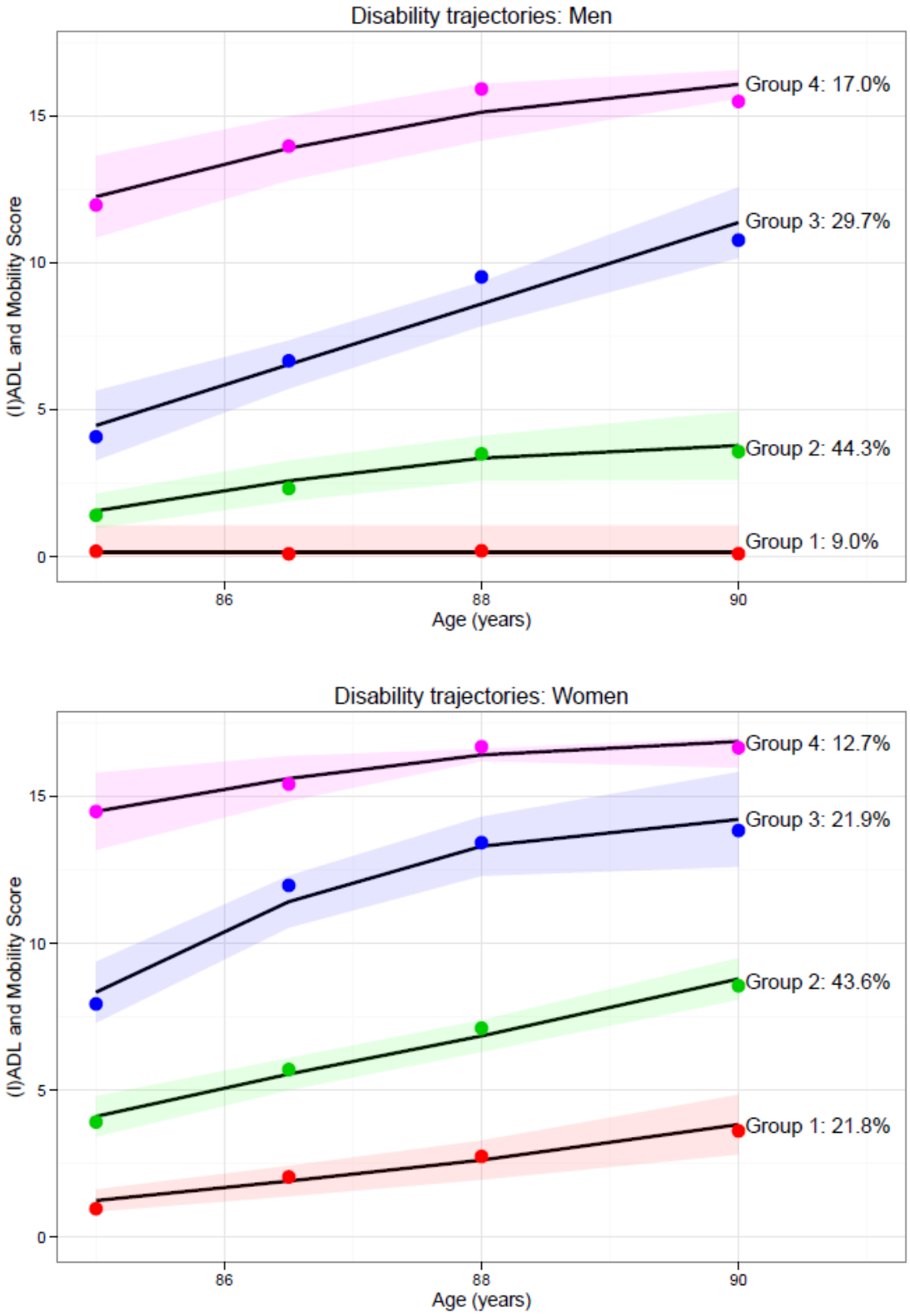


Figure 6.1: Disability Trajectories

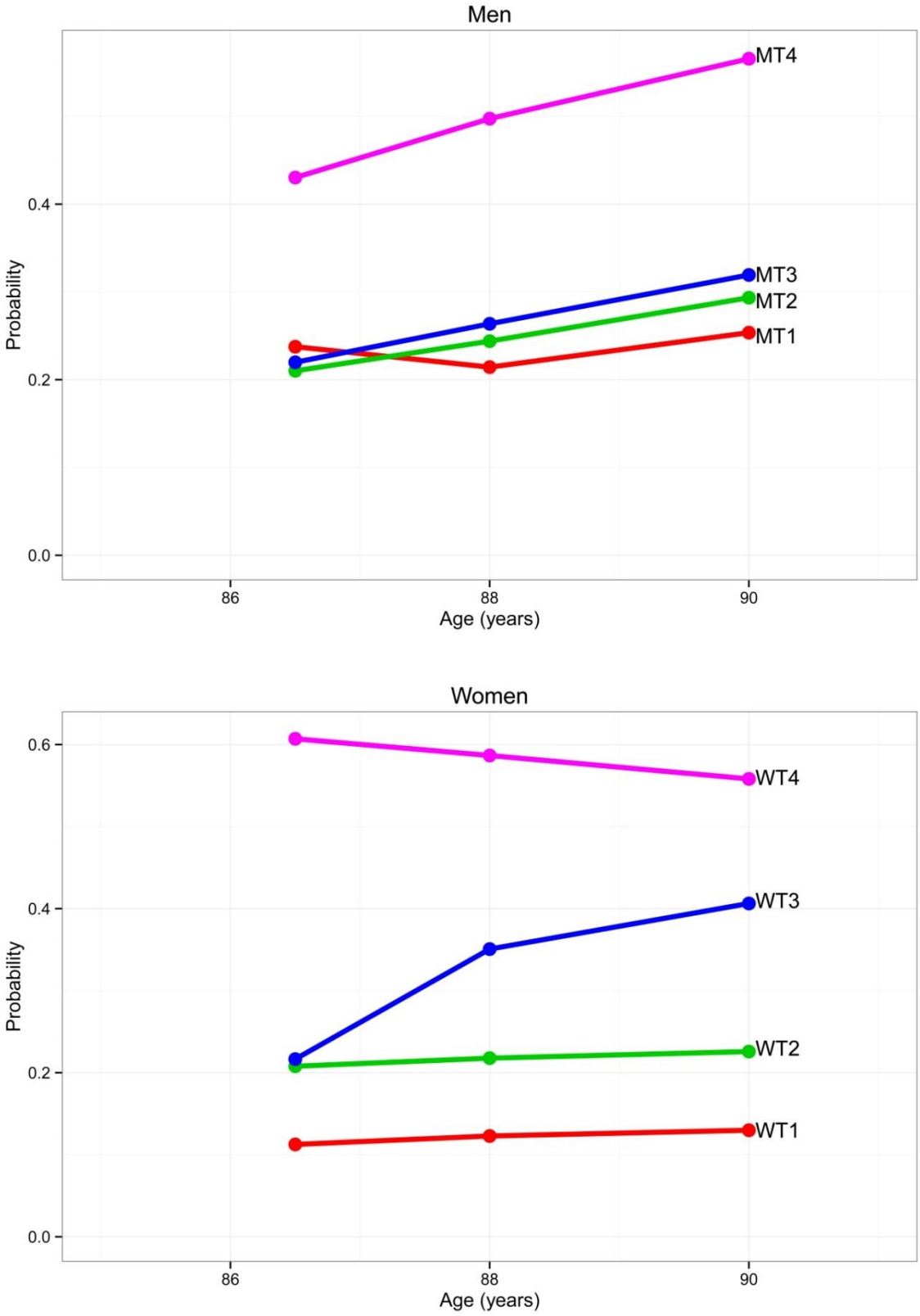


Figure 6.2: Mortality profiles

7 DISCUSSION

7.1 Introduction

Since 1800 we have seen huge increases in life expectancy, largely driven by declining early and mid-life mortality. The consequences of such a decline has given rise to a new phenomenon related to population ageing: declining age specific mortality rates in the very old (Oeppen and Vaupel, 2002). Our ability to understand the complex factors that influence health profiles in the very old are therefore of utmost importance if we are to plan for and deliver services to meet their needs. This is particularly relevant for those people who are living with disability, those close to moving to a disabled state, and for those at risk of shifting to institutional accommodation. Whilst these people may be the most difficult to recruit and retain in epidemiological studies their inclusion is vitally important as they are the primary source of information regarding their care needs. Further attention must also focus on understanding what drives transitions from independent, non-disabled states, to disabled states. It is by delaying such transitions, through effective management of their determinants, that the fiscal cost associated with the ageing population can be controlled and quality of life enhanced. Furthermore, ageing is intrinsically governed by deep biological processes that act over the life course and interact in an assortment of ways with disease mechanisms (often accompanied by considerable multimorbidity), lifestyle factors and behaviours yielding a wide spectrum of health even in the very old. As the heterogeneity of ageing extends to all levels, from the molecular, though to the tissue and organ level and eventually to individuals and populations (Kirkwood, 2002a; Kirkwood *et al.*, 2005), studies which have the ability to capture this variation are needed. Given the lack of knowledge regarding the health of the very old, this thesis adds significantly to the literature in terms of describing the diversity of health in those aged 85 and over, especially in terms of disability and its gender specific phenotype.

This chapter will first take each of the main results chapters (4-6), in order, and discuss them in terms of existing literature. They will then be brought together to discuss what they add to the understanding of disability in the very old, particularly from a public health perspective.

7.2 A hierarchy of loss of function in the very old

The loss of ability in a wide variety of instrumental and basic activities of daily living was found to follow a strong, definitive order in the very old. The ability to cut one's toenails was the first activity that an individual was likely to encounter difficulty with, and the ability to wash face and hands and feeding (gender dependent) the last. Item ordering confirmed previous studies using cross-sectional and longitudinal data (Kempen, 1995; Dunlop *et al.*, 1997; Ferrucci *et al.*, 1998b; Spector and Fleishman, 1998; Jagger *et al.*, 2001b; Njegovan *et al.*, 2001; Haley *et al.*, 2002; Jette *et al.*, 2002; Weiss *et al.*, 2007; Watson *et al.*, 2012) but on a more restricted set of items and predominantly in the younger old. Given this lack of information about the ordering of loss in function in the very old, this sub-study adds considerably to the literature base and confirms that the ordering does not change with age. Gender differences in disability item prevalence and hierarchy were detected in our single birth year cohort. They were expressed through the increased likelihood of women to report difficulty with most activities and a slightly altered hierarchical ordering when compared to men. Women were more likely to report difficulty with tasks that required strength (shopping and heavy housework) whereas men were more likely to report difficulty with tasks that required sustained balance over a period of time (walking). Altering the analytical outcome of the (I)ADL items to dependency (the need for help in completing the activities) instead of difficulty did not alter the conclusions. Initial investigations have shown that, using the methodology for multistate models, each (I)ADL was taken and the predicted probability of moving from a non-disabled state (i.e. no difficulty to difficulty) was calculated at one, two and three years post study commencement. This showed that the probability was greatest for those items at the start of the hierarchy and least for those at the end, thus confirming results found cross-sectionally.

Historical research has shown that the order in which people lose capability in (I)ADLS appears to being with the more items that are more difficulty i.e. the IADLs (Dunlop, 1997; Jagger *et al.*, 2001a; Njegovan *et al.*, 2001; Weiss *et al.*, 2007). This was found to broadly true of the (I)ADLs used in the Newcastle 85+ Study, however there was some overlap between those items that belong to IADL and the ADL domains and the results were found to be more consistent with the domains of disability outlined by Ferrucci *et al.* (Ferrucci *et al.*, 1998b). The domains outlined by Ferrucci (and denoted A-D in figure 4.3) are a combination of the (I)ADL and mobility

items into domains which reflect items that have a similar underlying impairments. The first of these domains is that which require complex manual dexterity and standing and balance. Examples of IADLs which related to this domain are cutting ones toenails and heavy housework. The next activities lost are those which belong to the domain that requires the capacity to walk long distances and the equivalent tasks in the Newcastle 85+ study being shopping, using steps and walking 400 yards. The next domain in deceasing difficulty relates to activities that require good standing balance and upper limb control and includes the items move around the home, transfer from chair/toilet/bed and dressing. The final domain, and the least difficult, requires good upper limb control in a seated position, these items being washing face and hands and feeding. There were two items that appeared out of step with our hierarchy and that determined by Ferrucci, these being heavy housework and light housework. A possible explanation for this discrepancy is that the perceived meanings of these tasks and their inherent nature may have evolved over time, more so than for other activities.

We had a small proportion of our sample (n=71, 8.5%) who had a diagnosis of dementia and these participants may lose ability to perform activities independently in a different order to those without dementia, for instance they may be able to walk 400 yards but may not be able to dress themselves. However, we repeated all analyses excluding those in institutions and the conclusions were unchanged. Nevertheless, when we originally included items more dependent on complex cognitive ability than physical ability ('managing money' and 'managing medication') we found that they did not satisfy all of the underlying assumptions of the scaling method and their subsequent exclusion strengthened the scale formed although the remaining items may be viewed as being more 'physical'.

The disability scale formed from the hierarchy performed well when examined alongside known predictors of disability (Stuck *et al.*, 1999). The ordering of loss of activities is of potential use to others selecting activities to measure a range of severity of disability both in the research and clinical setting.

7.2.1 The spectrum of 'difficulty' using the hierarchic scale

One of the key questions that must be asked from the hierarchic scale is whether the underlying continuum that (I)ADLs measure effectively captures a graduated decline

in function across the entire disability spectrum. The simple answer to this question from the Newcastle 85+ data is, no. The procedure used for calculating the 'difficulty' of each of the (I)ADLs showed a steep drop in the level of difficulty between items which measure in the instrumental aspect of disability (i.e. the capability of an individual to preserve independence within the larger community) versus the basic element (activities related to daily tasks and survival). This is highlighted in chapter four (figure 4.2) by the steep decline in the plot where the two elements (IADLs and ADLs) diverge in their difficulty levels. Although the Mokken procedure confirmed that all items do measure a single latent trait, when shifting from the instrumental activities of daily living to basic, there is very little capturing disability across this shift, although this effect was less pronounced in men than women. It suggests that there is room for improvement to capture disability in this intermediate phase of the disability spectrum, which could be achieved by the introduction of other items whose level of difficulty effectively lies between the two.

Gaps in the spectrum of 'difficulty' for the hierarchy of disability are not limited to this study, but have reported in numerous other age groups too (McHorney *et al.*, 1997; Spector and Fleishman, 1998; McHorney and Cohen, 2000; Fortinsky *et al.*, 2003; Dubuc *et al.*, 2004). Notwithstanding that the majority of these studies do not originate in the UK, they could provide some important insights for the introduction of items that fill gaps in the 'difficulty' where items used in the Newcastle 85+ study do not as they all have items that are not in common with each other, potentially measuring 'difficulty' at a level not achieved using the 17 items of this study.

In contrast, there are some items in the ADL spectrum that are redundant i.e. they are measuring disability at approximately the same level of difficulty and so some of these items could be removed to simplify the scale even further. However, not removing the items also has its advantages in terms of allowing adaptive testing with items that are more suited on an individual level (Meeks and Murrell, 2001).

Furthermore, a question persists regarding disability at the extremes of the spectrum. One cannot assume that the ability to cut toenails is the start of the disability process and neither the loss of ability in eating or washing face and hands the end (less so in this case). There are clear ceiling and floor effects using the items from the Newcastle 85+ Study and this is highlighted by the histogram of the disability score at

every wave of the study (chapter 4, figure 4.1). To extend the disability spectrum into the realm preceding the loss of the ability to cut ones toenails has been considered. This was measured in terms of the ability to run half a mile, or hike several miles, or walk on a slippery surface, or walk a brisk mile, or run to catch a bus (Haley *et al.*, 2002). However, this takes the measurement of disability beyond daily activities and though they may appear less appropriate for the very old, some of these items may separate out the highest functioning people from the rest and from whom much could be learned in terms of how they have maintained such high functional capacity where others have not.

Using a multi-state model for each (I)ADL, the probability of moving into a disabled state over a five year period (2006-2012) was calculated. The hierarchy that was determined from the cross-sectional data showed the same pattern longitudinally, for both men and women. However, these results are limited insofar as each (I)ADL was mutually exclusive. What is needed, ideally, is a model with 18 states; one for each (I)ADL and another for death, and these states need to be linked through the transition intensity matrix. This was not possible with the Newcastle 85+ data as information on the movement between the states was insufficient.

7.3 Transitions to disability and death

The goal of this sub-study was to determine potential reasons for the gender disability survival paradox in the very old, in particular the role of specific diseases on disability and mortality. The investigation was approached with a single question in mind: was the mortality and disability difference between men and women primarily driven by gender variation in the type and impact of diseases?

We found that at age 85 women already had a higher prevalence of disability than men and were more likely to have arthritis and hypertension. Despite women having marginally less CVD and cardiac disease than men at age 85, these conditions resulted in higher disability scores in women at baseline and prospectively were more likely to be disabling in women. Respiratory disease was also significantly more disabling in women than men although prevalence at age 85 was similar for men and women. Thus from age 85 women spent longer with disability than men overall (on average 2.2 years) and by disease. No gender differences were found in disease-specific recovery from disability and only for cancer was there a gender difference in

disease-specific risk of death. These findings were not a consequence of differences in education, current socio-economic status (as measured by IMD) or the presence of comorbidity. Neither were they due to men with more disability dying or withdrawing between assessments as comparison of disability scores in the interview prior to death or withdrawal again demonstrated excess disability in women over men. Thus we suggest that the disability-survival paradox in the very old is at least partly due to gender differences in the type and disabling impacts of diseases.

Earlier studies, mainly in younger age groups, have found that women are significantly more likely than men of the same age to have disabling rather than fatal diseases (Gold *et al.*, 2002; Case and Paxson, 2005; Whitson *et al.*, 2010). In this study, very old men have a marginally greater prevalence of diseases which are more likely to kill (cardiac disease, CVD and cancer), and women a higher prevalence of the chronic diseases (arthritis and hypertension). Nevertheless, this difference did not always translate to increased disability incidence or death. Arthritis was more disabling for men and cardiac disease for women, whilst cancer and cognitive impairment were the most fatal diseases for women (after becoming disabled). We can confirm that very old women (85+) do have a significantly greater prevalence of chronic diseases (arthritis, hypertension). Furthermore, the presence of certain fatal diseases increased the likelihood of incident disability more for women than men and increased the likelihood of death from a non-disabled state more for men than women. The presence of arthritis, cardiac disease, diabetes and cognitive impairment was significantly disabling for both genders and CVD and respiratory disease for women only. This is generally consistent with previous findings (Kim *et al.*, 2013) although in our study CVD and respiratory disease were significantly disabling in women only, perhaps caused by slight differences in criteria considered for a CVD diagnosis that may favour women compared to other studies. Furthermore we found cardiac disease, CVD, and respiratory disease to be more disabling for women compared with men whilst cognitive impairment was similarly disabling in both genders. Diabetes was also disabling for both genders, however the impact was noticeably worse for men (HR: 3.0, 95% CI: 2.4-3.8) compared to women (HR: 1.7, 95% CI: 1.3-2.2) (p=0.001).

Once health deteriorates, mortality rates increase more for men than women (Doblhammer and Hoffmann, 2010) and this is revealed by the impact of certain

diseases where some are disabling for women but detrimental to survival for men. Men who encounter diseases which increase mortality could be accelerated through the disability pathway (Verbrugge and Jette, 1994) (and ultimately death), however the time intervals of our study are too wide to capture this potential accelerated transit. Nevertheless, if, as posited, men traverse the disablement process faster than women once they encounter disease, it would further suggest that they do not just 'age faster' biologically than women (Blagosklonny, 2010). We suggest that these results point to two different biological mechanisms driving the gender disability-survival paradox: the difference is partially caused by a female heath disadvantage as well as being accompanied by a female mortality advantage, consistent with other findings (Strawbridge *et al.*, 1992; Ferrucci *et al.*, 1996; Thielke and Diehr, 2012). Our results suggest that the potential acceleration through the disablement pathway for men may be caused by the gender-specific effect of disease (and severity) and/or its potential subsequent sequelae. Alternatively, it could be that men and women follow different routes through the disability pathway and thus women will, intrinsically, always show more disability than men at a population level (Gorman and Read, 2006). Exploration of the biological mechanisms underlying the gender differences may assist our understanding and point the way to interventions to prevent or ameliorate the disabling effects of diseases.

One potential avenue, for exploration and explanation, is that which relates the survival paradox to the theory of The Disposable Soma (Kirkwood, 2000; Kirkwood, 2002b; Kirkwood, 2002a; Kirkwood, 2010). The foundation of this theory reflects that an organism has a finite flux of energy at its disposal and, under the pressure of natural selection, it must optimally allocate this energy to secure the highest biological fitness (ultimately, the capacity to produce viable progeny for future generations). As energy is limited, the various biological functions the organism needs to perform (growth, maintenance, reproduction, etc.) cannot all be maximised and so some functions must be traded off against others. In the case of the gender disability survival paradox, it is suggested that this trade-off is different in men and women. From an evolutionary perspective the reproductive roles of male and female animals are somewhat different biologically. Among mammals, which of course include our own species, females have evolved to give birth to children, then suckle the infant and care for them until early adolescence. Males have evolved to secure territory and maintain this and other resources such that their offspring have the best

possible chances of survival and in so doing maximise mating potential. As such, it is important for males to invest in maintaining reproductive capacity whilst they still have the ability to defend their families and territory, whereas females invest more in in maintaining biological function to care and nurture their children. Thus, the important thing for men is mating success whereas for women it is to raise children to adulthood and they will invest more energy resources in health maintenance. In short, the female soma is somewhat less disposable than the male soma. This essentially is a quid pro quo of two biological processes - somatic maintenance and reproduction - where men invest more in reproduction and less in somatic maintenance and women more in somatic maintenance than reproduction (Stoehr and Kokko, 2006). For humans, there are of course social and cultural differences that also affect the differences in health and longevity. Nevertheless, the biological mechanisms that govern ageing and health are buried deep within gender specific biology. As well as hormonal differences between men and women, some suggest gender-specific differences, primarily related to maintenance of immune function, could impact the gendered expression of disease and thus set the scene for the disability-survival paradox. Early results from one study support this assertion. Nunn *et al* have reported positive associations in sex difference and immune function and similarly gender differences in investment in mating (Nunn *et al.*, 2009). However, there is very little (if any) other data that can be used to test this hypothesis.

7.4 Trajectories of disability

The goal of the third sub-study was to use group-based trajectory modelling to investigate whether distinct disability trajectories were present for very old men and women, and the effect of life course SES on the trajectories.

Four distinct disability trajectories were evident for men and women, differentiated both by the initial level of disability and the pace of progression. Only in men did we detect a group (comprising 9%) who remained free of disability from age 85 to 90. Despite the disability free trajectory being absent in women, there were similarities in the initial level and progression of the remaining trajectories between the genders. Trajectories MT2 and MT3 for men (slight to mild disability and mild progressing to moderate respectively) were equivalent to the first two trajectories in women (FT1 and FT2), whilst the last trajectory for men (MT4: severe persistent disability) was between the final two trajectories for women (FT3, FT4), these being differentiated by

initial disability level (moderate versus severe) but all showing the effect of reaching a plateau in disability level by age 90.

There is little research examining disability trajectories, and even less that focuses on the very old including those living in institutional care. Using similar techniques to ours to account for decedents but with fewer measures of ADL limitations, a study of the very old in China also identified a group of consistently non-disabled men between the ages of 80 and 90 (Zimmer *et al.*, 2012), lending credence that this able group of men may exist in other populations regardless of geographical location. On the other hand older people surviving with persistent severe disability, as ours, have been identified in the US, although this study was restricted to community-dwelling older people aged 70 or more years interviewed monthly, not accounting for mortality (Gill *et al.*, 2010). Disability has been found to be a dynamic process over short periods of time and we have shown that this dynamism relaxes long term to form distinct trajectories. The number of trajectories we found is broadly consistent with other literature in younger ages and they are developmentally similar (Hardy *et al.*, 2005; Gill *et al.*, 2013a; Han *et al.*, 2013). The analyses revealed a disability-free trajectory in men but not women, and a persistently-disabled trajectory in women but not men; these gender differences suggest that analysis of men and women together might mask gender specific trajectories.

The analytic technique, group-based trajectory modelling, accounted for non-random subject attrition (mortality) and this reaffirmed that mortality and disability are intricately linked. As the level of disability increased within a trajectory, mortality also increased with its functional form aligned with that of the disability trajectory, i.e. mortality was a function of disability severity. Although male mortality is known to exceed that of women of the same age, the probability of death occurring before participation in the next wave was almost identical for men and women in similar trajectories. For example men in MT3 and women in FT2 both had a 22% chance of dying prior to wave 2 (age 86.5 years). It may be possible that, as the more acutely fatal conditions become less common, and men suffer long-term disabling conditions, that their mortality experience begins to resemble that of women. This would explain, at least in part, the more rapid increase in male compared to female life expectancy and the subsequent narrowing of the gender gap.

Although the effects of SES in mid-life (occupationally based) and late-life (area deprivation) on trajectory membership were attenuated after adjustment for potential confounders, the effect of early-life SES (education) remained, with men and women with the more education (12+ years) being significantly less likely to be in the most disabled trajectories.

The impact of SES on future health and functional status is widely researched in the younger old but there is a dearth of information in the very old. Early-life SES (education) still determines disability trajectories after age 85. Though mid (occupation) late-life SES (deprivation) gave similar pictures when assessed individually, only education remained significant when all SES variables were included and confounders adjusted for. Consistent with other research, having more education was significantly associated with less disabled trajectories at aged 85, irrespective of gender (Freedman and Martin, 1999; Hayward and Gorman, 2004; Vass *et al.*, 2005; Taylor, 2010). Our results lend credibility to the cumulative disadvantage hypothesis whereby those disadvantaged by less education in early life are potentially exposed to a greater degree of social inequality thereafter, and suggest that this inequality reaches right through the life course, influencing disability pathways beyond age 85 and is consistent with research which has shown that early life SES associated with inequalities in physical health in those aged over 75 (Ploubidis *et al.*, 2014). Conversely, we found no evidence that biological forces move to neutralise the impact of SES disparities in the very old (i.e. the age as leveller theory) and that disability in very late life is not simply explained by a person's disease profile. This suggests that future cohorts of very old people may be less disabled since they will have enjoyed more years of education.

Of the five biomarkers that were considered for an association with disability, none of them were significant for men. However, all three of the inflammatory markers were statistically significantly associated with disability trajectories for women, the direction being the greater their level of inflammation the more likely they were to belong to the most disabled trajectories. Whether these markers have any utility in predicting future disability in women is still unknown, however this study has shown that there is a direct association between the two and this is not mediated through or confounded by disease burden, BMI and depressive symptomatology. Whilst it was a surprising result that none of the biomarkers was found to be significant in men, this could be

related to The Disposable Soma theory (§7.3). Could it be that men do not have the same inflammatory response potential as women due investment in fertility? Could this also be the reason that men die off faster than women, if they no longer have the immune capability after investing more in fertility right throughout the life-course? These are questions that are still outstanding. The results do point the way to a potential avenue for further exploration of the biomarkers, especially for women as a potential mechanism to detect preclinical disability. Of the markers considered IL6 and TNF-α were associated with every trajectory whereas CRP was only associated with the most disabled trajectory. In that vein, it may be sensible to suggest that further investigation should focus on IL6 and TNF-α as they have a greater sensitivity to detect lower levels of disability whereas CRP does not. Furthermore, biological molecules that have the potential to detect preclinical disability are not limited to the five considered here. The Newcastle 85+ Study is unique in the breadth of biomarkers that it collected and that could be used to look for associations with disability and it may be that a totally different class of markers may be associated with disability for men, but this is as yet unknown from a longitudinal perspective.

7.5 Applicability to Public Health and Clinical Practice

In 1980, Fries *et al* posited the theory of compression of morbidity. Put simply, this states that as life expectancy increases then the age of onset of chronic conditions needs to rise at a faster rate if we are to witness compression (Fries, 1980) i.e. people spend less of their remaining life times in ill-health. To date there has been little evidence of this within the UK, mainly because the disability question routinely used has not covered the spectrum and severity of disability. The use of this type of scale has the potential to assess compression of morbidity using (I)ADLs and we call this *compression of functional decline* (CFD), which is a variation of the compression of morbidity theme, recast in disability terms.

The hierarchy has shown that once a person joins the disability process, it generally begins at the most difficult end of the scale i.e. difficulty cutting toenails and the journey from then will follow the hierarchy as outlined in the previous section. By using this hierarchical property, a system of managing disability on this basis is proposed. At an individual level, allowing for targeted interventions dependent upon where person currently is in their disability 'journey' could be split into three intervention intervals, as shown in the redefined figure below (figure 7.1). Results of

this analysis could provide information to help identify older people at risk of functional decline and for the allocation, and prioritisation of, community services and social support to enable independent living for as long as possible which is important for future ageing populations (Khaw, 1999).

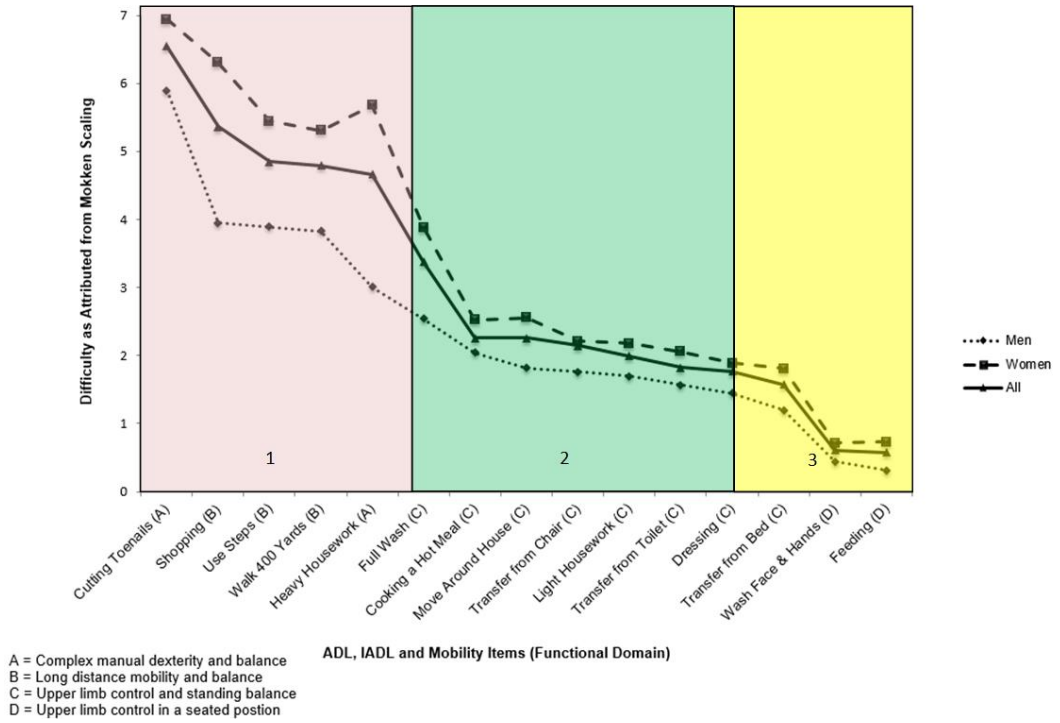


Figure 7.1: Hierarchy of disability - three interval

Stage 1 of the disability 'journey' generally involves those activities that require complex manual dexterity and balance and so people who have difficulty with these items could be targeted with interventions that focus on this functional area. Areas of exercise that concentrate attention on *strengthening body structures* that use this functional domain could be beneficial in terms of regaining or maintaining IADL ability. Stage 2 represents the threshold between items which are IADL and ADL items, signalling a more severe stage of the disability process and relates to the use of functional body domains that are focused around long distance mobility, upper limb control and balance. It is at this stage that interventions should be made available to help people maintain independence within their community through the use of *assistive technologies and environmental modifications*. These technological or environmental changes should be designed to maintain function in (I)ADLs. Finally, stage 3 is where a person is likely to require residential care or at least daily care from another individual. Although it is important that this form of care is made available, the premature use of the staging system of interventions must be avoided.

The use of interventions that overcompensate for a person's disability is likely to accelerate their decline and hasten their transit to a more severe stage of disability. In contrast, accurately targeting interventions is likely to maintain function within that disability domain for longer and therefore delay movement to more severe levels of disability and is consistent with other research (Keevil *et al.*, 2013; Pahor *et al.*, 2014). This approach has the potential to increase time spend in the least disabled end of the spectrum and decrease time at the most disabled end if life expectancy is not increased.

While it is an interesting finding that we discovered 9% of men remained disability free over the course of the study, it is important to note that all other participants showed increasing levels of disability over time. If these trajectories remain static over the course of the next fifteen years (to 2030) and with the increases in the very old population (aged 85 and over: 47.3% for men and 38.6% for women) we will see increases in the region of 50,000 people (in the UK) who belong to the most disabled trajectories (WT3/MT3-WT4/MT4). This will have important implications for policy makers and health care providers to ensure services have the capacity to cope with this increase. However, further exploration of the trajectories in terms of their disease, syndromes and psychosocial profile could yield important information (in terms of aetiology and identification of risk factors) and increase our understanding of the disability process, leading to potential interventions that could positively augment the disability trajectories themselves.

7.5.1 The role of disease

In the Newcastle 85+ Study, few recoveries from disability were observed regardless of the presence or absence of specific diseases, and were particularly low in the presence of cognitive impairment. Indeed cognitive impairment was detrimental for disability incidence, recovery and mortality for both genders as previously found (Stuck *et al.*, 1999; Kim *et al.*, 2013; Takata *et al.*, 2013). Gill *et al* analysed trajectories of disability on a monthly basis (Gill *et al.*, 2009) and showed that among people in advanced stages of dementia, 67.9% had persistent severe disability. Results from this sub-study similarly showed that those who became cognitively impaired moved swiftly into disability and then death. This adds to the already strong argument for better preventative care in those at higher risk of developing cognitive impairment, especially as projection modelling from large cohort studies has

predicted the link between ageing populations, dementia and disability. Despite concerns about screening for mild cognitive impairment and dementia (Le Couteur *et al.*, 2013) the very old should perhaps be considered a 'high risk' population worthy of targeted case finding, in view of the findings and the fast progression from cognitive impairment to disability (Jagger *et al.*, 2009). Furthermore, cognitive impairment was shown to be the most disabling disease, confirming its importance as a primary determinant of disability (Der Wiel *et al.*, 2002). Using the same measure of cognitive impairment, a UK study reported that its elimination would save around 3.5 total life years and 4.3 years free of disability at age 65, and therefore with a greater impact on disability. In terms of slowing the deterioration in global functioning of people with dementia, anti-cholinesterase drugs have been shown to be cost-effective in both the early and moderate stages of Alzheimer's disease (Bond *et al.*, 2012), with recent evidence showing benefit also in advanced stages (Howard *et al.*, 2012). Evidence is growing around the effectiveness of some non-drug interventions, such as cognitive stimulation in routine dementia care, although there remains uncertainty about the most cost-effective way of delivering such interventions in practice. There is also an increasingly strong argument for better preventative care in those at higher risk of developing dementia. Based on the findings this may be particularly the case for women. More timely diagnoses would lead to earlier intervention which may delay the onset of significant disability from the moderate and advanced stages of cognitive impairment.

Greater fatality in men with respiratory disease (with no disability) may explain the greater disabling impact observed in women, by means of accelerated transit through the disablement process to death for men, a process for which we found no evidence in women. However the greater disabling impact of cardiac disease and CVD in women cannot be explained this way. Global estimates of the prevalence of angina have been shown to be significantly greater for women but men diagnosed with the same disease have an excess MI (Hemingway *et al.*, 2008). Whilst little is known about the etiological causes it could go some way to explain our results since, if men diagnosed with angina are at greater risk of MI (Bittner, 2008) compared with their female counterparts, they may be more likely to die before we could detect disability. These results indicate that cardiac disease is disabling for both men and women but such men have increased mortality whilst this is not true for women. However, once disabled, men and women with cardiac disease are more likely to die than their

counterparts without the disease. This suggests that care packages for those with cardiac disease should be tailored towards reducing mortality in men and reducing disability in both genders.

7.6 Strength and limitations

We collected information from over 800 older people aged 85 years of age on their situational disability (questions being framed as 'can you' rather than 'do you') from 17 IADLs, BADLs and mobility items, a much larger number than previous studies and with minimal missing data. The Newcastle 85+ Study has a broad range of health measures and is representative of the larger population of older people in Newcastle upon Tyne (Collerton *et al.*, 2009).

A major strength of the study is the large number of individual (I)ADL items constituting the disability score, thus providing a greater spectrum of disability; validation of the self-report ADL items with the objectively measured TUG; comprehensive follow-up of the study participants with little attrition other than death; and the study design of a single birth cohort of a total population (community dwelling: inclusive of those living in care homes (nursing/residential) who are socio-demographically nationally representative (Collerton *et al.*, 2009).

Unlike other studies, our population came from a single birth cohort with a high response rate and included those in institutions. Thus the gender difference we found in the order of loss of activities was not due to the greater average age of women compared to men in general older populations. Inclusion of those in institutions where there is a high prevalence of dementia may be viewed as a limitation.

Gender differences in self-reported disease were avoided in our study, as disease was ascertained from general practice records; however this can be viewed as both a strength and a limitation. Whilst in general women are more likely to consult health professionals than men, general practitioner consultation rates among the very old are high overall, and in our study did not differ between men and women. However we had previously found that women had lower rates of outpatient attendance than men (Collerton *et al.*, 2009). Our diagnosis of disease was an 'ever' diagnosis (with the exception of cancer which was within the previous five years only) and we did not have information on disease severity, though analysis of disease duration showed no

significant gender difference. Given disease was ascertained from general practice records, there may have been gender differences in undiagnosed disease. Through further measurements in the health assessment we have explored rates of undiagnosed disease for diabetes and hypertension and found rates of undiagnosed diabetes were low with no gender difference and, though the prevalence of undiagnosed hypertension was high (based on a single-occasion blood pressure measurement) again no gender difference was detected (Collerton *et al.*, 2009).

Given that only 19.4% of the sample had no disability at baseline, it may be that the interpretation of the impact of diseases on disability incidence should be treated with caution. This is particularly true for diabetes where the effect is large. There are inherent difficulties examining the impact of disease on disability incidence in the presence of high levels of both. However, the method used (multi-state modelling) analyses the impact of transitions which allow for recovery, therefore potentially increasing the number of transitions per person and strengthening statistical power. An alternative method would have been to examine the impact of diseases on disability progression and incidence together – extending it to at least a four-state model although in this case more information would be needed on the transitions to and from the various disabled states, information that was lacking in the Newcastle 85+ dataset due to only having four time points. This limited the choice of model to one of incidence *or* progression and given that the progression of disability would be investigated through GBTM, the model for incidence was chosen. Furthermore, given the age of the participants and their increased mortality risk, a method was chosen that allowed one to incorporate this into the analyses such that any results were not confounded by mortality. Nevertheless, it is acknowledged as an important and significant line of investigation and will be considered for future analyses. This will be discussed further in terms of trajectories analysis (§7.7).

The method chosen to investigate trajectories of disability was made in the hope that this would have the capability to detect trajectories with different shapes and directions. Other studies have shown a trajectory that displayed a rapid decline over time (Gill *et al.*, 2006; Gill *et al.*, 2013b; Gill *et al.*, 2015). Although this trajectory was visible in the Newcastle 85+ Study with five trajectories, there was insufficient statistical power to justify including this trajectory i.e. it did not significantly reduce the BIC to qualify for inclusion.

In section 6.2 I posed the question: 'are there meaningful subgroups of individuals within a population whose developmental trajectory (by whatever measure of health) is unlikely to be identified ex-ante by a given set of predictor variables?' The answer to this question is equivocal based on the results from the four waves of the study. It is unlikely that those men who remained disability-free over the course of the study would have been detected by any other method. However, it was disappointing that the analysis was limited by the statistical power to detect further trajectories that are unlikely to been identified ex-ante from a given set of predictor variables – particularly a rapidly declining trajectory. Nevertheless, further data from the study is due to be collected and it is hoped that this will add strength to fully elucidate further trajectories. In addition, further analyses could be conducted to examine potential reasons for particular trajectories. Moreover, once more data from the study becomes available and more people have died, it may be more sensible to change the temporal metric to time-to-death.

Although the time interval between disability measures was only 18 months for the first three study waves, we may have missed some disability movements which could have resulted in fluctuating trajectories. However such fluctuations may be noise around an otherwise steady downward progression. Secondly, the study relied on proxy measures of disadvantage earlier in life (education and occupation) in contrast to cohort studies which follow individuals from birth and which can collect contemporaneous data to measure disadvantage. Education and occupation are unlikely to be subject to recall bias but they cannot capture the whole picture of early-life disadvantage, however it is recognised that better measures of life course SES are needed (Grundy and Holt, 2001).

7.7 Future research directions

The Newcastle 85+ Study dataset offers a unique insight into ageing in the very old from many perspectives. Future work from this thesis can take a variety of directions, some of which are detailed below.

i) **The impact of disease on the change in disability score:** This investigation would build upon the analysis conducted in chapter 5. As has been discussed, there are difficulties in interpreting the impact of disease on disability incidence when the prevalence of both is high. Future analyses would focus on the change in disability score over the course of the study and the impact that disease

diagnoses have on this outcome. Further thought would be needed to determine the methods used for this analysis, the time frame over which it would be considered and how mortality would be incorporated.

ii) **The time to onset of (I)ADLs:** The work on the hierarchy of disability has provided important insights about the order that people lose function with (I)ADLs. However, it is limited insofar as it does not capture a temporal aspect to the process, in terms of the interval between items, and whether some are lost together, close in time. Future work intends to look at the time interval between the loss of (I)ADLs by extending the methodology of multistate modelling (§5.2.1) in other cohort studies with a wider age range but shorter intervals between assessment.

iii) Utilising the hierarchy as a tool for targeting interventions:
It has been discussed in section 7.2 that the hierarchic scale could be adapted for targeted interventions dependent upon where a person currently is on the hierarchical scale in terms of their disability and the speed through which they are progressing. A system could be developed using the three stages of; strengthening body structures, assistive technologies and the need for care in the home, alongside a health assessment if progression is deemed to be faster than expected. It is of interest to see if using this system would help individuals maintain functional capacity and thus reduce the time spent in care.

iv) Crossing the Rubicon of disablement: Is there a point at which a person becomes so disabled that they have no possibility of recovery? Does this take place at a certain point in the hierarchic scale? Is this related to the loss of function in certain body structures? Is this gender specific and how is it phenotypically expressed? Answers to these questions would inform the potential for and timing of different interventions.

v) The influence of joint pain on the incidence and progression of disability:
Studies of the very old have estimated the prevalence of joint pain to be between 12.9% and 63.1% (Bagge *et al.*, 1991; van Schaardenburg *et al.*, 1994; Odding *et al.*, 1995; Al Snih *et al.*, 2001; Donald and Foy, 2004). Cross-sectionally, in older individuals, disability and functional limitation is increased in those with pain

and arthritis (Dunlop *et al.*, 1998; Onder *et al.*, 2006; Weaver *et al.*, 2009) and these individuals have been shown to develop functional limitation many years earlier (Covinsky *et al.*, 2009). However, there are limited longitudinal studies on the association of musculoskeletal pain with the incidence and progression of disability and even less so in the every old. Pain was one of the factors that was associated with the disability trajectories in women but not in men. Further investigation could inform other questions to ask alongside position on the hierarchy.

vi) **Assessing the utility of biomarkers as predictors of incident disability and progression:** This thesis has already demonstrated the disabling effect of different diseases, but could they be picked up earlier through biomarkers? Initial investigations have shown an association between some of the inflammatory biomarkers and trajectories of disability, but only for women. In addition other biomarkers were associated with disability but only cross-sectionally (Martin-Ruiz *et al.*, 2011). The Newcastle 85+ Study has a range of over 70 biomarkers which provide a rich source to explore the potential of individual biomarkers (or combinations) that could be combined with findings validated in other cohorts.

APPENDIX A

Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study

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RESEARCH

Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study

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ABSTRACT

Objectives The Newcastle 85+ Study aims to systematically study the clinical, biological, and psychosocial attributes of an unselected cohort of 85 year olds and to examine subsequent health trajectories as the cohort ages; health at baseline is reported.

Design Cross sectional analysis of baseline data from a cohort study.

Setting Newcastle upon Tyne and North Tyneside primary care trusts, United Kingdom.

Participants 1042 people born in 1921 and registered with the participating general practices.

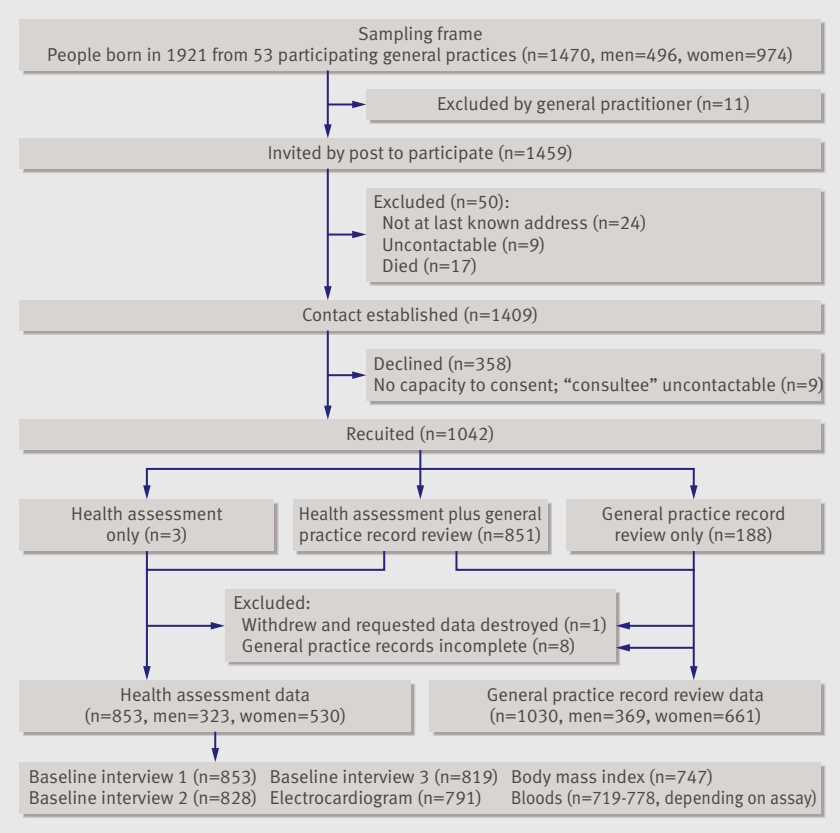
Main outcome measures Detailed health assessment and review of general practice records (disease, medication, and use of general practice services); participants could decline elements of the protocol.

Results Of the 1453 eligible people, 851 (58.6%) were recruited to health assessment plus record review, 188 (12.9%) to record review only, and 3 (0.2%) to health assessment only. Data from record review are reported on a maximum of 1030 and from health assessment on a maximum of 853; individual denominators differ owing to withdrawal and missing values. Of the health assessment sample (n=853), 62.1% (n=530) were women and 10.4% (n=89) were in institutional care. The most prevalent diseases were hypertension (57.5%, 592/1030) and osteoarthritis (51.8%, 534/1030). Moderate or severe cognitive impairment was present in 11.7% (96/824) of participants, severe or profound urinary incontinence in 21.3% (173/813), hearing impairment in 59.6% (505/848), and visual impairment in 37.2% (309/831). Health assessment identified participants with possible disease but without a previous diagnosis in their medical record for hypertension (25.1%, 206/821), ischaemic heart disease (12.6%, 99/788), depression (6.9%, 53/772), dementia (6.7%, 56/840), and atrial fibrillation (3.8%, 30/788). Undiagnosed diabetes mellitus and thyroid disease were rare (1%, 7/717 and 6/762, respectively). A median of 3 (interquartile range 1-8) activities of daily living were undertaken with difficulty. Overall, 77.6% (646/832) of participants rated their health compared with others of the same age as good, very good, or excellent. High contact rates in the previous year with general practitioners (93.8%, 960/1024) were recorded. Women had significantly higher disease counts (medians: women 5, men 4; P=0.033) and disability scores (medians: women 4, men 2; P=0.0006) than men, but were less likely to have attended outpatient clinics in the previous three months (women 29% (150/524), men 37% (118/320), odds ratio 0.7, 95% confidence interval 0.5 to 0.9).

Conclusions This large cohort of 85 year olds showed good levels of both self rated health and functional ability despite significant levels of disease and impairment. Hypertension, ischaemic heart disease, atrial fibrillation, depression, and dementia may be underdiagnosed. Notable differences were found between the sexes: women outnumbered men and had more disease and disability.

INTRODUCTION

The world's population is ageing. In developed countries in 2000 almost one fifth of the population was aged 60 or more, and by 2050 this is expected to rise to one third. Although the proportion of older people is still low in less developed regions, the pace of population ageing is even more rapid.[1] Whereas the notable increase in life expectancy over much of the last two centuries was driven chiefly by declines in mortality in early and middle life, since the 1950s increasing longevity has been dominated by falling age specific death rates among the oldest age groups.[2] The oldest old, defined variously as those aged 80 or 85 years or more, are now the fastest growing sector of the population worldwide.[1] Many of the oldest old experience disease, disability, and dependency, with high costs of health and social care,[3] but detailed data on the spectrum of health in this age group and the individual health trajectories followed in the later years of a long life are lacking. It is unclear whether the decline in disability levels seen in the younger old in certain countries will translate to the oldest old[4] and there is little



Recruitment profile for cohort

information on factors that maintain health and independence in this age group. Effective service planning requires detailed population health needs assessment.

Although studies provide information on the health of the oldest old in several countries, few comprise single year birth cohorts[5-7] despite these offering distinct advantages for studying the complexity of the ageing process with its inherent variability. In addition, a review of population based cohort studies of ageing in developed countries[8] highlighted the need for new studies to recruit the oldest old at baseline and to include people living in institutions. The oldest old have evaded the risks of mortality associated with specific adverse factors and are therefore particularly likely to be informative about the effects of intrinsic ageing. Within the United Kingdom, previous cohort studies have provided valuable information but are limited by the exclusion of those living in institutions[9 10]; a lack of detailed coverage of physical, psychological, social, functional, and biological domains[9 11]; a reliance on self report for data on disease rather than on medical records[9-12]; outdated information[9 11]; and a lack of comprehensive follow-up data.[12] Similarly, UK cross sectional studies that include this age group are limited by small numbers,[13] exclusion of those living in institutions or who are unable to provide consent,[13] and a lack of comprehensive information on health.[13 14]

The Newcastle 85+ Study aims to determine the full spectrum of health within an inception cohort of 85 year olds, selected without regard to health status, and to examine health trajectories and outcomes as the cohort ages and the association between these outcomes and a complex array of clinical, biological, and psychosocial factors. This paper reports the health status of the cohort at baseline, together with information about undiagnosed disease and use of health services.

METHODS

The sampling frame comprised all people born in 1921 who were permanently registered with a participating general practice in Newcastle upon Tyne or North Tyneside primary care trusts in the UK. We approached all 64 general practices in these trusts to participate in the study. The general practitioners were asked to review patient lists before mail-out and to exclude only those with end stage terminal illness and those who might pose a safety risk to a nurse visiting alone. Excepting these exclusions, all those remaining in the sampling frame were sent a letter of invitation by the study team, whether living at home or in an institution and regardless of their state of health. Recruitment and assessment took place over a 17 month period during 2006-7.

Measures

Details of the study protocol have been reported.[15] Participation at baseline entailed a detailed multidimensional health assessment, comprising questionnaires, measurements, function tests, a fasting blood sample, and a review of medical records held by the general practice; participants could decline elements of the protocol. Further details of the measures reported in this paper together with the study questionnaires and the proforma used for record review are available in the web extra and on the Newcastle 85+ Study website (www.ncl.ac.uk/iah/research/programmes/85plus.htm).

Procedures

Assessment was carried out in the participant's usual residence (home or institution) by a research nurse. Participants who were temporarily admitted to hospital at the time of recruitment were assessed after discharge. Information was collected during three interviews, with one further visit to collect a fasting blood sample and to measure body weight. Data were entered directly onto a laptop computer.

A research nurse reviewed the general practice medical records to collect information on diseases, current medication, and use of general practice services. All computerised and paper records were reviewed, including hospital correspondence and the results of investigations. A predetermined list of key diseases was used and all diagnoses of listed diseases were recorded, together with the date of first diagnosis. Medication included any prescribed item—that is, drugs and items such as wound management products, elastic hosiery, catheter and stoma products, and food preparations.

The 11 research nurses underwent training for six weeks in the standardised protocols to be used, with

regular updates. Inter-rater reliability for data extraction from general practice records was examined for 24 randomly selected participants across a core set of variables. Intraclass correlations[16] for binary variables ranged from 0.45 to 0.79; mean 0.57 (angina 0.6, myocardial infarction 0.45, heart failure 0.45, hypertension 0.57, and stroke 0.79), indicating moderate or better agreement between the nurses. Analysis of inter-rater reliability for ordinal variables including the total number of prescribed medications; number of medications for cardiovascular, central nervous system, and gastrointestinal conditions; number of consultations with a general practitioner or practice nurse; and number of consultations at home and at the general practice, showed the only significant disagreement between the nurses to be in the total number of prescribed medications.

Written informed consent was obtained from participants. Where people lacked capacity to consent—for example, because of dementia—an opinion was sought from a relative or carer (a "consultee") according to the requirements of the UK Mental Capacity Act.[17]

Disease prevalence and undiagnosed diseases

For most diseases we determined prevalence on the basis of a review of data from general practice records alone. Exceptions were atrial fibrillation or flutter, renal impairment, and anaemia, which we took from the relevant health assessment data.

Box 1: Diseases included in disease count

- Hypertension
- Ischaemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Heart failure
- Atrial flutter or fibrillation
- Arthritis (osteoarthritis or cervical or lumbar spondylosis or rheumatoid arthritis or other arthritis or non-specified arthritis)
- Osteoporosis
- Chronic obstructive pulmonary disease or asthma
- Other respiratory disease
- Diabetes
- Hypothyroidism or hyperthyroidism
- Cancer diagnosed within past five years (excluding non-melanoma skin cancer)
- Eye disease (cataract or age related macular degeneration or glaucoma or diabetic eye disease or registered blind or partially sighted)
- Dementia
- Parkinson's disease
- Renal impairment

For ischaemic heart disease, diabetes, and thyroid disease, presence was defined as diagnosis either in general practice records or from health assessment test; for atrial fibrillation or flutter from an electrocardiogram (health assessment test); for renal impairment from estimated glomerular filtration rate <30 ml/min/1.73 m^2 (health assessment test); and for anaemia, a haemoglobin concentration <11.5 g/dl (<115 g/l) (health assessment test). For all other diseases the presence was taken from record review data alone.

We estimated the extent of possible undiagnosed hypertension, ischaemic heart disease, diabetes, hypothyroidism, and hyperthyroidism by taking account of health assessment measures in those without the particular diagnosis recorded in the general practice records. For depression, dementia, and atrial fibrillation we estimated the point prevalence of possible disease from health assessment data and then checked if that particular diagnosis was recorded in the general practice records. We defined the presence of disease from health assessment data by standard cut-off points (see web extra for details of measures and cut-off points used).

Disease count

We derived a simple disease count (maximum score 18) from selected chronic diseases (box 1). Only participants in whom all variables were scored as present (score 1) or absent (score 0) were included in the analysis of disease count.

Statistical analysis

We present normally distributed continuous data as means and standard deviations, and variables with a non-Gaussian distribution as medians and interquartile ranges. When appropriate we present categorical data as percentages and 95% confidence intervals. To compare men with women we used logistic or ordinal regression as appropriate, with odds ratios and 95% confidence intervals, Mann-Whitney U test for non-normally distributed continuous variables, and χ^2 tests for categorical variables. P values were two sided. We used version 1.0 of the dataset.

In general we excluded missing values from the analysis and calculated percentages from the number of valid responses. Where individual items were missing within two measures reported as categorical data—the 15 item geriatric depression scale[18] and the standardised mini-mental state examination[19]—we compared scoring the missing item as zero or the maximum possible for that item with data retained only if a participant was classified in the same category in either case.

We considered a sample size of 800 sufficient to give a confidence interval of 3.5% either way on a prevalence of 50% and to provide sufficient power for analyses of major subgroups.

RESULTS

The figure summarises the recruitment profile. Of the 1453 people eligible to participate—that is, registered with a participating general practice and still alive—1042 (71.7%) participated. In total, 851 (58.6% of those eligible) people were recruited to health assessment plus review of general practice records, with an additional 188 (12.9%) to record review only, and 3 (0.2%) to health assessment only. Box 2 gives some technical details about the health assessment. One participant who agreed to a health assessment plus record review subsequently withdrew and requested the data to be destroyed; this participant was excluded from the health assessment and record review analysis. In eight

Table 1 | Sociodemographic data, smoking status, and body mass index of population aged 85, by sex. Values are percentages (numbers) unless stated otherwise

Variables	All	Women	Men	Census (2001) Newcastle and North Tyneside (%)	Census (2001) England and Wales (%)	P value*
Men	37.9 (323)	—	—	33.5	32.6	—
Women	62.1 (530)	—	—	66.5	67.3	—
Housing:						0.007
Standard	76.8 (655)	73.0 (387)	83.0 (268)	—	—	
Sheltered	12.7 (108)	14.2 (75)	10.2 (33)	—	—	
Institution	10.4 (89)	12.6 (67)	6.8 (22)	12.0	11.2	
Other	0.1 (1)	0.2 (1)	0 (0)	—	—	
Living arrangements†:						<0.001
Alone	61.0 (465)	73.3 (338)	42.2 (127)	57.0	55.0	
With spouse only	28.1 (214)	13.9 (64)	49.8 (150)	—	—	
With others	10.9 (83)	12.8 (59)	8.0 (24)	—	—	
Marital status:						<0.001
Widowed	59.0 (500)	70.4 (371)	40.2 (129)	62.3‡	61.2‡	
Married	30.0 (254)	16.3 (86)	52.3 (168)	27.0‡	27.6‡	
Never married	8.3 (70)	9.9 (52)	5.6 (18)	8.0‡	8.2‡	
Divorced or separated	2.8 (24)	3.4 (18)	1.9 (6)	2.8‡	2.4‡	
Ethnic origin:						0.304
White	99.6 (846)	99.8 (526)	99.4 (320)	99.3‡	89.2‡	
Non-white	0.4 (3)	0.2 (1)	0.6 (2)	0.7‡	10.8‡	
Born in north east England	77.0 (652)	79.7 (419)	72.6 (233)	—	—	0.018
Smoking status:						<0.001
Current smoker	5.8 (49)	6.5 (34)	4.7 (15)	—	—	
Former regular smoker	53.5 (453)	45.7 (241)	66.3 (212)	—	—	
Former occasional smoker	5.0 (42)	5.9 (31)	3.4 (11)	—	—	
Never smoker	35.8 (303)	41.9 (221)	25.6 (82)	—	—	
Body mass index (kg/m^2)§:						
Underweight (<18.50)	6.4 (48)	7.8 (35)	4.4 (13)	—	—	
Normal range (18.50-24.99)	51.3 (383)	51.2 (230)	51.3 (153)	—	—	
Pre-obese (25.00-29.99)	32.5 (243)	30.3 (136)	35.9 (107)	—	—	
Obese (30.00-39.99)	9.5 (71)	10.2 (46)	8.4 (25)	—	—	
Morbidly obese (≥40.00)	0.3 (2)	0.5 (2)	0.0 (0)	—	—	

Data from health assessment.
*Sex difference.
†Excludes people in institutional care.
‡Average of 80-84 and 85-89 age groups.
§Odds ratio (95% confidence interval) women to men 0.9 (0.7 to 1.2).

cases (four each from the record review group and the health assessment plus record review group) the general practice paper records were unavailable and these participants were excluded from the record review analysis. To ensure maximum use of available data, variables from the general practice record review are reported on a maximum sample of 1030 people (representing 70.9% of those eligible) and from the health assessment on a maximum sample of 853 people (representing 58.7% of those eligible); sample sizes for individual variables may differ owing to missing values. Tables detailing the number of valid responses and missing values for each variable are given in the web extra.

Box 2: Health assessment technical details

- The mean (standard deviation) total time taken for the health assessment (excluding the short visit for taking fasting blood samples and measuring body weight) was 206 (55) minutes over a median 25 days (interquartile range 16-36.5 days)
- An informant supplied information in at least one of the interviews for 29% (247/853) of the participants in the health assessment group
- 96% of the 778 participants who had blood taken gave fasting samples

Representativeness of study sample

Overall, 53 of the 64 (83%) general practices in Newcastle upon Tyne and North Tyneside primary care trusts agreed to participate. Practices that participated were similar to those that did not for median practice size (6709 *v* 6000; Mann-Whitney U test P=0.78), proportion that were training practices (32% *v* 36%; χ^2=0.1, P=0.78), median score from the UK National Health Service (NHS) quality and outcomes framework for 2006-7[20] (993.5 *v* 981.7; Mann-Whitney U test P=0.23), and median index of multiple deprivation

score for 2004[21] using the practice postcode (22.1 *v* 20.7; Mann-Whitney U test P=0.37).

On comparing participants' sociodemographic status with equivalent figures from the 2001 national census for Newcastle upon Tyne and North Tyneside and for England and Wales (table 1), the Newcastle 85+ cohort is broadly representative of the local population, although there was slight under-representation of women (62.1% (530/853) in health assessment sample, 64.2% (661/1030) in record review sample, 66.5% in local census data). Sociodemographically, Newcastle upon Tyne and North Tyneside are generally comparable to England and Wales except for ethnic diversity (census data for non-white population in Newcastle upon Tyne and North Tyneside 0.7% and in England and Wales 10.8%). To investigate whether differential response might affect results, a comparison was made between refusers (n=358), record review only participants (n=184), and those agreeing to health assessment plus record review (n=846) on sex and index of multiple deprivation score, excluding cases with incomplete general practice records. Deprivation did not differ significantly but significantly fewer females were in the health assessment plus record review group (62.3%, 527/846) than in the record review only group (73%, 134/184) and refusers (74%, 265/358) (χ^2=21.3, df=2, P<0.001).

Table 2 | Disease, by sex. Values are percentages (numbers) unless stated otherwise

Diseases	All	Women	Men	Odds ratio (95% CI) women to men
Cardiovascular:				
Hypertension*	57.5 (592)	60.1 (397)	52.9 (195)	1.3 (1.0 to 1.8)
Any atherosclerotic disease*	47.2 (486)	42.8 (283)	55.0 (203)	0.6 (0.5 to 0.8)
Ischaemic heart disease*	31.4 (323)	28.3 (187)	36.9 (136)	0.7 (0.5 to 0.9)
Cerebrovascular disease*	20.1 (207)	17.6 (116)	24.7 (91)	0.7 (0.5 to 0.9)
Peripheral vascular disease*	6.8 (70)	5.3 (35)	9.5 (35)	0.5 (0.3 to 0.9)
Heart failure*	11.1 (114)	10.1 (67)	12.7 (47)	0.8 (0.5 to 1.2)
Atrial fibrillation†	14.0 (111)	12.3 (59)	16.8 (52)	0.7 (0.5 to 1.1)
Atrial flutter†	0.5 (4)	0.4 (2)	0.7 (2)	0.6 (0.1 to 8.9)
Musculoskeletal*:				
Osteoarthritis	51.8 (534)	57.0 (377)	42.6 (157)	1.8 (1.4 to 2.3)
Cervical or lumbar spondylosis	29.6 (305)	30.4 (201)	28.2 (104)	1.1 (0.8 to 1.5)
Rheumatoid arthritis	3.5 (36)	5.1 (34)	0.5 (2)	10.0 (2.5 to 85.9)
Other arthritis (specified)	3.3 (34)	3.0 (20)	3.8 (14)	0.8 (0.4 to 1.7)
Arthritis (type not specified)	9.0 (93)	10.0 (66)	7.3 (27)	1.4 (0.9 to 2.3)
Joint replacement	13.5 (139)	15.6 (103)	9.8 (36)	1.7 (1.1 to 2.6)
Osteoporosis	14.2 (146)	20.0 (132)	3.8 (14)	6.3 (3.6 to 12.1)
Eye*:				
Cataract	46.9 (483)	51.6 (341)	38.5 (142)	1.7 (1.3 to 2.2)
Cataract surgery	36.2 (373)	39.2 (259)	30.9 (114)	1.4 (1.1 to 1.9)
Age related macular degeneration	13.8 (142)	14.8 (98)	11.9 (44)	1.3 (0.9 to 1.9)
Glaucoma	8.6 (89)	8.9 (59)	8.1 (30)	1.1 (0.7 to 1.8)
Diabetic eye disease	1.5 (15)	1.4 (9)	1.6 (6)	0.8 (0.3 to 2.9)
Registered blind	2.2 (23)	1.8 (12)	3.0 (11)	0.6 (0.2 to 1.5)
Registered partially sighted	3.2 (33)	4.1 (27)	1.6 (6)	2.6 (1.0 to 7.7)
Cancer*:				
Any cancer	23.9 (246)	19.8 (131)	31.2 (115)	0.6 (0.4 to 0.7)
Any cancer, excluding non-melanoma skin cancer	15.1 (155)	12.3 (81)	20.1 (74)	0.6 (0.4 to 0.8)
Any cancer <5 years since diagnosis‡	6.5 (67)	5.2 (34)	9.0 (33)	0.6 (0.3 to 0.9)

*Data from general practice record review.
†Data from health assessment 12 lead electrocardiogram.
‡Excluding non-melanoma skin cancer.

Sociodemographics

Three quarters (655/853) of the health assessment sample lived in standard housing, with only 12.7% (n=108) in sheltered accommodation and 10.4% (n=89) in institutional care (table 1); all those in institutional care were living in care homes. Of those not in institutional care, 61.0% (465/762) were living alone. Women outnumbered men by 1.6 to 1 and were more likely to be living in institutional care or sheltered accommodation, living alone, or widowed.

Disease prevalence and undiagnosed diseases

The most prevalent diseases were hypertension (57.5%, 592/1030) and osteoarthritis (51.8%, 534/1030); other common diseases were atherosclerosis (47.2% 486/1030) and cataract (47.0%, 483/1030; tables 2 and 3). Women were 10 times more likely than men to have rheumatoid arthritis, eight times more likely to have a diagnosis of hyperthyroidism, three times more likely to have a diagnosis of hypothyroidism, and six times more likely to have osteoporosis. Women also had a significantly higher prevalence of cataract, osteoarthritis, joint replacement, renal impairment (by the modification of diet in renal disease formula[22] but not the Mayo Clinic quadratic equation),[23] and anaemia (Joosten's criterion).[24] Men were significantly more likely to have a diagnosis of atherosclerotic disease and cancer.

Table 4 gives estimates of the prevalence of possible undiagnosed disease; data are reported for those participants with both the general practice record review and the relevant test from the health assessment available. For hypertension, ischaemic heart disease, diabetes, and thyroid disease the prevalence of diagnosed disease is reported from record review data followed by the prevalence of possible undiagnosed disease taken from the relevant health assessment data in those without a previous diagnosis. For depression, dementia, and atrial fibrillation, an estimate of the point prevalence of possible disease is reported from health assessment data followed by the prevalence of possible disease in the absence of a previous diagnosis in the general practice records. Although hypertension would not be diagnosed from a single time point, review of the measured blood pressure in those without a recorded diagnosis of hypertension suggested an additional 25.1% (206/821) with possible at least grade 1 hypertension, of whom half had grade 2. Of those with a diagnosis of hypertension recorded in the general practice records, only 35% (164/475) had both a systolic blood pressure below 140 mm Hg and a diastolic blood pressure below 90 mm Hg, although 87% (411/475) were using antihypertensive drugs. In addition to the 33.0% (260/788)

Table 3 | Disease, by sex, continued from table 2. Values are percentages (numbers) unless stated otherwise

Diseases	All	Women	Men	Odds ratio (95% CI) women to men
Respiratory*:				
Chronic obstructive pulmonary disease	16.5 (170)	14.5 (96)	20.1 (74)	0.7 (0.5 to 1.0)
Asthma†	4.8 (49)	5.8 (38)	3.0 (11)	2.0 (1.0 to 4.4)
Other respiratory disease	2.7 (28)	1.8 (12)	4.3 (16)	0.4 (0.2 to 0.9)
Endocrine*:				
Diabetes mellitus	13.1 (135)	12.1 (80)	14.9 (55)	0.8 (0.5 to 1.2)
Hypothyroidism	12.0 (124)	15.7 (104)	5.4 (20)	3.3 (2.0 to 5.7)
Hyperthyroidism	2.8 (29)	4.1 (27)	0.5 (2)	7.8 (1.9 to 68.1)
Neurological and psychiatric*:				
Dementia	8.4 (86)	9.1 (60)	7.1 (26)	1.3 (0.8 to 2.2)
Parkinson's disease	1.5 (15)	1.2 (8)	1.9 (7)	0.6 (0.2 to 2.1)
Anaemia‡:				
WHO criteria for haemoglobin concentration§	29.8 (225)	27.5 (126)	33.3 (99)	0.8 (0.6 to 1.1)
Joosten's criterion for haemoglobin concentration: <11.5 g/dl (<115 g/l)	14.2 (107)	17.7 (81)	8.8 (26)	2.2 (1.4 to 3.7)
Renal function¶ using modification of diet in renal disease formula:				1.7 (1.3 to 2.3)
Normal	1.0 (8)	0.9 (4)	1.3 (4)	
Mildly reduced	36.4 (283)	31.5 (149)	43.9 (134)	
Moderately reduced(stage 3††)	59.5 (463)	64.3 (304)	52.1 (159)	
Severely reduced (stage 4††)	2.4 (19)	2.8 (13)	2.0 (6)	
Very severely reduced (stage 5††)	0.6 (5)	0.6 (3)	0.7 (2)	
Renal function¶ using Mayo Clinic quadratic equation:				0.8 (0.6 to 1.1)
Normal	3.6 (28)	0.0 (0)	9.2 (28)	
Mildly reduced	61.4 (478)	69.6 (329)	48.9 (149)	
Moderately reduced (stage 3††)	31.8 (247)	27.7 (131)	38.0 (116)	
Severely reduced (stage 4††)	2.2 (17)	2.1 (10)	2.3 (7)	
Very severely reduced (stage 5††)	1.0 (8)	0.6 (3)	1.6 (5)	
Median (interquartile range) disease count‡‡	5 (3-6)	5 (4-6)	4 (3-6)	

*Data from general practice record review.
†Excluded in combination with chronic obstructive pulmonary disease.
‡Data from health assessment measured haemoglobin concentration.
§Men <13 g/dl (<130 g/l), women <12 g/dl (<120 g/l).
¶Data from health assessment measured creatinine concentration. Estimated glomerular filtration rate ranges for renal function categories for both formulas: normal >89 ml/min/1.73 m^2, mildly reduced 60-89 ml/min/1.73 m^2, moderately reduced 30-59 ml/min/1.73 m^2, severely reduced 15-29 ml/min/1.73 m^2, and very severely reduced <15 ml/min/1.73 m^2.
††Stage of chronic kidney disease; US National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification (see www.kidney.org/PROFESSIONALS/kdoqi/guidelines_ckd/toc.htm).
‡‡18 diseases: hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial flutter or fibrillation, arthritis, osteoporosis, chronic obstructive pulmonary disease or asthma, other respiratory disease, diabetes, hypothyroidism or hyperthyroidism, cancer diagnosed within past five years (excluding non-melanoma skin cancer), eye disease, dementia, Parkinson's disease, renal impairment, and anaemia.

of the sample who had a recorded diagnosis of ischaemic heart disease, electrocardiography in those with no diagnosis revealed a further 12.6% (99/788) with evidence of definite (2.4%, 19/788) or probable (10.2%, 80/788) myocardial ischaemia. There was little evidence of undiagnosed diabetes or thyroid disease. With respect to depression, 8.4% (65/772) had a geriatric depression scale score suggestive of severe depression, of whom 82% (53/65) had no diagnosis recorded in the general practice records in the previous year. A standardised mini-mental state examination score suggesting moderate or severe cognitive impairment was found in 12.5% (105/840) of participants, of whom 53% (56/105) had no diagnosis of dementia in the general practice records. Atrial fibrillation was evident on electrocardiography in 13.8% (109/788) of participants, of whom 28% (30/109) had no diagnosis apparent in the general practice records. Levels of undiagnosed disease did not differ significantly between men and women.

The disease count is reported on the 729 participants in whom all required variables were present. No participant was free of all 18 diseases and the maximum count was 11 (men 10, women 11). Women had a significantly higher number of diseases than men (P=0.033).

Geriatric syndromes, impairments, self rated health, and disability

Hearing impairment was reported by 59.6% (505/848) of the participants, visual impairment by 37.2% (309/831), pain in the past month (lasting a day or longer) by 50.0% (402/805), at least one fall in the previous year by 38.3% (312/815) (8.0% (65/815) reporting three or more falls), severe or profound urinary incontinence by 21.3% (173/813), and faecal incontinence by 8.6% (70/816) (table 5). Seventy eight per cent of participants (646/832) rated their health compared with others of the same age as good, very good, or excellent, with only 3.5% (29/832) rating it as poor. Almost one fifth (165/842) of the cohort had no difficulty with any of 17 activities of daily living; the median (interquartile range) for the number of items carried out with difficulty or requiring an aid, appliance, or personal help was 3 (1-8). Women had significantly higher disability scores than men (P=0.0006) and were also significantly more likely to have visual impairment or urinary incontinence and to be rated as depressed on the geriatric depression scale.

Health service use

Almost one third (268/844) of the sample had attended outpatient clinics in the three months before the study (table 6). In the previous year, 22.1% (188/850) had had at least one overnight stay in hospital, spending, on average, seven days in total over the stays. Almost all (93.8%, 960/1024) of the sample had seen their general practitioner within the past year (median consultation rate over the year for those who consulted of 5); 61.7% (3752/6085) of consultations took place at the general practice surgery, 23.5% (1430/6085) were home visits, 13.5% (822/6085) were telephone consultations, and 1.0% (80/6085) were by letter. Only 6.0% (58/971) had contact with the general practice out of hours service. Just over three quarters (780/1008) had seen the practice nurse (median consultation rate over the year for those who consulted of 2) with 90.0% (2768/3074) of contacts in the general practice surgery. In the previous month, 95.0% (979/1030) were taking medication prescribed by their general practice team, with a mean (standard deviation) of 6.7 (3.7) items: men 6.3 (3.5), women 6.9 (3.7), P=0.07. Coding according to

the *British National Formulary*,[25] the top three categories of prescribed medication were for the cardiovascular system (40.3%, 2639/6547), central nervous system (13.4%, 879/6547, including analgesics but excluding non-steroidal anti-inflammatory drugs), and gastrointestinal system (10.6%, 692/6547). The only sex difference in health service use was a significantly lower proportion of women having outpatient attendances and consultations with a practice nurse.

DISCUSSION

The Newcastle 85+ Study secured a high level of participation from 85 year olds, including those living in institutions and those with cognitive impairment. Perhaps the most striking findings were the low levels of disability and people living in institutional care, and positive self rated health (compared with others of the same age) despite high levels of disease and impairment. The prevalence of diagnosed hypertension, atherosclerotic disease, osteoarthritis, and cataract were each close to 50%, and almost 90% of participants had at least three diseases. Two thirds reported hearing impairment, one third visual impairment, almost 40% had had falls, and 20% had notable urinary incontinence. A meta-analysis[26] found higher levels of optimism for self rated health in people aged 75 or more compared with younger age groups, when comparative measures (compared with people of the same age) as opposed to

Table 4 | Potential undiagnosed disease, by sex. Values are percentages (numbers) unless stated otherwise

Diseases	All	Women	Men	Odds ratio (95% CI) women to men
Hypertension				
Measured blood pressure and record review available:	100 (821)	100 (508)	100 (313)	
Hypertension diagnosis in record review	57.9 (475)	60.8 (309)	53.0 (166)	
No diagnosis; systolic ≥140 mm Hg or diastolic ≥90 mm Hg	25.1 (206)	24.0 (122)	26.8 (84)	0.9 (0.6 to 1.2)
No diagnosis; systolic ≥160 mm Hg or diastolic ≥100 mm Hg	12.3 (101)	12.0 (61)	12.8 (40)	0.9 (0.6 to 1.5)
No diagnosis; systolic ≥160 mm Hg and diastolic <90 mm Hg	8.5 (70)	7.9 (40)	9.6 (30)	0.8 (0.5 to 1.4)
Ischaemic heart disease				
ECG and record review available:	100 (788)	100 (480)	100 (308)	
Ischaemic heart disease diagnosis in record review	33.0 (260)	30.6 (147)	36.7 (113)	
No diagnosis; ECG evidence of definite ischaemic heart disease	2.4 (19)	2.3 (11)	2.6 (8)	0.9 (0.3 to 2.6)
No diagnosis; ECG evidence of probable ischaemic heart disease	10.2 (80)	10.8 (52)	9.1 (28)	1.2 (0.7 to 2.1)
Diabetes				
Fasting glucose and record review available:	100 (717)	100 (432)	100 (285)	
Diabetes diagnosis in record review	13.5 (97)	13.9 (60)	13.0 (37)	
No diagnosis; fasting glucose ≥7 mmol/l	1.0 (7)	0.9 (4)	1.1 (3)	0.9 (0.2 to 6.0)
Hypothyroidism				
Hypothyroid blood screen and record review available:	100 (762)	100 (465)	100 (297)	
Hypothyroidism diagnosis in record review	12.3 (94)	16.6 (77)	5.7 (17)	
No diagnosis; hypothyroid screen positive	0.5 (4)	0.4 (2)	0.7 (2)	0.6 (0.1 to 8.8)
Hyperthyroidism				
Hyperthyroid blood screen and record review available:	100 (762)	100 (465)	100 (297)	
Hyperthyroidism diagnosis in record review	2.9 (22)	4.3 (20)	0.7 (2)	
No diagnosis; hyperthyroid screen positive	0.3 (2)	0.2 (1)	0.3 (1)	0.6 (0.0 to 50.2)
Depression				
GDS-15 score* and record review available:	100 (772)	100 (474)	100 (298)	
GDS-15 ≥8 (suggestive of severe depression)	8.4 (65)	9.3 (44)	7.1 (21)	
GDS-15 ≥8 and no record review diagnosis of depression in past year	6.9 (53)	7.6 (36)	5.7 (17)	1.4 (0.7 to 2.6)
Dementia				
SMMSE score and record review available:	100 (840)	100 (523)	100 (317)	
SMMSE ≤21 (moderate or severe cognitive impairment)	12.5 (105)	14.2 (74)	9.8 (31)	
SMMSE ≤21 and no record review diagnosis of dementia	6.7 (56)	7.3 (38)	5.7 (18)	1.3 (0.7 to 2.6)
SMMSE ≤17 (severe cognitive impairment)	6.9 (58)	7.3 (38)	6.3 (20)	
SMMSE ≤17 and no record review diagnosis of dementia	3.0 (25)	3.3 (17)	2.5 (8)	1.3 (0.5 to 3.5)
Atrial fibrillation				
ECG and record review available:	100 (788)	100 (480)	100 (308)	
Atrial fibrillation on ECG (Minnesota code 8-3-1)	13.8 (109)	12.1 (58)	16.6 (51)	
Atrial fibrillation on ECG and no record review diagnosis of atrial fibrillation	3.8 (30)	3.1 (15)	4.9 (15)	0.6 (0.3 to 1.4)

ECG=electrocardiogram; GDS=geriatric depression scale; SMMSE=standardised mini-mental state examination.
*GDS-15 omitted if score <15 on SMMSE.

Table 5 | Geriatric syndromes, impairments, disability, and self rated health, by sex. Values are percentages (numbers) unless stated otherwise

Variables	All	Women	Men	Odds ratio (95% CI) women to men
Hearing impairment	59.6 (505)	56.9 (300)	63.9 (205)	0.8 (0.6 to 1.0)
Visual impairment	37.2 (309)	40.7 (209)	31.6 (100)	1.5 (1.1 to 2.0)
Pain in past month (lasting ≥1 days)	49.9 (402)	53.0 (262)	45.0 (140)	1.4 (1.0 to 1.9)
Falls in past year:				1.0 (0.7 to 1.3)
None	61.7 (503)	61.8 (312)	61.6 (191)	
1	20.5 (167)	21.2 (107)	19.4 (60)	
2	9.8 (80)	8.9 (45)	11.3 (35)	
≥3	8.0 (65)	8.1 (41)	7.7 (24)	
Urinary incontinence:				2.1 (1.6 to 2.8)
None	56.7 (461)	49.9 (251)	67.7 (210)	
Minimal	10.7 (87)	11.3 (57)	9.7 (30)	
Moderate	10.1 (82)	10.9 (55)	8.7 (27)	
Severe or profound	21.3 (173)	26.6 (134)	12.6 (39)	
Catheterised for past year	1.2 (10)	1.2 (6)	1.3 (4)	
Faecal incontinence	8.6 (70)	9.3 (47)	7.4 (23)	1.3 (0.8 to 2.3)
Depression (GDS-15 score*):				1.6 (1.1 to 2.3)
None (0-5)	79.1 (601)	76.4 (356)	83.3 (245)	
Mild or moderate (6-7)	12.4 (94)	14.2 (66)	9.5 (28)	
Severe (8-15)	8.6 (65)	9.4 (44)	7.1 (21)	
Cognitive impairment (SMMSE score):				1.1 (0.8 to 1.5)
Normal (26-30)	73.1 (602)	73.1 (372)	73.0 (230)	
Mild (22-25)	15.3 (126)	14.0 (71)	17.5 (55)	
Moderate (18-21)	5.1 (42)	6.5 (33)	2.9 (9)	
Severe (0-17)	6.6 (54)	6.5 (33)	6.7 (21)	
Median (interquartile range) disability score†	3 (1-8)	4 (1-9)	2 (0-6)	—
Self rated health (compared to others of same age):				1.3 (1.0 to 1.7)
Excellent	10.3 (86)	9.5 (49)	11.7 (37)	
Very good	29.7 (247)	28.1 (145)	32.3 (102)	
Good	37.6 (313)	38.2 (197)	36.7 (116)	
Fair	18.9 (157)	20.2 (104)	16.8 (53)	
Poor	3.5 (29)	4.1 (21)	2.5 (8)	

GDS=geriatric depression scale; SMMSE=standardised mini-mental state examination.
Data from health assessment.
*GDS-15 omitted if score <15 on SMMSE.
†No of activities of daily living carried out with difficulty or requiring an aid, appliance, or personal help.

absolute measures were used. Notable sex differences were apparent from our study in line with previous reports;[27] although women were more likely to survive to age 85 (female to male ratio 1.6:1), they were more likely to be living in institutional care, to have a higher total disease count and higher prevalence of many diseases (excepting two important life threatening conditions, atherosclerosis and cancer, where the prevalence was higher in men, potentially contributing to differences in survival), to have more visual impairment, urinary incontinence, and depression, and higher levels of disability, despite the tight age criteria. Men born in 1921 would have been 18 in 1939 at the outbreak of the second world war, which could have contributed to differences in survival. Although women had higher levels of disease and disability, they were less likely to have had an outpatient attendance in the previous three months.

Possible underdiagnosis of important clinical conditions

Despite the high contact rates of the participants with primary care in the previous year, our data raise the possibility of underdiagnosis of important clinical conditions, although the interpretation of this should be appropriately cautious. In collecting data from general practice records, a diagnosis was noted as present if recorded anywhere in the records, irrespective of date. In some cases—for example, cataract and thyroid disease—a disease may have been successfully treated, so the diagnosis would no longer be current; this should be considered when reviewing the data on disease in tables 2 and 3. The data on diabetes and thyroid disease from our two sources were in close agreement. Given what is known more generally about underdiagnosis, our data for hypertension, atrial fibrillation, ischaemic heart disease, dementia, and depression are not surprising. While our assessment of hypertension should be treated with caution, as blood pressure was measured on one occasion, 25% of the sample had a measured blood pressure in the hypertensive range, without a diagnosis of hypertension in the general practice records; with proper clinical assessment a proportion of these would subsequently be within the normal range. Similarly, for around two thirds of those with a known diagnosis of hypertension, the blood pressure measured in the study was outside the target ranges recommended by guidelines.[28,29] Given that the recent Hypertension in the Very Elderly Trial[30] showed that treatment of hypertension was beneficial in those aged 80 and older, a more aggressive approach to case finding and control of blood pressure may be warranted in this age group. However, considering the strict exclusion criteria applied in clinical trials, the utility and feasibility of this approach in unselected populations of older people remains to be established. The prevalence of undiagnosed dementia was estimated at 7% and although the screen used for dementia is not diagnostic, the overall prevalence of moderate to severe cognitive impairment of 13% was close to the prevalence of dementia found in the MRC-CFAS study,[11] which used instruments more sensitive to dementia case finding. We have shown previously[31] that differences in consultation patterns can be observed up to four years before a formal diagnosis of dementia, indicating that general practitioners do attend to possible signs of early dementia. It is not, however, practicable to use the systematic review of primary care records to facilitate earlier diagnosis without identifying large numbers of false positive results requiring investigation. Undiagnosed depression is not just a feature of the oldest old, and in a population with other chronic illness its presence is perhaps not surprising. What is less clear is how this could be readily detected in a routine setting and what might be the uptake and effects of treatment. We found a high prevalence of moderate renal impairment, particularly in women, using the widely accepted modification of diet in renal disease formula, in common with recent findings.[32] Using the Mayo Clinic quadratic equation resulted in almost half of those classified as moderately

impaired by the modification of diet in renal disease formula moving to a less severe category, in line with the findings of another study,[33] and we conclude that the Mayo Clinic quadratic equation may be more appropriate for use in older people.

Strengths and limitations of the study

A key strength of our study is the high response rate achieved from both general practices and participants. Eighty three per cent of general practices in the region agreed to participate and participating and non-participating practices were similar in terms of practice size, training practice status, NHS quality and outcomes framework score, and index of multiple deprivation on the basis of practice postcode. Fifty nine per cent of eligible people were recruited to both health assessment and review of general practice records, with an additional 13% recruited to review of records only; good participation rates, considering the age group of the sample and the extensive assessment involved. A major concern in any cohort study is whether the participants are representative of the population from which they are drawn. It is possible that the non-responders or refusers to our study were frailer than the participants, which could lead to an underestimate in the reported levels of disease (both diagnosed and undiagnosed), disability, and poor self rated health. The reason for non-response or refusal to participate were available in 57% of non-participants for the health assessment and 49% for the review of general practice records, and in only 30% and 28% of these was non-response or refusal related to poor health. We have shown that by comparison with local census data the sample we recruited to health assessment was sociodemographically broadly representative of the local population, although women were slightly under-represented. Importantly, our sample was representative in terms of the proportion of people living in institutions and also included people who were cognitively impaired; two groups excluded from many previous studies.

In terms of study design, a major strength of the Newcastle 85+ Study is its success in securing a high recruitment of participants with two things in common; year of birth and registration with a general practice in Newcastle upon Tyne or North Tyneside. The focus on a single year birth cohort and a closely circumscribed geographical area, with known population stability and little ethnic diversity, will be a major strength when carrying out comparisons within a cohort to explore factors that influence health status, as this will lessen extraneous variability. However, we acknowledge that this strength might also constitute a weakness by limiting the generalisabilty of the health survey findings to other populations. Comparison of the Newcastle 85+ cohort with sociodemographic data from the national census 2001 showed our sample to be broadly representative of England and Wales but with a notable difference in ethnic diversity, and it is known that people from ethnic minority groups have different health risk profiles from those of white populations. In addition, Newcastle and North Tyneside are urban areas, which might limit application of our findings to rural settings. Home based assessment was vital for this high recruitment; 50% of participants in our pilot study stated that they would have been less likely to participate if hospital attendance was required (unpublished data). Additional strengths are the comprehensive nature of the health data collected and the use of a

Table 6 | Health service use, by sex. Values are percentages (numbers) unless stated otherwise

Variables	All	Women	Men	Odds ratio (95% CI) women to men	P value*
Previous 3 months†:					
Any outpatient attendance	31.8 (268)	28.6 (150)	36.9 (118)	0.7 (0.5 to 0.9)	
Median (interquartile range) No of outpatient attendances	1 (1-2)	1 (1-2)	1 (1-2)	—	0.218
Any accident and emergency attendance	7.1 (60)	7.2 (38)	6.8 (22)	1.1 (0.6 to 1.9)	
Median (interquartile range) No of accident and emergency attendances	1 (1-1)	1 (1-1)	1 (1-1)	—	0.858
Any emergency ambulance use	5.1 (43)	5.1 (27)	5.0 (16)	1.0 (0.5 to 2.1)	
Previous year:					
Any overnight hospital admission†	22.1 (188)	21.4 (113)	23.2 (75)	0.9 (0.6 to 1.3)	
Median (interquartile range) total stay in hospital (days) †	7 (3-20)	8.5 (3-20)	7 (2-16)	—	0.458
Any respite care†‡	2.9 (24)	3.2 (16)	2.5 (8)	1.3 (0.5 to 3.5)	
Median (interquartile range) total stay in respite care (days)† ‡	14 (7-22.5)	14 (12.5-22.5)	11.5 (7-28)	—	0.829
Any day hospital attendance†	7.5 (63)	7.8 (41)	6.8 (22)	1.2 (0.7 to 2.1)	
Any other intermediate care contact†	7.6 (64)	8.5 (44)	6.2 (20)	1.4 (0.8 to 2.5)	
Any consultations with own general practitioner (including out of hours contacts)§	93.8 (960)	93.8 (616)	93.7 (344)	1.0 (0.6 to 1.8)	
Median (interquartile range) No of own general practitioner consultations§	5 (2-8)	5 (2-8)	5 (2-8)	—	0.661
Any consultations with out of hours general practice service§	6.0 (58)	6.6 (41)	4.8 (17)	1.4 (0.8 to 2.7)	
Any consultations with practice nurse§	77.4 (780)	73.8 (477)	83.7 (303)	0.6 (0.4 to 0.8)	
Median (interquartile range) No of practice nurse consultations§	2 (1-4)	2 (0-4)	2 (1-5)	—	0.008

*Sex difference.
†Data from health assessment.
‡Excludes those in institutional care for previous year.
§Data from general practice record review.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Those aged 85 or older (the oldest old) are the fastest growing group in the UK and many other countries

The full spectrum of health of the oldest old, and the complex factors influencing their health trajectories, need better description to assist health care and service planning

WHAT THIS STUDY ADDS

Levels of self rated health and functional ability are good among 85 year olds, despite substantial levels of disease and impairment

Hypertension, ischaemic heart disease, atrial fibrillation, depression, and dementia may be underdiagnosed in 85 year olds whereas diabetes and thyroid disease are not

combination of detailed assessment of participants with review of general practice records for data on diseases and medication, rather than reliance on self report. Previous studies[34 35] have shown self report to be less reliable than a doctor diagnosis for certain diseases, particularly in older age groups and in those with multiple morbidities or cognitive impairment. Inter-rater reliability for data extraction from general practice records showed moderate or better agreement for the diseases assessed; false positive and false negative results are possible, which could lead to overestimates or underestimates in the disease prevalence (tables 2 and 3) and also affect the prevalence of undiagnosed disease (table 4). The discordance that was found between nurses on the recording of the total number of medications necessitates some caution; however, the number of medications in the three most common categories showed no significant disagreement. We recognise that, despite a high level of recruitment and retention of participants throughout an intensive series of assessments, the greatly varying capabilities of the participants has the potential to introduce some bias through incompleteness of assessment, although this was not large.

Conclusions and policy implications

It is difficult to estimate to what extent this cohort of 85 year olds represents a "healthy elite," given that life expectancy at birth for the 1921 cohort was 61 years for men and 68 years for women, with only 18% of men and 33% of women surviving to age 85.[36] Information from the study is none the less valuable. For planners of services, on the basis of present demographic trends, we can say that in the UK by 2020 the 85 year old population will increase by 33%,[37] 10% of whom currently require institutional care, 32% of whom have had an outpatient attendance, and 7% an attendance at an accident and emergency department in the past three months; it is likely that these figures will be closely paralleled in other high income countries. In addition, 61% of older people not in institutional care were living alone, which has implications for the availability of help with activities of daily living and hence to providers of social care. The survey findings highlight the potential unmet health and social care needs of this age group mirroring the findings of a study[38] in the late 1950s. In times of scarce resources for health and social care these findings can be used by local and national policy makers to help target those in greatest need. In summary, these 85 year olds seemed optimistic, most rating their overall health as good, very good, or excellent compared with others of the same age. Our study shows the opportunities available to intervene to improve health further in this age group. If the data are extrapolated to the future, much larger, populations of 85 year olds in developed countries, implications for health and social care and the resources needed to provide these are profound.

Future work

The baseline phase of the Newcastle 85+ Study has resulted in a uniquely rich dataset. This paper provides a comprehensive picture of health and disease among 85 year olds in north east England at a particular time, which will serve as a baseline for the prospective monitoring of changes in health status of study participants and as a comparison with future cohorts of the oldest old to monitor changes in population health. The full potential of these data has yet to be exploited; further work is in progress tackling particular health domains in more detail, together with an exploration of factors underlying the variability in health. The identification of biomarkers of ageing is a major avenue of research. Future work will include the development of a frailty index to combine the vast array of health measures into one variable of greater complexity and utility than the simple disease count included in this paper. The full potential of the study will be realised through longitudinal study of the cohort, when health trajectories and outcomes and their associations with underlying biological, medical, and social factors will be examined to identify factors that maintain health and independence.

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Contributors: JC participated in the design and execution of the study; data collection; data preparation, analysis, and interpretation; and the development and writing of the paper. KD participated in the study design, data collection, and data preparation. CJ participated in the study design, the development and writing of the paper, and supervised the analysis. AK participated in the analysis and interpretation of data and writing of the paper. JB participated in the design and conduct of the study, analysis, and writing of the paper. MPE participated in the design and conduct of the study, analysis, and writing of the paper. LAR participated in recruitment, data collection, and writing the paper. CM-R participated in the study set-up and blood collection and blood tests. TvZ participated in the study design and data collection. OFWJ participated in the study design, data interpretation, and development and writing of the paper. TBLK conceived the study, secured funding, and oversaw all aspects as principal investigator. He participated in the design and execution of the study; data management and analysis; and the development and writing of the paper. JC and TBLK are the guarantors. All authors saw and approved the final manuscript, had full access to all of

the data (including statistical reports and tables) in the study, and can take responsibility for the integrity of the data and the accuracy of the data analysis. In addition to the authors the following contributed to the Newcastle 85+ Study as members of the management team or Academic Stakeholders Group: Ashley Adamson, Fraser Birrell, John Burn, Patrick Chinnery, Mike Clarke, Daniel Collerton, Paul Corris, Chris Day, Andrew Fisher, Gary Ford, Roger Francis, Tim Goodship, John Isaacs, Bernard Keavney, Roseanne Kenny, John Mathers, Janet McComb, Ian McKeith, Simon Pearce, Robert Pickard, Brian Saxby, Therese Small, Jimmy Steele, Angus Walls, and Keith Wesnes.

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Competing interests: None declared.

Ethical approval: This study was approved by the Newcastle and North Tyneside 1 research ethics committee.

Data sharing: No additional data are available.

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CORRECTIONS

Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study

The authors of this Research paper (*BMJ* 2009;339:b4904, doi:10.1136/bmj.b4904) have alerted us to an error in table 1. Under the column heading "England and Wales (%)" the percentage for "white" should have been 98.5% [not 89.2%], and the percentage for "non-white" should have been 1.5% [not 10.8%]. This correction necessitates further corrections to the paper.

Under the section "Representativeness of study sample" the second sentence in the second paragraph should read: "Sociodemographically, the 85 year olds living in Newcastle upon Tyne and North Tyneside are generally comparable to those in England and Wales." The fourth sentence in the second paragraph of the section "Strengths and limitations of the study" also needs to be corrected. This sentence should read: "Comparison of the Newcastle 85+ cohort with sociodemographic data from the national census 2001 showed our sample to be broadly representative of England and Wales."

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APPENDIX B

Losing the ability in activities of daily living in the oldest old: a hierarchic disability scale from the Newcastle 85+ study

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Losing the Ability in Activities of Daily Living in the Oldest Old: A Hierarchic Disability Scale from the Newcastle 85+ Study

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Abstract

Objectives: To investigate the order in which 85 year olds develop difficulty in performing a wide range of daily activities covering basic personal care, household care and mobility.

Design: Cross-sectional analysis of baseline data from a cohort study.

Setting: Newcastle upon Tyne and North Tyneside, UK.

Participants: Individuals born in 1921, registered with participating general practices.

Measurements: Detailed health assessment including 17 activities of daily living related to basic personal care, household care and mobility. Questions were of the form 'Can you …' rather than 'Do you…' Principal Component Analysis (PCA) was used to confirm a single underlying dimension for the items and Mokken Scaling was used to determine a subsequent hierarchy. Validity of the hierarchical scale was assessed by its associations with known predictors of disability.

Results: 839 people within the Newcastle 85+ study for whom complete information was available on self-reported Activities of Daily Living (ADL). PCA confirmed a single underlying dimension; Mokken scaling confirmed a hierarchic scale where 'Cutting toenails' was the first item with which participants had difficulty and 'feeding' the last. The ordering of loss differed between men and women. Difficulty with 'shopping' and 'heavy housework' were reported earlier by women whilst men reported 'walking 400 yards' earlier. Items formed clusters corresponding to strength, balance, lower and upper body involvement and domains specifically required for balance and upper/lower limb functional integrity.

Conclusion: This comprehensive investigation of ordering of ability in activities in 85 year olds will inform researchers and practitioners assessing older people for onset of disability and subsequent care needs.

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Activities that are required to function independently in daily life, so called activities of daily living (ADLs), have long been seen as essential measures of disability in ageing studies and in clinical practice to assess care needs. When Basic (personal care) Activities of Daily Living (BADLs), for instance feeding, bathing, and toileting [1], are combined with Instrumental Activities of Daily Living (IADLs) which measure the ability to self-care within a household through activities such as shopping, cooking and doing housework [2], they better describe the spectrum of disability for a broader range of people [3]. In addition some researchers discriminate between BADLs, IADLs and mobility items such as walking a short distance, using steps and moving around the home, the latter comprising functional limitations (specific actions) rather than compound actions that form activities.

The hierarchical structure to the order in which loss of ability in both BADL and IADL items occurs has been confirmed by cross-sectional and longitudinal studies [3–7]. When both BADL and IADL items are considered together, difficulty with IADL items precedes difficulty with BADL items within the hierarchy [3]. The order of loss of ability to perform activities has also been classified in terms of four domains with each domain containing multiple activities that are similar in terms of their need for specific functional integrity combinations of dexterity, balance, strength and upper or lower extremity involvement [5]. For example the first abilities lost require manual dexterity and the last upper rather than lower limb control.

A number of issues remain unresolved in terms of the hierarchy of activities. Most studies have included only a small set of items, typically five or six and, if not selected to span the full range of disability, may result in floor effects. Few studies have investigated hierarchies separately for men and women, particularly important for IADLs such as cooking, which may be confounded with sex-specific household roles, so-called situational disability as opposed to 'true' functional disability [8]. In addition few studies have included large numbers of the oldest old, those aged 85 years and older, who represent the fastest growing section of the population [9].

The aims of this paper were to develop a hierarchical disability scale, using a much wider range of BADL, IADL and mobility items than previously employed which was appropriate for the men and women using cross-sectional (baseline) data from a birth cohort of over 800 85 year old participants in the Newcastle 85+ Study [10,11]. In addition we aimed to validate the scale by examining its relationship with known predictors of disability.

We feel that further confirmation of the ordering of loss of BADLs and IADLs in this unselected single year birth cohort across a much wider range of activities, would assist researchers and clinicians in choosing subsets of activities that span the whole spectrum of disability and deepen understanding of the order in which older people lose functional capacity, thereby facilitating the design of more appropriate aids and appliances and the targeting of resources during the onset and progression of disability.

Results

The study population for analysis comprised 839 of the health assessment sample (98.8%) this being participants who had both a health assessment with complete data on all BADL, IADL and mobility items, and a review of general practice records. Table 1 shows that women formed 62% (520) of the study population; 10.1% (85) of the study population resided in an institution and women were at least twice as likely to live in an institution compared with men ($p = 0.004$,OR = 2.1), 7.0% (58) had severe cognitive impairment (SMMSE 0–17) with no difference in prevalence between men and women ($p = 0.54$), and 25.5% (211) had three or more long standing illnesses, again with no difference between men and women ($p = 0.15$). Women were nearly twice as likely to take more than 12 seconds to complete the timed up-and-go compared to men ($P<0.001$, OR = 1.9). There was no statistically significant difference in the number of prescribed medications between men and women ($p = 0.07$) or in the number of diagnosed diseases they had ($p = 0.10$).

Participants experienced most difficulty with cutting toenails, shopping and using steps and least with washing hands and face and feeding (Table 2). Women experienced significantly more difficulty than men with all items except dressing and light housework.

PCA identified for men that one component (eigenvalue = 12.8) explained 75.4% of the variance with the second component (eigenvalue = 1.1) capturing only 6.7% further. Similar results were found for women, with the first component (eigenvalue = 11.0) capturing 71.8% of the variance and the second component (eigenvaue = 1.2) explaining a further 7.2%. This was further confirmed when men and women were analysed together; component 1 accounted for 76.2% of variation (eigenvalue 11.9); component 2 explained 6.2% of the variation (eigenvalue = 1.1). Whether men and women were analysed together or separately we

Table 1. Basic Descriptive Statistics of the Study Population by Sex.

	Men - %(n)	Women - %(n)	All - %(n)	p-value
Living arrangements				
Community	93.7 (299)	87.5 (455)	89.9 (754)	p = 0.0040
Institutions	6.3 (20)	12.5 (65)	10.1 (85)	
Years of education				
< = 9	60.8 (194)	64.4 (335)	63.1 (529)	p = 0.5350
10–11	24.1 (77)	21.2 (110)	22.3 (187)	
>11	15.1 (48)	14.4 (75)	14.7 (123)	
MMSE				
0–17	6.6 (21)	7.2 (37)	7.0 (58)	p = 0.0920
18–21	3.1 (10)	6.8 (35)	5.4 (45)	
22–25	18.2 (58)	14.7 (76)	16.1 (134)	
26–30	72.0 (229)	71.3 (368)	71.6 (597)	
No. of longstanding illnesses				
None	18.7 (59)	20.7 (106)	20.0 (165)	p = 0.1510
1	33.0 (104)	28.2 (144)	30.0 (248)	
2	26.4 (83)	23.3 (119)	24.5 (202)	
3+	21.9 (69)	27.8 (142)	25.5 (211)	
Timed up and go test				
≤12 seconds	43.5 (127)	28.5 (128)	34.4 (255)	p<0.0001
>12 seconds	56.5 (165)	71.5 (321)	65.6 (486)	
Number of prescribed medications (median (IQR))	6 (4–8)	6 (4–9)	6 (4–9)	p = 0.0723
Simple disease count (median (IQR))	4 (3–6)	5 (4–6)	5 (3–6)	p = 0.0999

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Table 2. Prevalence of 'Difficulty' in (I)ADL and Mobility Items - %(n).

(I)ADL or Mobility Item	Men	Women	All	OR (95% CI)[§]
Cutting Toenails	58.9 (188)	69.4 (361)	65.4 (549)	1.6 (1.2, 2.1)*
Shopping	38.2 (122)	63.1 (328)	53.6 (450)	2.8 (2.0, 3.7)*
Use Steps	38.9 (124)	54.4 (283)	48.5 (407)	1.9 (1.4, 2.5)*
Walk 400 Yards	39.5 (126)	53.1 (276)	47.9 (402)	1.7 (1.3, 2.3)*
Heavy Housework	30.1 (96)	56.7 (295)	46.6 (391)	3.0 (2.2, 4.1)*
Full Wash	25.4 (81)	38.8 (202)	33.7 (283)	1.9 (1.4, 2.6)*
Manage Money	19.7 (63)	27.1 (141)	24.3 (204)	1.5 (1.1, 2.2)*
Move Around House	17.6 (56)	25.6 (133)	22.5 (189)	1.6 (1.1, 2.3)*
Cooking a Hot Meal	18.2 (58)	25.2 (131)	22.5 (189)	1.5 (1.1, 2.2)*
Transfer from Chair	20.4 (65)	22.1 (115)	21.5 (180)	1.1 (0.8, 1.6)
Light Housework	16.9 (54)	21.7 (113)	19.9 (167)	1.4 (0.9, 2.0)
Transfer from Toilet	14.4 (46)	20.6 (107)	18.2 (153)	1.5 (1.0, 2.3)*
Manage Medications	14.4 (46)	20.0 (104)	17.9 (150)	1.5 (1.0, 2.2)*
Dressing	15.7 (50)	18.8 (98)	17.6 (148)	1.2 (0.8, 1.9)
Transfer from Bed	11.9 (38)	18.1 (94)	15.7 (132)	1.6 (1.1, 2.5)*
Wash Face & Hands	4.4 (14)	7.1 (37)	6.1 (51)	1.7 (0.9, 3.4)
Feeding	3.1 (10)	7.3 (38)	5.7 (48)	2.4 (1.2, 5.6)*

*Statistically significant gender difference at $\alpha = 0.05$.
[§]- Odds ratio: Women: Men.
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found strong evidence of unidimensionality with component one always producing a far greater eigenvalue than component two and with approximate equal loading factors across all items (factor loadings all: minimum = 0.188, maximum = 0.262; men: minimum = 0.186, maximum = 0.271; women: minimum = 0.192, maximum = 0.268). However when men and women were analysed together, the second component indicated larger loading factors for the 'manage money' and 'manage medication' items, suggesting that this could be a dimension related to cognition, although this was less evident for men alone.

Mokken Scaling indicated that a hierarchy was present within the data and confirmed the unidimensionality conclusions of the PCA (Loevinger Scalability Co-efficient = 0.68). All items satisfied the assumption of single monotonicity thus suggesting that each item forms at distinct loci on a disability scale i.e. no items were measuring disability at exactly the same level. However, five items violated the assumption of double monotonicity: 'transfer from chair', 'transfer from toilet', 'manage medications', 'move around the home' and 'manage money' (women only) (Table 3). As the PCA indicated a possible second dimension related to cognition, loading on 'managing money' and 'managing medications', and since these items also failed the assumption of double monotonicity when men and women were analysed separately, the Mokken Scaling was repeated with these items removed. Removal of these items increased the strength of the hierarchical scale (Loevinger Scalability Coefficient $\geq$0.71) (Table 1), removed any further violation of assumptions and was significantly better than when cognition items were included. All analyses reported subsequently were calculated with the cognition items removed.

For both men and women, 'cutting toenails' was the first activity with which participants had difficulty, and feeding was the last. The scaling algorithm constructed a numerical ordering for the items which indicated whether items had a tendency to be clustered together in terms of difficulty. When the scores of relative difficulty in performance of the items were plotted (Figure 1), clear areas of clustering of items was evident, corresponding with previously reported domains requiring particular combinations of lower and upper body strength combined with balance [5]; these being indicated in Figure 1 by; (A) – involving complex manual dexterity and balance; (B) – long distance mobility and balance; (C) – upper limb control and standing balance and (D) – upper limb control in a seated position.

The disability scale formed from assigning participants to the highest hierarchical position of the items with which a participant had difficulty, was highly correlated with the more usual scale formed by summing the number of items (out of 15) with which the participant had difficulty (Spearman's $\rho = 0.94$) and it had very strong internal consistency (Cronbach's $\alpha = 0.937$). Further validation by comparison with known predictors of disability (Table 4) showed a significant association with all measures apart from education.

Exclusion of those residing in institutions had no effect on either the PCA or the Mokken Scaling procedure. Similarly, using a cut point of 'needing help' rather than 'difficulty' for the BADL, IADL and mobility items did not alter the conclusions.

Methods

The Newcastle 85+ Study [10,11] recruited a cohort of 1040 85 year olds from general practices in Newcastle and North Tyneside, UK. Eligible individuals were all those born in 1921 (aged around 85 at the time of recruitment) and who were permanently registered with a general practice in the study area. 83% (53/64) of general practices agreed to take part; those who declined were similar on practice size, the proportion who were training practices, National Health Service (NHS) Quality and Outcomes Framework score Index of Multiple Deprivation score (IMD) for 2004 to those agreeing. Participating general practitioners were asked to review patient lists prior to mail-out and to exclude only those individuals with end stage terminal illness (n = 11). All those

Table 3. Hierarchy of Loss of Ability in (I/B)ADL and Mobility Items Formed by Mokken Scaling.

Hierarchy Position	All	Men	Women
1 – Most 'difficult' (lost first)	Cutting Toenails	Cutting Toenails	Cutting Toenails
2	Shopping	Walk 400 Yards	Shopping
3	Use Steps/Stairs	Use Steps/Stairs	Heavy Housework
4	Walk 400 Yards	Shopping	Use Steps/Stairs
5	Heavy Housework	Heavy Housework	Walk 400 Yards
6	Wash all over	Full Wash	Full Wash
7	Manage Money	Transfer from Chair	Manage Money*
8	Cook a Hot Meal	Manage Money*	Move Around House*
9	Move Around House*	Cook a Hot Meal*	Cook a Hot Meal
10	Transfer from Chair*	Move Around House	Transfer from Chair
11	Light Housework	Light Housework	Light Housework
12	Transfer from Toilet*	Dressing	Transfer from Toilet*
13	Manage Medication*	Transfer from Toilet*	Manage Medication*
14	Dressing	Manage Medication*	Dressing
15	Transfer from Bed	Transfer from Bed	Transfer from Bed*
16	Wash Face & Hands	Wash Face & Hands	Feeding
17 – Least 'difficult (lost last)'	Feeding	Feeding	Wash Face & Hands
Loevinger Scalability Coefficient	0.68	0.68	0.68
Loevinger Scalability Coefficient (with cognition items removed)	0.72	0.71	0.72

*Violated double monotonicity assumption (when cognition items were included).
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who met these inclusion criteria were invited to participate (n = 1459), whether living at home or in an institution, and regardless of their state of health with recruitment and assessment taking place over a 17 month period during 2006–2007. A total of 358 people (24.5%) declined to participate, these being similar in terms of sex and deprivation to those who agreed to take part [10]. Study participants were assessed in their normal place of residence, including institutional care, by trained research nurses with a series of questionnaires, measurements, function tests, a blood test and a review of general practice records. Participants could decline parts of the assessments. Of the potential sample of 1040 people, 849 agreed to the health assessment and a review of general practice records; 188 to GP record review only and 3 agreed only to take part in the health assessment. Fewer females were in the health assessment plus record review group (62.0%, 526/849) than in the record review only group (72.3%, 136/188) (full details of the design of the study can be found elsewhere [10,11]).

The present analysis was confined to those participants who had the health assessment since this was the only source of information on ADLs. During the health assessment, participants were asked if they were able to do the following activities: cut toenails, wash all over, transfer from a bed/toilet/chair, dress and undress, wash face and hands and self-feed (including cutting up food), shop for groceries, do light housework, do heavy housework, manage money, manage medications and prepare and cook a hot meal. In addition participants were asked three questions on mobility: get around in the house, go up and down stairs/steps, and walk at least 400 yards? Each question was framed as 'can you' rather than 'do you' to have greater capacity to assess true levels of disability [12] accounting for situational responses. Responses to all items were: I have no difficulty doing this by myself/ I have some difficulty doing this by myself/ I can only do this by myself if I use an aid or appliance/ I am unable to do this by myself, I need someone's help.

Socio-demographic information included sex, years of education, and institutional status, with additional variables including the number of longstanding illnesses; the number of prescribed medications (extracted from GP records); a disease count from the presence of 18 selected chronic diseases [10] and the timed up and go test [13] with a cut point that determines those with normal function as performing the test in 12 seconds or less [14]. Cognitive function was also measured by the Standardised Mini-Mental State Examination [15,16] with severe cognitive impairment classified by a score of 17 or less out of 30, this cut point having high sensitivity for moderate and severe dementia [17].

Ethnical approval was obtained from Newcastle & North Tyneside Local Research Ethics Committee One and informed written consent was obtained from all participants.

To determine whether the BADL, IADL and mobility items formed a single dimension we used Principal Component Analysis (PCA) based on the polychoric correlations between items and with whole ordinal scales. The number of dimensions was determined using Kaiser's Criterion, including only eigenvalues greater than one [18]. Having identified a single dimension, we dichotomised the items using a cut point of no difficulty/some difficulty (from a four category response of 'no difficulty', 'some difficulty', 'only with and aid' and 'unable to do this'). We then used Mokken Scaling to verify the unidimensionality and to determine the hierarchy from the Loevinger Scalability Coefficient (H) [19] with values of H between 0.3–0.39 being taken to suggest a weak Mokken scale; between 0.4–0.49 an acceptable Mokken scale and greater than 0.5 a strong Mokken scale [20]. Items were deleted from the scale if they did not satisfy the assumption of

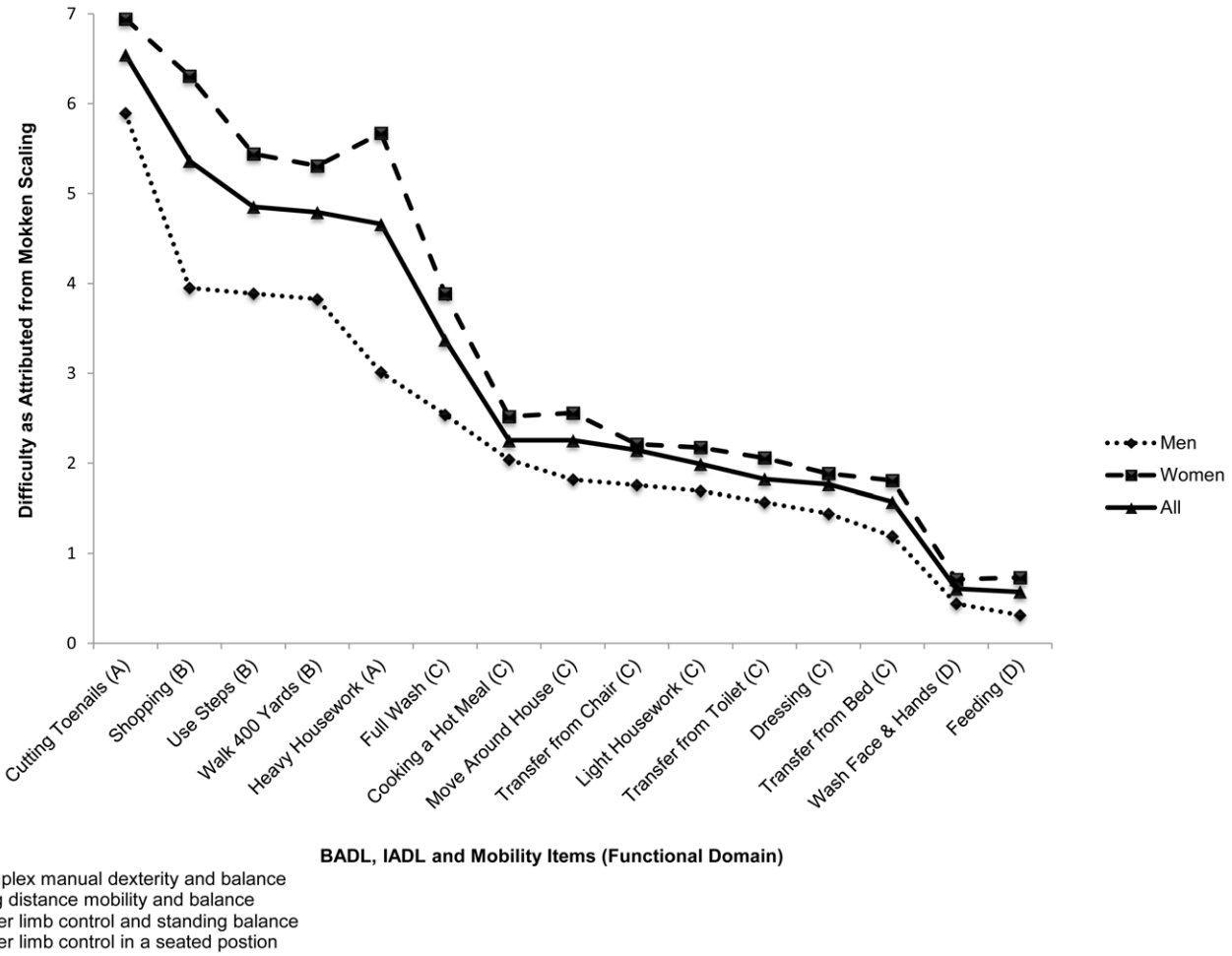

Figure 1. Relative Difficulty of BADL, IADL and Mobility Items (Domain of Disability [5]). Abbreviations: BADL – Basic Activities of Daily Living. IADL – Instrumental Activities of Daily Living.
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single monotonicity (each item forms at a distinct loci on a scale of decreasing difficulty) and double monotonicity (the Item Characteristic Curves are non-overlapping). As Mokken scaling uses multiple tests on the data a Bonferroni correction was implemented to reduce the type I error. A scoring system was formed based on the highest item in the hierarchy with which the participant had difficulty (a score of 1 being low indicating difficulty with the first (most difficult) item in the hierarchy and a score of 17 being the highest indicating difficulty with then last (least difficult) item in the scale). Participants having no difficulty with all items in the scale were assigned a score of zero. Cronbach's alpha [21] was used to assess the internal consistency of the scale with values close to one suggesting a strong scale and values close to zero indicative of poor internal consistency. We constructed a disability scale corresponding to the highest hierarchical position of the items with which the participant had difficulty. After separation into four categories; difficulty with no items, difficulty with 1–5 items, difficulty with 6–10 items and difficulty with 11–15 items (to allow for nonlinear associations) the scale was validated against known predictors of disability [22].

Separate analyses were carried out for men and women. Sensitivity analyses were undertaken excluding the participants living in institutions and using the alternative cut-point for performance of no help required/help required. All analyses were carried out in Stata 10.1 [StataCorp. 2009. Statistical Software: Release 10.1. College Station, TX: Stata] with statistical significance at $\alpha = 0.05$.

Discussion

We found a strong hierarchical ordering to loss of ability in a wide range of basic and instrumental activities of daily living and the items measuring mobility in an unselected population aged 85 years in 2006. 'Cutting toenails' was the first item with which participants found difficulty and 'washing hands and face' and 'feeding' the last items. The ordering of the items in our hierarchic scale confirms previous studies using cross-sectional [3,5,6,23] and longitudinal [4,7] data, but which are now 10–20 years and were based on a more restricted set of items predominantly in the younger old. Thus our study adds considerably to the evidence that the order of loss of activities does not vary with age. Sex differences were evident from our single birth year cohort; not only were women more likely to report difficulty with each activity than were men but we also found that the ordering of loss differed between men and women of the same age with women reporting more difficulty with activities requiring strength ('shopping' and 'heavy housework') whilst men were earlier in reporting difficulty walking. Moreover the ordering and our conclusions were

Table 4. Association of the Hierarchical Disability Scale with Known Predictors of Disability - %(n).

		Hierarchic Scale			
	None	**1–5**	**6–10**	**11–15**	**p-value**
Living arrangements - %(n)					
Community	98.8 (168)	99.6 (264)	89.4 (160)	72.0 (162)	p<0.001
Institutions	1.2 (2)	0.4 (1)	10.6 (19)	28.0 (63)	
Years of education - %(n)					
<=9	61.8 (105)	63.8 (169)	62.0 (111)	64.0 (144)	
10–11	17.7 (30)	26.4 (70)	24.6 (44)	19.1 (43)	p = 0.8886
>11	20.6 (35)	9.8 (26)	13.4 (24)	16.9 (38)	
MMSE - %(n)					
0–17	87.1 (148)	81.5 (216)	66.5 (119)	51.8 (114)	
18–21	11.2 (19)	14.0 (37)	17.9 (32)	20.9 (46)	p<0.001
22–25	1.8 (3)	4.2 (11)	7.8 (14)	7.7 (17)	
26–30	0.0 (0)	0.4 (1)	7.8 (14)	19.6 (43)	
No of longstanding illnesses - %(n)					
None	40.6 (69)	18.6 (49)	15.3 (27)	9.3 (20)	
1	36.5 (62)	34.1 (90)	21.0 (37)	27.3 (59)	p<0.001
2	15.9 (27)	23.9 (63)	34.1 (60)	24.1 (52)	
3+	7.1 (12)	23.5 (62)	29.6 (52)	39.4 (85)	
Timed up and go test - %(n)					
≤12 seconds	66.7 (112)	39.2 (100)	17.5 (28)	9.5 (15)	p<0.001
>12 seconds	33.3 (56)	60.8 (155)	82.5 (132)	90.5 (143)	
Number of prescribed medications (median (IQR))	4 (2–7)	5 (3–8)	7 (5–10)	7 (5–10)	p<0.001
Simple disease count (median(IQR))	4 (3–5)	4 (4–6)	5 (4–6)	5 (4–6)	p<0.001

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unchanged if inability to perform was defined as requiring the help of another person rather than the more unbiased having difficulty performing alone. However measuring disability by the requirement for 'help' may depend on the availability of help which may therefore bias results [24] and thus our primary measure based on 'difficulty' adds strength to our study.

Previous research has indicated that disability in later life appears to progress with difficulty in IADLs preceding that with BADLs [4,6,7,23]. Though this was broadly true in our analysis; there was overlap in the ordering of IADLs and BADLs and our ordering was much more consistent with the domains of disability defined by Ferrucci et al [5] which combine IADL, BADL and mobility items requiring similar underlying impairments. They defined the first domain in which difficulty would be as activities requiring complex manual dexterity coupled with balance such as 'cutting toenails' and 'heavy housework'. Activities in the next domain require balance and involve the capacity to walk long distances, the equivalent activities in our study being 'shopping', 'use steps', 'walk 400 yards', 'full wash', 'cooking a hot meal', 'light housework'. The third domain in decreasing difficulty contained activities requiring standing balance and good upper limb control; 'move around the home', 'transfer from chair', 'toilet', 'dressing' and 'transfer from bed'. The final domain, and the easiest to perform, related to good upper limb control when in a seated position; 'washing face and hands' and 'feeding'. Only two items appeared out of step between our hierarchy and Ferrucci's four domains; 'heavy housework' and 'light housework' and it may be that the perceived meanings and the nature of these tasks have changed more over time than for other activities.

Our disability scale formed from the hierarchy performed well when examined alongside known predictors of disability. The ordering of loss of activities is of potential use to others selecting activities to measure a range of severity of disability both in the research and clinical setting. We collected information from over 800 older people aged 85 years of age on their situational disability (questions being framed as 'can you' rather than 'do you') from 17 IADLs, BADLs and mobility items, a much larger number than previous studies and with minimal missing data. The Newcastle 85+ Study has a broad range of health measures and is representative of the larger population of older people in Newcastle upon Tyne [10].

The main limitation of our study is the cross-sectional nature of the data although our results were in agreement with the previous longitudinal studies [4,7] Nevertheless, unlike other studies, our population came from a single birth cohort with a high response rate and included those in institutions. Thus the sex difference we found in the order of loss of activities was not due to the greater average age of women compared to men in general older populations. Inclusion of those in institutions where there is a high prevalence of dementia may be viewed as a limitation. We had a small proportion of our sample (n = 71, 8.5%) who had a diagnosis of dementia and these participants may lose ability to perform activities independently in a different order to those without dementia, for instance they may be able to walk 400 yards but may not be able to dress themselves. However, we repeated all analyses excluding those in institutions and the conclusions were unchanged. Nevertheless, when we originally included items more dependent on complex cognitive ability than physical ability

('managing money' and 'managing medication') we found that they did not satisfy all of the underlying assumptions of the scaling method and their subsequent exclusion strengthened the scale formed although the remaining items may be viewed as being more 'physical'.

Results of this analysis could therefore provide information to help identify older people at risk of functional decline and for the allocation, and prioritisation of, community services and social support to enable independent living for as long as possible. We found in terms of the ranking of difficulty that a number of items were ranked similarly suggesting that if these items alone were selected for inclusion in a disability scale, or indeed for assessment purposes, then the range of severity would be limited. 'Cutting toenails' and 'shopping' were the items with which our population most commonly reported difficulty. The former requires good balance and manual dexterity whilst the latter requires upper body strength and mobility. Physical activity programmes to delay the onset of disability should perhaps focus on exercises to improve these functions; in addition our results could support an argument for the essential core provision of specific services such as chiropody within the community care, as opposed to the current limited provision.

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Author Contributions

Conceived and designed the experiments: AK JC KD JB LR CJ. Performed the experiments: AK JC KD JB LR CJ. Analyzed the data: AK CJ. Wrote the paper: AK JC KD JB LR CJ.

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APPENDIX C

The contribution of diseases to the male-female disability-survival paradox in the very old: results from the Newcastle 85+ study

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The Contribution of Diseases to the Male-Female Disability-Survival Paradox in the Very Old: Results from the Newcastle 85+ Study

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Abstract

Background: Explanations for the male-female disability-survival paradox - that woman live longer than men but with more disability - include sex differences in diseases and their impact on disability and death. Less is known about the paradox in the very old. We examine sex differences in the presence and impact of disabling and fatal diseases accounting for the male-female disability-survival paradox in very late life.

Methods: We use data from the Newcastle 85+ Study, a cohort of people born in 1921 and all recruited at age 85 in 2006. Participants underwent a health assessment (HA) at baseline, 18 months, 36 months, 60 months, and a review of their GP records (GPRR) at baseline and 36 months. We used multi-state modelling to assess the impact of specific diseases on disability and death. Disability (measured via ADLs/IADLs) was categorised as no disability (difficulty with 0 activities), or disabled (difficulty with one or more activities). Diseases were ascertained from review of general practice records and cognitive impairment which was defined as an sMMSE of 21 or less (from health assessment).

Results: In participants who had complete HA and GPRR, women had more arthritis (RR = 1.2, 95% CI: 1.1–1.3) and hypertension (RR = 1.2, 95%CI 1.0–1.3), more disability, and were more likely disabled at all follow-ups. From multistate models, women with cerebrovascular disease (HR: 2.6, 95% CI: 2.1–3.4) or respiratory disease (HR: 2.0, 95% CI: 1.4–3.0) were more likely to become disabled than those without but this did not hold for men (sex difference $p<0.01$). Men were more likely to die from respiratory disease (HR: 2.2, 95% CI: 1.8–2.8) but this did not hold for women ($p = 0.002$).

Conclusion: The disability-survival paradox was still evident at age 85 and appears due to sex differences in the types of diseases and their impact on the disability pathway.

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Introduction

Women live longer than men on average, but their longer life expectancy is accompanied by more years with disability, both in absolute terms and as a proportion of remaining life [1].

Understanding the basis of this "disability-survival paradox" [2,3] is important for addressing the different health challenges faced by very old men and women, the fastest growing age group in many countries [4], and could inform more effective clinical practice. The paradox may derive from intrinsic differences (biological, social or behavioural) between men and women [3,5,6]. Women are reported to have a greater number of acute and non-fatal chronic diseases, whereas men have fewer diseases in total but more of these are life-threatening [5,7,8]. A potential basis for a biological difference between men and women is the actions of sex hormones. Female sex hormones bring benefits for women by modulating lipid levels, and hence cardiovascular risk, and by affecting the immune response [5]. A recent report describes longer lifespans for Korean eunuchs than intact men, which is consistent with the idea that male sex hormones, notably testosterone, may be a risk factor for earlier mortality [9], notwithstanding the limitations of such historical studies. Behavioural differences between women and men include their perception of symptoms and readiness to consult with healthcare professionals. Sex differences in physician diagnostic patterns and self-reporting of disease may also contribute [10]. It is also possible that the progression of disease to disability may be more marked for women than men, especially if women are under-treated for some conditions [11]. Men's higher mortality may also result from a greater severity of disease, which is inadequately captured in analyses based on the simple presence/absence of a condition. The

contribution of such distortion has previously been reported to be small but it cannot altogether be discounted [2].

The Newcastle 85+ Study is a population-based longitudinal study of health and ageing in the very old. The comprehensive, multidimensional health assessment performed in this study, combined with the high level of success in recruiting from this age group [12], has provided a rich resource from which we can determine whether there are sex differences in the impact of specific diseases on disability and survival beyond age 85. More specifically we have examined the disability-survival paradox with a single hypothesis in mind: that the gender disparity in mortality and disability is driven by sex differences in the type of disease and their impact on disability.

Methods

Recruitment and Study Protocol

The sampling frame for the Newcastle 85+ Study comprised all surviving adults born in 1921, who turned 85 in 2006 when the study commenced, and who were permanently registered with a participating general practice in Newcastle or North Tyneside NHS Primary Care Trusts in North-East England. Full details of study design and participant recruitment have been reported [12–14]. At baseline, participants underwent a detailed multidimensional health assessment conducted by a trained research nurse in their usual place of residence (own home or institution). Data on diagnosed diseases (with date of first diagnosis) and prescribed medication were obtained from participants' general practice (GP) medical records. Following baseline assessment, participants were re-assessed at 18, 36 and 60 months.

Disability Measures

At baseline and follow-up assessments, participants were asked about their ability to perform 15 activities comprising Instrumental and Basic Activities of Daily Living (IADLs, BADLs) and mobility items (Figure 1) [15]; these were taken predominantly from the Groningen Activity Restriction Scale [16]. As loss of ability for individual items formed a single hierarchy, similar for men and women [17], we calculated a disability score scoring 0 for each item reported to be performed without difficulty and 1 for each item performed with difficulty (maximum score 15). Participants were classified as having disability (difficulty with one or more items) or no disability (difficulty with no items). The association between self-reported performance in mobility items and an objectively measured timed-up-and-go (TUG) [18] test was high, and similar in both men and women [15].

Instrumental and Basic Activities of Daily Living and Mobility items
Are you able to get in and out of bed?
Are you able to get and out of a chair?
Are you able to get on and off the toilet?
Are you able to manage money?
Are you able to up and down stairs/steps?
Are you able to manage medications?
Are you able to dress and undress yourself?
Are you able to wash your face and hands?
Are you able to wash yourself all over?
Are you able to cut your own toenails?
Are you able to feed yourself?
Are you able to cook a hot meal?
Are you able to shop for your groceries?
Are you able to do light housework?
Are you able to do heavy housework?
Possible responses (score):
I have no difficulty doing this by myself (0)
I have some difficulty doing this by myself (1)
I can do this by myself if I use an aid or appliance (1)
I am unable to do this by myself; I need someone else's help (1).

Figure 1. Intrumental and Basic Activites of Daily Living (IADLs, BADLs) and mobility items included in the disability score with possible repsonses.
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Disease Status

Disease status at baseline was ascertained predominantly from GP medical records; data extraction was conducted by trained research nurses following a standard protocol. Inter-rater reliability assessment demonstrated at least moderate agreement between the nurses for all diseases [13]. In the UK, patients are registered with a single general practice which acts as a gatekeeper to secondary care and receives details of all hospital admissions and outpatient attendances. The review of general practice records included hospital correspondence to ensure that all pre-existing diagnoses were extracted irrespective of where the diagnosis was made (from both paper and electronic formats). The only exception to ascertainment from GP records was for cognitive impairment, which we defined by a Standardised Mini-Mental State Examination (SMMSE) score of 21 or below [19]; SMMSE was conducted as part of the participant health assessment.

For the purpose of this analysis, we focused on the eight most prevalent diseases in our cohort; in some cases we grouped multiple conditions into a category (e.g. all arthritic diseases) whilst other diseases were retained as single entities (e.g. hypertension) (Figure 2). For each participant we calculated a disease count (maximum score 8). A further review of GP records was conducted at 36 months and the SMMSE was re-administered at wave three and four. Individual diseases and conditions and the disease count were therefore updated and included in the models as time-varying covariates.

Mortality

Participants' medical records were flagged with the National and Social Care Information Service to provide date and cause of death. Survival time was calculated from date of baseline health assessment to date of death or censored at 1st September 2012.

Statistical Methods

Sex differences in the prevalence of each disease were analysed by Generalised Linear Models and presented as relative risk (RR) with 95% confidence intervals. We assessed gender differences in IMD and education at baseline by ordinal logistic regression and presented them as odds ratios (OR) with 95% confidence intervals. Sex differences in the level of disability at baseline were analysed by Tobit regression [20] to account for the 'floor effects' in the disability score and adjusted for: years of full-time education (0–9 years/10–11 years/12+ years); Index of Multiple Deprivation (IMD), an area level measure of socio-economic disadvantage (categorised as $<20^{th}$ centile, 20–80^{th} centile, $>80^{th}$ centile) [21]; and disease count. A similar approach was used to compare sex differences in baseline disability associated with each specific disease with adjustment for residual disease count (disease count excluding the disease of interest), IMD and education. We present the difference in disability scores with 95% confidence interval.

To assess the contribution of specific diseases to transitions to and from disability and to death over five years, we fitted a multistate model in continuous time with three states: no disability,

Disease Group	Data source and ascertainment criteria
Arthritis*	GP records: any recorded diagnosis of Generalised Osteoarthritis, Hand, Hip and Knee Osteoarthritis Rheumatoid, Degenerative, Poly, Gouty, Septic, Peri, Lumbar Spondylosis, Cervical Spondylosis, Anklyosing Spondylitis and Psoriatic Arthropathy
Hypertension*	GP records: any recorded diagnosis of Hypertension
Cardiac disease*	GP records Heart Failure, Ischaemic heart disease (Angina, Myocardial Infarction., Coronary Artery Bypass Graft, Coronary Angioplasty/Stent)
Respiratory disease*	GP records Bronchiectasis, Pulmonary Fibrosis, Fibrosing Alveolitis, Asbestosis, Pneumoconiosis, Asthma, Chronic Bronchitis, Emphysema, COPD
Cerebrovascular disease*	GP records Stroke, Transient Ischaemic Attack, Carotid Endarterectomy
Diabetes mellitus*	GP records Type I, Type II and type unspecified
Cancer*	GP records Any cancer diagnosis in past 5 years excluding non-melanoma skin cancer
Cognitive Impairment†	Standardised Mini-Mental State Examination (sMMSE) score of ≤21

* Data taken from GP record review
† Score calculated from multi-dimensional health assessment (sMMSE)

Figure 2. Conditions examined with data sources and ascertainement criteria.
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disability, and death (absorbing state). We used this model to estimate the instantaneous rate of transition between the states (presented as hazard rates with 95% confidence intervals and mean time in the state) making the assumption that transition from no disability to death was via disability. Models were fitted with each disease individually and then adjusted for the residual disease count. Models were further adjusted for IMD and education. Since participants were all born in 1921 (and all aged 85 at baseline) we did not adjust for age in any models. Analyses were carried out in R version 2.9.1 using the msm package [22].

Ethical Issues

Ethical approval was obtained from Newcastle & North Tyneside Local Research Ethics Committee One. Written informed consent was obtained from participants; where people lacked capacity to consent, for example because of cognitive impairment, a formal written opinion was sought from a consultee, usually a relative or carer.

Results

Selection and Key Characteristics of Study Population

At baseline, data from both participant assessment and GP records was available for 854 participants; 2 people subsequently withdrew and requested all data destroyed; 2 did not have complete data on disability and 7 did not have complete GP records. The remaining 843 had complete data for disability and disease status and formed the sample for analysis. The majority (61.9%, n = 522) were female. Of the key characteristics at baseline, only level of deprivation showed a significant sex difference with women having higher levels of disadvantage than men (OR F:M = 1.3, 95% CI: 1.0–1.7) (Table 1).

Disease and Disability Prevalence at Baseline

At baseline, women were more likely to have a diagnosis of arthritis (RR: 1.2, 95% CI: 1.1–1.3) or hypertension (RR: 1.2, 95% CI: 1.0–1.3) and less likely to have a diagnosis of cerebrovascular disease (CVD) (RR: 0.8, 95% CI: 0.6–1.0) (Table 1). There was no evidence of any sex difference in the total number of diseases (p = 0.68) or in disease duration (time since first diagnosis) for any disease. Table S1 details the disease duration by gender.

Sex differences in the baseline disability score, between participants with and without specific diseases at baseline, demonstrated a broadly similar disabling impact for men and women (Table 2). For both sexes, cognitive impairment (SMMSE≤21) conferred the greatest disability, by approximately 7 points compared to those cognitively intact, then CVD with a difference in disability score of 3 points in women and 2 in men. Compared to men, women had a significantly greater disability score at baseline for all diseases except cognitive impairment and cancer where no difference was evident (Table 2). Where disease was not present levels of disability remained higher for women than men across all disease groups even after adjustment for potential confounders (deprivation, education and residual disease count).

Overall, women reported difficulty with almost two more activities on average than men (difference in mean disability score: 2.0, 95% CI: 1.2–2.7), even after adjusting for education, deprivation and disease count (Table 3).

Impact of Disease on Transitions to Disability and Death over 5 years

At each of the 18, 36 and 60 month follow-ups, over 70% of participants remained in the study (18 month: n = 626; 36 months: n = 482; 60 months: n = 342), 7–12% withdrew (18 month: n = 151; 36 months: n = 51; 60 months: n = 59) whilst around 15% died (18 month: n = 66; 36 months: n = 92; 60 months: n = 81) (Table 3).

Higher levels of disability found in women at baseline were also manifest at subsequent follow-up waves (Table 3). This pattern was unlikely to result from men being less likely to report difficulty in performance than women, as the relationship between reported

Table 1. Study population key characteristics.

	Male (n = 321)	Female (n = 522)	All (n = 843)	P-Value[§]	Sex Difference (95% CI)
Education (years)					
0–9	61.99 (199)	65.71 (343)	64.29 (542)	0.288	0.86 (0.65–1.14)*
10–11	24.92 (80)	21.65 (113)	22.89 (193)		
12+	13.08 (42)	12.64 (66)	12.81 (108)		
Area deprivation (measured by IMD)					
Low (<25 centile)	29.91 (96)	21.65 (113)	24.79 (209)	0.031	1.33 (1.02–1.74)*
Middle (25–75 centile)	47.04 (151)	52.87 (276)	50.65 (427)		
High (>75 centile)	23.05 (74)	25.48 (133)	24.56 (207)		
Disease at baseline					
Arthritis	60.44 (194)	71.84 (375)	67.50 (569)	0.001	1.19 (1.07–1.32)[†]
Hypertension	52.34 (168)	59.96 (313)	57.06 (481)	0.034	1.15 (1.01–1.30)[†]
Cardiac disease	42.06 (135)	35.63 (186)	38.08 (321)	0.060	0.85 (0.71–1.01)[†]
Cerebrovascular disease	24.61 (79)	18.97 (99)	21.12 (178)	0.050	0.77 (0.59–1.00)[†]
Respiratory disease	22.43 (72)	22.61 (118)	22.54 (190)	0.953	1.01 (0.78–1.30)[†]
Diabetes mellitus	14.33 (46)	12.64 (66)	13.29 (112)	0.483	0.88 (0.62–1.25)[†]
Cognitive impairment	10.28 (33)	14.56 (76)	12.93 (109)	0.076	1.42 (0.96–2.08)[†]
Cancer	8.10 (26)	5.36 (28)	6.41 (54)	0.104	0.65 (0.39–1.09)[†]
Disease count median (mean(sd))	2.4 (1.3)	2.4 (1.3)	2.4 (1.3)	0.680	0.06 (−0.11–0.24)[‡]

*Ordinal logistic regression – Odds ratio - men: women.
[†]Generalised linear model - Relative Risk - men: women.
[‡]T-test – difference in disease count - men: women.
[§]P-value for gender difference.
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performance on mobility items and the objectively measured TUG test were similar in men and women, at baseline and subsequent waves. Compared to men, women had higher levels of disability in the interview prior to dropout, whether dropout was due to death or withdrawal (Table 3).

We used multistate models to explore sex differences in the progression to disability and death for each disease after adjustment for residual disease count, education and deprivation (Table 4). Diabetes conferred the highest risk of incident disability in men (HR: 3.0, 95% CI: 2.4–3.8) and women (HR: 1.7, 95% CI: 1.3–2.2) (Table 4). Despite the prevalence of arthritis being highest in women, its impact on incident disability was greater for men (HR: 1.7, 95% CI: 1.2–2.5) than women (HR: 1.2, 95% CI: 1.0–1.5) but arthritis conferred a significantly increased risk of becoming disabled in both sexes. Both men (HR: 1.6, 95% CI: 1.3–1.9) and women (HR: 2.4, 95% CI: 1.9–3.0) with cardiac disease had significantly greater risk of incident disability but the risk was higher for women (p = 0.003). A greater risk of incident

Table 2. Disability by disease status at baseline.

	Disability Score - Median (IQR)							
	Men			Women			Sex difference in disability score[†]	
	With disease	Without disease	Disability score difference (95% CI)*	With disease	Without disease	Disability score difference (95% CI)*	With disease	Without disease
Arthritis	2 (1–5)	1 (0–4)	1.55 (0.27,2.83)	3(1–7)	2(0–5)	1.68 (0.68,2.67)	1.82 (0.94,2.70)	1.78 (0.32,3.23)
Hypertension	1 (0–4)	2 (0–6)	−0.92 (−2.16,0.32)	3(1–7)	3(1–7)	0.01 (−0.90,0.92)	2.37 (1.39,3.35)	1.51 (0.34,2.69)
Cardiac Disease	2 (0–5)	1 (0–5)	−0.17 (−1.43,1.09)	4(2–8)	3(1–6)	1.26 (0.34,2.18)	2.80 (1.69,3.90)	1.46 (0.45,2.48)
CVD	2 (1–6)	1 (0–4)	2.15 (0.75,3.56)	6(3–11)	3(1–6)	3.10 (2.01,4.20)	2.99 (1.28,4.69)	1.86 (1.05,2.67)
Respiratory disease	2 (0–5)	1 (0–4)	0.69 (−0.79,2.17)	4(2–8)	3(1–6)	0.94 (−0.11,2.00)	2.12 (0.68,3.56)	1.92 (1.05,2.80)
Diabetes	2.5 (0–6)	1 (0–4)	0.64 (−1.12,2.41)	4(3–7)	3(1–7)	1.18 (−0.14,2.51)	2.37 (0.53,4.21)	1.91 (1.09,2.73)
Cognitive Impairment	11 (6–13)	1 (0–3)	7.85 (6.14,9.56)	9(5.5–13.5)	3(1–5)	6.28 (5.15,7.40)	0.37 (−2.00,2.74)	1.79 (1.11,2.46)
Cancer	2 (1–3)	1 (0–5)	0.72 (−1.46,2.90)	2.5(1–7)	3(1–7)	−0.23 (−2.22,1.76)	1.19 (−1.39,3.77)	2.12 (1.33,2.90)

*Tobit regression: difference in disability score for those with and without disease.
[†]Tobit regression: sex difference in disability score for those with and without disease: women compared to men.
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Table 3. Disability by gender and participation status at baseline and follow-up waves.

	Disability Score at interview			Disability Score at previous interview		
	Median (IQR)			Median (IQR)		
	Men	Women	Sex difference*	Men	Women	Sex difference*
Baseline (n = 843)	0 (1–5)	3 (1–7)	1.97 (1.21,2.72)	–	–	–
18 months (Wave 2)						
Participant (n = 626)	2 (1–6)	4.5 (2–9)	1.90 (1.11–2.70)	1 (0–4)	3 (1–5.5)	1.79 (1.01–2.58)
Died before W2 (n = 66)	–	–	–	6 (1–12)	9 (4–14)	3.53 (0.29–7.35)
Withdrawn before W2 (n = 151)	–	–	–	2 (1–6)	5 (2–9)	2.54 (0.85–4.24)
36 months (Wave 3)						
Participant (n = 482)	4 (1–8)	5 (3–9)	1.33 (0.41–2.26)	2 (1–6)	4 (2–7)	1.76 (0.91–2.61)
Died before W3 (n = 52)	–	–	–	5 (2–8)	11 (3–14)	4.23 (1.06–7.40)
Withdrawn before W3 (n = 92)	–	–	–	3 (1–8)	7 (4–12)	2.29 (0.20–4.39)
60 months (Wave 4)						
Participant (n = 342)	4 (1–7)	5 (3–9)	1.74 (0.60–2.87)	3 (1–7)	4 (3–7)	1.04 (0.55–2.02)
Died before W4 (n = 81)	–	–	–	5 (1–10)	11 (5–13)	2.98 (0.51–5.44)
Withdrawn before (n = 59)	–	–	–	5 (1.5–10.5)	7 (3–11)	2.20 (−0.95–5.35)

*Tobit regression sex difference compared women to men.

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disability was also evident for cognitive impairment (men HR: 1.3, 95% CI: 1.1–1.6; women HR: 1.7, 95% CI: 1.0–2.9). On the other hand CVD (HR: 2.6, 95% CI: 2.1–3.4) and respiratory disease (HR: 2.0, 95% CI: 1.4–3.0) increased the risk of incident disability for women only.

Significant sex differences in the risk of death for those without disability were observed only for cancer (men: HR: 4.1, 95% CI 2.4–7.1; women: HR: 1.1, 95% CI: 0.7–1.9) and respiratory disease (men: HR: 2.2, 95% CI 1.7–2.8; women: HR: 1.0, 95% CI: 0.5–2.0) with male participants being at increased risk compared to their female counterparts (Table 4). Men with cardiac disease (HR: 1.4, 95% CI: 1.2–1.8) or CVD (HR: 1.3, 95% CI: 1.1–1.6) were at increased risk of death from a non-disabled state but this did not differ significantly from their female equivalents. The risk of death from a non-disabled state was significantly increased for both men and women with cognitive impairment (men: HR: 1.7, 95% CI: 1.4–2.0; women HR: 1.4, 95% CI: 1.0–1.9).

Recovery from disability was rare and lowest for participants with cognitive impairment though similarly for men (HR: 0.2, 95% CI: 0.1–0.3) and women (HR: 0.2, 95% CI: 0.03–0.9) and in both cases significantly less likely compared to participants without cognitive impairment (Table 4).

Hazard ratios for the risk of death once disabled were of similar magnitude for those with cognitive impairment (men HR: 2.5, 95% CI: 1.8–3.5; women HR 2.6, 95% CI: 1.8–3.8) and cardiac disease (men HR: 1.5, 95% CI: 1.2–1.8; women HR: 1.4, 95% CI: 1.1–1.8). CVD increased the risk of death once disabled for women only (HR: 1.4, 95% CI: 1.0–1.8) as did respiratory disease (HR: 1.4, 95% CI: 1.1–1.9) and cancer (HR: 1.5, 95% CI: 1.1–2.1).

The varied way in which different diseases impact on transitions to and from disability and to death for men and women is illustrated in Figure 3 for two diseases: cognitive impairment and respiratory disease. Cognitive impairment confers a very high risk of disability with little chance of recovery from disability and a high risk of death, but little difference exists between men and women. Respiratory disease on the other hand is significantly disabling only in women and has a higher risk of death for men initially disability free and women initially disabled.

Mean Time with and without Disability

Overall, and regardless of disease status, more years are spent after age 85 with disability than without for both men and women, with women spending 2.2 years more on average with disability and 0.5 years less without disability than men (Table 5).

For hypertension and arthritis, men and women spent longer with disability for both sexes than those without the disease, reflecting the low fatality and disabling effects of these conditions. This was additionally true for women with diabetes. For any of the diseases examined, women with the disease spent fewer years without disability compared to women without the disease. This was also broadly similar for men although men with hypertension spent more years (0.35 years) disability-free than men without hypertension and men with cognitive impairment spent 1.32 years longer disability-free than men without cognitive impairment.

Discussion

The goal of this paper was to determine potential reasons for the male-female disability survival paradox in the very old, in particular the role of specific diseases on disability and mortality. We approached the investigation with a single question in mind: was the mortality and disability difference between men and women primarily driven by sex variation in the type and impact of diseases [23].

We found that at age 85 women already had a higher prevalence of disability than men and were more likely to have arthritis and hypertension. Despite women having marginally less CVD and cardiac disease than men at age 85, these conditions resulted in higher disability scores in women at baseline and prospectively were more likely to be disabling in women. Respiratory disease was also significantly more disabling in women than men although prevalence at age 85 was similar for men and women. Thus from age 85 women spent longer with disability

Table 4. Hazard rates (HR) and 95% confidence intervals (95% CI) for transitions between disability states and death adjusted for comorbidity, deprivation, and education.

	Men	Women	Sex Difference *p*-value
Incident Disability	Referent*	1.26 (1.12–1.41)	0.041
Arthritis	1.72 (1.19–2.48)	1.23(1.02–1.49)	0.942
Hypertension	0.87 (0.48–1.58)	1.09(0.56–2.12)	0.315
Cardiac Disease	1.60 (1.32–1.93)	2.39(1.92–2.97)	0.003
Cerebrovascular Disease	1.11 (0.76–1.63)	2.63(2.06–3.35)	0.000
Respiratory disease	0.98 (0.74–1.29)	2.02(1.35–3.01)	0.002
Diabetes	3.03 (2.43–3.79)	1.67(1.26–2.22)	0.001
Cognitive Impairment	1.31 (1.06–1.62)	1.71 (1.02–2.86)	0.174
Cancer	0.84 (0.29–2.42)	1.85(0.71–4.80)	0.139
Death from no disability	Referent*	0.89(0.73–1.08)	0.216
Arthritis	0.70 (0.33–1.50)	0.99(0.47–2.13)	0.260
Hypertension	0.62 (0.28–1.34)	1.01(0.44–2.31)	0.200
Cardiac Disease	1.42 (1.17–1.73)	1.48 (0.97–2.26)	0.569
Cerebrovascular Disease	1.31 (1.09–1.57)	1.00(0.59–1.70)	0.173
Respiratory disease	2.16 (1.67–2.79)	1.00(0.49–2.04)	0.046
Diabetes	1.20 (0.88–1.62)	1.01(0.24–4.17)	0.592
Cognitive Impairment	1.68 (1.41–2.01)	1.38(1.01–1.89)	0.857
Cancer	4.10 (2.35–7.13)	1.10(0.65–1.86)	0.001
Disability recovery	Referent*	0.96 (0.80–1.15)	0.328
Arthritis	0.73 (0.42–1.28)	0.96(0.72–1.27)	0.196
Hypertension	1.63 (0.94–2.81)	0.79(0.30–2.08)	0.899
Cardiac Disease	0.94 (0.57–1.56)	0.96(0.49–1.88)	0.481
Cerebrovascular Disease	1.63 (0.50–5.38)	0.41(0.03–5.03)	0.837
Respiratory disease	1.07 (0.58–1.97)	0.82(0.26–2.66)	0.651
Diabetes	0.85 (0.28–2.57)	0.89(0.54–1.47)	0.470
Cognitive Impairment	0.17 (0.09–0.31)	0.17(0.03–0.88)	0.500
Cancer	0.94 (0.67–1.33)	0.90(0.53–1.54)	0.547
Death from disabled	Referent*	0.84 (0.72–0.98)	0.042
Arthritis	0.84 (0.61–1.17)	0.92(0.51–1.66)	0.403
Hypertension	0.81 (0.59–1.10)	1.08(0.76–1.52)	0.111
Cardiac Disease	1.46 (1.21–1.77)	1.40(1.11–1.78)	0.601
Cerebrovascular Disease	1.09 (0.62–1.92)	1.36(1.03–1.80)	0.244
Respiratory disease	1.39 (0.82–2.35)	1.42(1.05–1.92)	0.474
Diabetes	1.27 (0.87–1.87)	1.11(0.76–1.63)	0.693
Cognitive Impairment	2.49 (1.76–3.54)	2.62(1.81–3.78)	0.428
Cancer	1.43 (0.92–2.22)	1.51(1.10–2.08)	0.416

*Referent category for assessing gender difference adjusted for full disease count.
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than men overall (on average 2.2 years) and by disease. No sex differences were found in disease-specific recovery from disability and only for cancer was there a sex difference in disease-specific risk of death. These findings were not a consequence of differences in education, current socio-economic status (as measured by IMD) or the presence of comorbidity. Neither were they due to men with more disability dying or withdrawing between assessments as comparison of disability scores in the interview prior to death or withdrawal again demonstrated excess disability in women over men. Thus we suggest that the disability-survival paradox in the very old is at least partly due to sex differences in the type and disabling impacts of diseases.

Very old men have a marginally greater prevalence of diseases which are more likely to kill (cardiac disease, CVD and cancer), and women a higher prevalence of the chronic diseases (arthritis and hypertension). Nevertheless, this difference did not always translate to increased disability incidence or death. Arthritis was more disabling for men and cardiac disease for women, whilst cancer and cognitive impairment were the most fatal diseases for women (after becoming disabled). Earlier studies, mainly in younger age groups, have found that women are significantly more likely than men of the same age to have disabling rather than fatal diseases [3,5,6]. We can confirm that very old women (85+) do have a significantly greater prevalence of chronic diseases

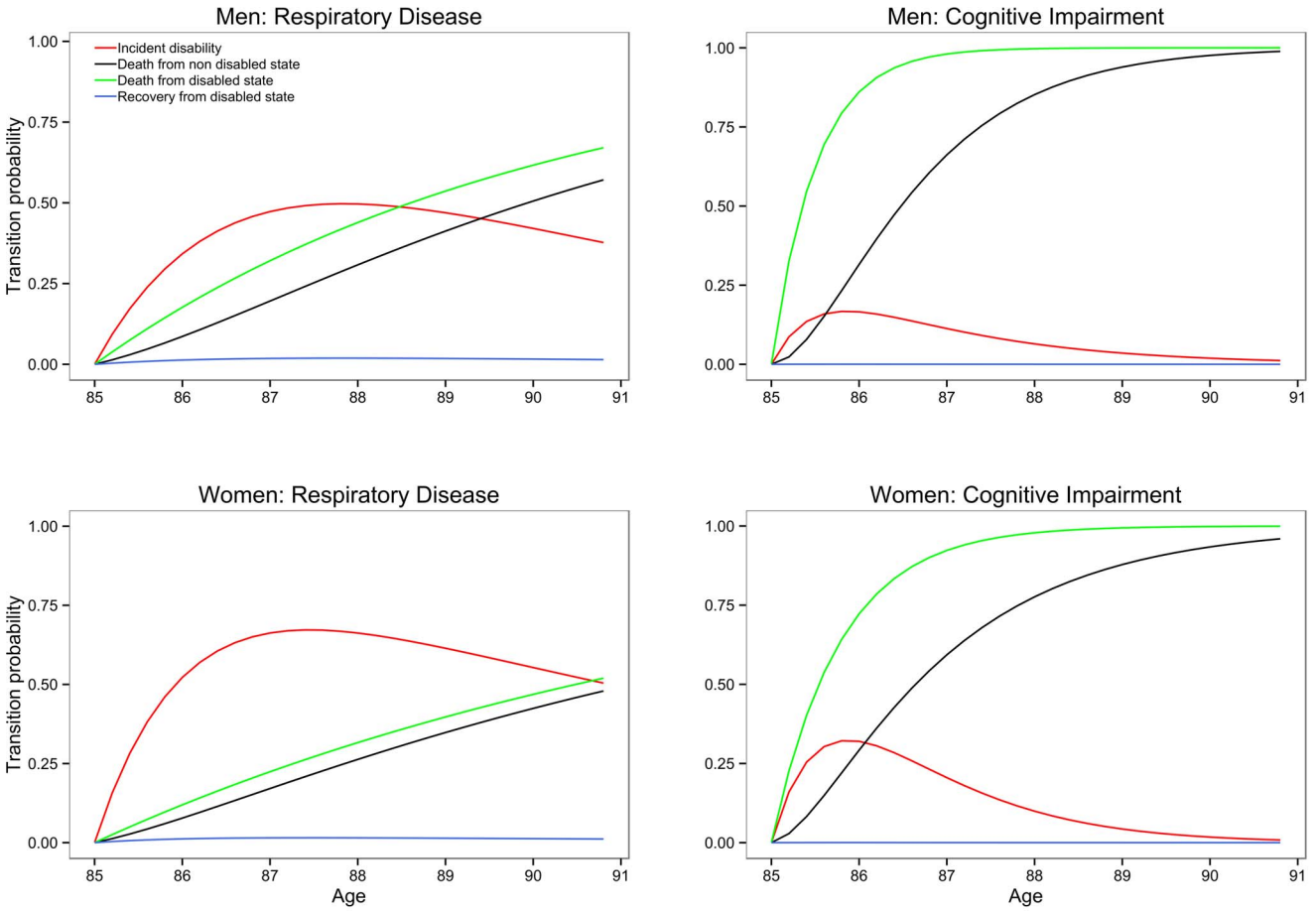

Figure 3. Transition probabilties for two diseases by gender.
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(arthritis, hypertension). Whilst men of the same age had greater prevalence of fatal diseases (cardiac disease, CVD and cancer) than women the differences were not statistically significantly different. Furthermore, the presence of certain fatal diseases increased the likelihood of incident disability more for women than men and increased the likelihood of death from a non-disabled state more for men than women.

Longitudinally, the presence of arthritis, cardiac disease, diabetes and cognitive impairment was significantly disabling for both sexes and CVD and respiratory disease for women only. This is generally consistent with previous findings [24] although in our study CVD and respiratory disease were significantly disabling in women only, perhaps caused by slight differences in criteria considered for a CVD diagnosis that may favour women compared to other studies. Furthermore we found cardiac disease, CVD, and respiratory disease to be more disabling for women compared with men whilst cognitive impairment was similarly disabling in both sexes. Diabetes was also disabling for both sexes, however the impact was noticeably worse for men (HR: 3.0, 95% CI: 2.4–3.8) compared to women (HR: 1.7, 95% CI: 1.3–2.2) ($p = 0.001$).

Implications for Clinical Practice

Few recoveries from disability were observed regardless of the presence or absence of specific diseases, and were particularly low in the presence of cognitive impairment. Indeed cognitive impairment was detrimental for disability incidence, recovery and mortality for both sexes as previously found [24–26]. Gill *et al* analysed trajectories of disability on a monthly basis [27] and showed that among people in advanced stages of dementia, 67.9% had persistent severe disability. Our results similarly showed that those who became cognitively impaired moved swiftly into disability and then death (figure 3). This adds to the already strong argument for better preventative care in those at higher risk of developing cognitive impairment, especially as projection modelling from large cohort studies has predicted the link between ageing populations, dementia and disability. Despite concerns about screening for mild cognitive impairment and dementia [28] the very old should perhaps be considered a 'high risk' population worthy of targeted case finding, in view of our findings and the fast progression from cognitive impairment to disability [29]. Furthermore, cognitive impairment was shown to be the most disabling disease, confirming its importance as a primary determinant of disability [30]. Using the same measure of cognitive impairment, a UK study reported that its elimination would save around 3.5 total life years and 4.3 years free of disability at age 65, and therefore with a greater impact on disability. In terms of slowing the deterioration in global functioning of people with dementia, anti-cholinesterase drugs have been shown to be cost-effective in both the early and moderate stages of Alzheimer's disease [31], with recent evidence showing benefit also in advanced stages [32]. Evidence is growing around the effectiveness of some non-drug interventions, such as cognitive stimulation in routine dementia care, although there remains uncertainty about the most cost-

Table 5. Mean sojourn times in state (years) by disease group.

	Without disability		With Disability	
	Without disease	**With disease**	**Without disease**	**With disease**
	Women			
	1.31		6.44	
Arthritis	1.47	1.20	6.12	6.51
Hypertension	1.37	1.26	5.97	6.70
Cardiac Disease	1.53	0.64	6.95	5.29
CVD	1.38	0.53	6.61	5.67
Respiratory disease	1.46	0.72	6.86	5.26
Diabetes	3.46	2.07	4.36	5.20
Cognitive Impairment	3.58	2.23	4.64	3.04
Cancer	1.36	0.73	6.58	4.67
	Men			
	1.82		4.20	
Arthritis	2.52	1.60	4.09	5.11
Hypertension	1.87	2.22	4.34	5.00
Cardiac Disease	2.46	1.57	5.44	3.88
CVD	2.12	1.92	4.85	4.25
Respiratory disease	2.15	1.56	4.74	3.89
Diabetes	2.28	0.81	4.86	3.97
Cognitive Impairment	2.04	3.36	5.21	2.41
Cancer	2.04	1.81	4.79	3.43

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effective way of delivering such interventions in practice. There is also an increasingly strong argument for better preventative care in those at higher risk of developing dementia. Based on our findings this may be particularly the case for women. More timely diagnoses would lead to earlier intervention which may delay the onset of significant disability from the moderate and advanced stages of cognitive impairment.

Greater fatality in men with respiratory disease (with no disability) may explain the greater disabling impact observed in women, by means of accelerated transit through the disablement process to death for men, a process for which we found no evidence in women. However the greater disabling impact of cardiac disease and CVD in women cannot be explained this way. Global estimates of the prevalence of angina have been shown to be significantly greater for women but men diagnosed with the same disease have an excess MI [33]. Whilst little is known about the etiological causes it could go some way to explain our results since, if men diagnosed with angina are at greater risk of MI [34] compared with their female counterparts, they may be more likely to die before we could detect disability. Our results indicate that cardiac disease is disabling for both men and women but such men have increased mortality whilst this is not true for women. However, once disabled, men and women with cardiac disease are more likely to die than their counterparts without the disease. This suggests that care packages for those with cardiac disease should be tailored towards reducing mortality in men and reducing disability in both sexes.

Strengths and Limitations

Our study has strengths and limitations mainly in regard to measurement of disease and disability. That sex differences in self-reported disease were avoided in our study, as disease was ascertained from general practice records, can be viewed as both a strength and a limitation. Whilst in general women are more likely to consult health professionals than men, general practitioner consultation rates among the very old are high overall, and in our study did not differ between men and women. However we had previously found that women had lower rates of outpatient attendance than men [13]. Our diagnosis of disease was an 'ever' diagnosis (with the exception of cancer which was within the previous five years only) and we did not have information on disease severity, though analysis of disease duration showed no significant sex difference. Given disease was ascertained from general practice records, there may have been sex differences in undiagnosed disease. Through further measurements in the health assessment we have explored rates of undiagnosed disease for diabetes and hypertension and found rates of undiagnosed diabetes were low with no sex difference and, though the prevalence of undiagnosed hypertension was high (based on a single-occasion blood pressure measurement) again no sex difference was detected [13]. A further strength is that we investigated two levels of disability, milder and more severe, but this did not alter the conclusions. Finally, self-report of mobility items included in the disability score were highly correlated with objective measures (timed up-and-go) similarly in men and women.

Conclusion

Once health deteriorates, mortality rates increase more for men than women [35] and this is revealed in our results where the impacts of certain diseases are disabling for women but detrimental to survival for men. Men who encounter diseases

which increase mortality could be accelerated through the disability pathway [36] (and ultimately death). However the time intervals of our study are too wide to capture this potential, accelerated transit. Nevertheless, if, as posited, men traverse the disablement process faster than women once they encounter disease, it would further suggest that they do not just 'age faster' biologically than women [37]. We suggest that our results point to two different biological mechanisms driving the male-female disability-survival paradox: the sex difference is driven by a female heath disadvantage as well as being accompanied by a female mortality advantage, consistent with other findings [38–40]. Our results suggest that the potential acceleration through the disablement pathway for men may be caused by the gender-specific effect of disease (and severity) and/or its potential subsequent sequelae. Alternatively, it could be that men and women follow different routes through the disability pathway and thus women will, intrinsically, always show more disability than men at a population level [41]. Exploration of the biological mechanisms underlying the sex differences may assist our understanding and point the way to interventions to prevent or ameliorate the disabling effects of diseases.

By age 85 women have significantly more disability and disabling diseases such as arthritis and hypertension. Whilst hypertension may be asymptomatic, its potential sequelae such as ischemic heart disease, heart failure and CVA could be the driving forces behind its disabling effects. Although men have slightly, though not significantly, more fatal diseases (cardiac disease and CVD), women with these diseases, as well as with respiratory disease, are more likely to become disabled. Men without disability are significantly more likely to die from cancer and respiratory disease but all other transitions from a disabled or non-disabled state were similar for men and women. In addition, we found that overall disability was more of a risk factor for male mortality (disease count adjusted) compared to women and is supported by recent findings [42].

We conclude that the disability-survival paradox is still evident in the very old and appears due to sex differences in the types and impacts of disease.

Supporting Information

Table S1 Disease duration (years) by sex – median (IQR).
(DOCX)

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Author Contributions

Analyzed the data: AK CJ. Wrote the paper: AK KD JC LR RD JB TBLK CJ.

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APPENDIX D

The enduring effect of education–socioeconomic differences in disability trajectories from age 85 years in the Newcastle 85+ study

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The enduring effect of education-socioeconomic differences in disability trajectories from age 85 years in the Newcastle 85+ Study

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ABSTRACT

Objective: Little is known about disability progression in very old age despite this being vital for care planning. We investigate whether distinct trajectories of disability are evident from age 85 to 90 and their association with socio-economic status (SES).

Methods: The Newcastle 85+ Study recruited people born in 1921 through participating general practices in Newcastle and North Tyneside. Participants underwent a health assessment (HA) at baseline, 18, 36 and 60 months and a GP record review (GPRR) at baseline, 36 and 60 months. Disability was measured via difficulty in 17 Activities of Daily Living. Trajectory identification was assessed by gender stratified, mortality adjusted, group-based trajectory modelling (GBTM) and the impact of life-course SES (level of education; occupational class; deprivation) on trajectory membership evaluated (adjusting for confounding variables).

Results: 851 participants agreed to HA and GPRR, 840 (98.7%) with complete disability data. Four distinct trajectories were evident for both sexes. A disability-free trajectory between age 85 and 90 was identified in men only (9% of the sample). The most disabled trajectories had severe disability at age 85 progressing to profound disability by age 90. After adjusting for confounders education remained significant; men and women with most education being less likely to be in the most disabled trajectory (Men: OR = 0.80, 95% CI 0.65–0.98; women: OR = 0.59, 95% CI 0.42–0.83).

Conclusion: Distinct disability trajectories are evident in the very old and these are influenced by education, suggesting SES disadvantages cumulate throughout the life-course to create health and mortality inequalities later.

1. Introduction

Knowledge of how disability changes with advancing age is important not only for allocating the health and care resources required for our rapidly growing aging populations, but also for individuals and families to plan for increasing dependency and moves to assisted living environments. Disability in later life is affected by experiences throughout the life course, including socio-economic status as measured by education, income, or occupation (Verbrugge, Reoma, & Gruber-Baldini, 1994). SES is a strong predictor of disability onset and mortality, as well as the combined measure of disability-free life expectancy (Jagger et al., 2007; Lynch, 2008; Marmot, Shipley, Brunner, & Hemingway, 2001; Marmot & Martin, 1996; Montez, Hayward, Brown, & Hummer, 2009; Stringhini et al., 2011). More years of education are particularly associated with slower declines in disability prevalence, lower incidence and greater recovery over time (Jagger et al., 2007). Education is one factor that will change predictably as statutory school leaving ages in the United Kingdom have increased and future cohorts of older people, especially women, who have had greater access to higher education.

Mechanisms linking education and disability are ostensibly associated with behaviors that impact risk factor decision-making, mastery over one's life and/or postponed gratification (Freedman & Martin, 1999). Two popular hypotheses seek to explain the

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mechanisms driving the impact of SES on health in old age: the 'cumulative disadvantage' hypothesis and the 'age-as-leveler' hypothesis. The cumulative disadvantage hypothesis posits that socio-economic disparities amplify across the life course, largely as a result of differential exposure to risk factors associated with low SES, for example smoking, alcohol consumption, occupation, education and physical exercise (O'Rand, 2002). The cumulative insult of negative health behaviors/circumstances associated with low SES creates the health and mortality discrepancy. In contrast, the effect of differential SES exposures may be leveled out over the life course, perhaps due to those with low SES dying. In addition, age can bring with it many challenges in terms of sustaining homeostatic equilibrium across many body systems. This could serve to outweigh the differential impact of SES exposures which produces divergent health trajectories in younger cohorts as, in older cohorts, age-related biological forces become more influential determinants of poor health and mortality. This is known as the 'age-as-leveler' hypothesis (Lynch, 2008).

Most disability research focuses on onset/incidence, prevalence, or transition, and has been conducted mainly in the younger old age group (Chiu & Wray, 2011; Taylor, 2004; Verbrugge et al., 1994). There is limited research addressing disability from a pathway or trajectories perspective, particularly in the very old (aged 85 and older). The majority of previous trajectory analyses have used growth curve modeling or subjective pathway classification, both of which have limitations (Ferrucci et al., 1996; Taylor & Lynch, 2004; Zimmer, Martin, Nagin, & Jones, 2012). Furthermore, many studies fail to fully account for loss to follow up (through death or withdrawal, both of which occur more often in the very old) with a resulting bias (Wolinsky, Armbrecht, & Wyrwich, 2000). In this paper we explore associations between SES and disability trajectories, specifically in the very old, using data from the Newcastle 85+ Study; we use group-based trajectory modelling to improve upon previous analyses (Nagin, 2005). The common underlying assumptions of the majority of previous analyses center on the distribution of trajectory parameters and require these to follow a continuous multivariate normal distribution. The technique we use (GBTM) is less restrictive and allows for clusters of unique developmental trajectories that are potentially a function of different disability aetiologies, thus giving scope to further understand the disability process in the very oldOur paper has two objectives. Firstly, we investigate for the first time whether distinct trajectories of disability are evident in a cohort of the very old, after accounting for mortality. Secondly, we examine the extent to which early, mid and/or late life SES predicts specific disability trajectories. We hypothesise that if the age-as-leveler theory is true, then early-life markers of SES will not prove differential across trajectories in the very old. Conversely, if the cumulative disadvantage hypothesis is true then SES throughout the life course will associate with disability patterns in the very old.

2. Methods

2.1. Participants

Data were drawn from the Newcastle 85+ Study; full details of the study design, protocol and participant recruitment have been described previously (Collerton et al., 2009). In brief, this is a longitudinal study of adults in Newcastle upon Tyne and North Tyneside (North-East England) who was born in 1921, who turned 85 years of age in 2006 when recruitment commenced, and who were registered with a participating general practice. At baseline (wave 1), trained research nurses carried out a detailed multidimensional health assessment (MDHA) of participants in their own home or other permanent place of residence (including institutional care settings) together with a detailed review of their general practice medical records (GPRR). Follow up MDHAs were carried out at 18, 36 and 60 months post-baseline with a further GPRR at 36 and 60 months.

2.2. Disability

Disability was assessed at baseline and all follow-up MDHAs through participants' self-report of their ability to perform 17 Instrumental and Basic Activities of Daily living (IADLs and BADLs) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963; Lawton & Brody, 1969) (Supplementary Fig. 1). Participants scored one for each activity they had any difficulty with and zero for each activity performed without difficulty; summation over the 17 activities produced a total disability score (range 0–17) with a higher score indicating a higher level of disability. Activities which predominantly involved mobility (getting around the house, getting in and out of a chair, shopping, going up and down stairs, walking at least 400 yards) were highly correlated with objectively measured timed-up-and-go test times for both men and women (Jagger et al., 2011).

2.3. Mortality

Date and cause of death were obtained through the Health and Social Care Information Service Centre. Survival time was constructed from date of baseline MDHA to date of death and censored at wave 4 (60 months from baseline). For the purposes of this analysis we considered all-cause mortality.

2.4. Measures of socio-economic status

Early-life SES was measured through the number of years of full-time education. Mid-life SES was assessed by main working life occupation, classifying participants through the National Statistics Socio-economic Classification system (NS-SEC) into three categories (routine and manual occupations, intermediate occupations and higher managerial, administrative and professional occupations) (ONS, 2010). As a proxy for current (late-life) SES we derived the area Index of Multiple Deprivation (IMD) from participants' postcodes; this combines a number of indicators chosen to reflect a range of economic, social and housing issues into a single deprivation score with higher scores representing those living in more deprived areas (and therefore greater disadvantage) (Office of the Deputy Prime Minister, 2004).

2.5. Confounding variables

Models were adjusted for some of the major factors associated with both disability and SES: disease burden, Body Mass Index (BMI); and depressive symptomatology. Presence of specific diseases during the participants' lifetime was recorded in the GPRR and disease burden calculated as the number of diseases present from a list of the eight most prevalent (Kingston et al., 2014) (Supplementary Fig. 2). BMI was calculated from height (derived from demi-span) and weight. Depressive symptomatology was measured using the 15 item Geriatric Depression Scale (Yesavage & Brink, 1983).

2.6. Statistical methods

Gender differences in SES and key health characteristics were assessed as follows: education, IMD (ordinal logistic regression); NS-SEC (multinomial logistic regression); disease count, BMI (*t*-test); and disability (Tobit regression to account for the floor effects (Austin, Escobar, & Kopec, 2000)). To explore patterns of

Table 1
Socio-economic and key health characteristics of study sample.

	Men	Women	All	Gender difference *p*-value	Magnitude of gender difference
Gender – % (*n*)	38.10 (320)	61.90 (520)	100.00 (840)	–	–
Education (no. of years) – % (*n*)					
0–9	61.78 (194)	65.69 (335)	64.20 (529)	0.3040	0.86 (0.65–1.16)[a]
10–11	24.84 (78)	21.57 (110)	22.82 (188)		
12+	13.38 (42)	12.75 (65)	12.99 (107)		
NS-SEC 3 – % (*n*)					
Routine occupations	53.05 (165)	51.03 (247)	51.82 (412)	–	Referent[b]
Intermediate occupations	7.400 (23)	18.39 (89)	14.09 (112)	<0.001	2.58 (1.57–4.26)
Professional/managerial occupations	39.55 (123)	30.58 (148)	34.09 (271)	0.1670	0.80 (0.59–1.10)
Deprivation (IMD) – % (*n*)					
>75th centile	22.81 (73)	25.58 (133)	24.52 (206)	0.0250	1.35 (1.04–1.76)[a]
25th ≤ centile ≤ 75th	46.88 (150)	52.50 (273)	50.36 (423)		
<25th centile	30.31 (97)	21.92 (114)	25.12 (211)		
Disability score – median (IQR)					
Wave 1 (*n* = 840)	2 (0–6)	4 (1–8)	3 (1–8)	<0.001	2.23 (1.39–3.07)[c]
Wave 2 (*n* = 625)	4 (1–8)	6 (3–10)	5 (2–9)	<0.001	2.13 (1.24–3.02)[c]
Wave 3 (*n* = 480)	5 (2–10)	7 (4–11)	6 (3–10)	0.0010	1.49 (0.48–2.51)[c]
Wave 4 (*n* = 341)	5 (2–9)	7 (4–11)	7 (3–11)	0.0010	2.03 (0.76–3.29)[c]
Depression (15 item GDS) – median (IQR)	3 (1–4)	3 (2–5)	3 (2–5)	0.0057	–
Disease count – mean (SD)	2.15 (1.35)	2.08 (1.33)	2.11 (1.34)	0.5066	0.06 (−0.12 – 0.25)[d]
Body mass index – mean (SD)	24.58 (3.82)	24.42 (4.73)	24.49 (4.39)	0.6286	0.16 (−0.48–0.81)[d]

[a] Ordinal logistic regression.
[b] Multinomial logistic regression.
[c] Tobit regression.
[d] *T*-test.

individual trajectories of disability we used group-based trajectory modelling (Nagin, 2005). This technique first determines the number of distinct trajectories via polynomial functions in time using a censored normal distribution. Non-random subject attrition, in particular due to mortality, was accounted for by a group-specific function linked to the probability of death by age (Haviland, Jones, & Nagin, 2011). We explored a number of trajectory models with the best fitting model selected by the Bayesian Information Criterion (BIC) and the fit further assessed by ensuring the posterior probability of group membership for all participants exceeded 70%. All participants satisfied this condition in the final model (Nagin, 2005).

We examined the effect of SES measures on the disability trajectories by multinomial logistic regression, first fitting SES measures singly, then with adjustment for confounders, and finally with all SES measures together. As we have previously shown in this cohort that females are at a disadvantage in terms of disability (Collerton et al., 2009), we fitted trajectory models separately for men and women. Sensitivity analyses were undertaken to determine the effects of combining both mortality and participants lost to follow-up into one category. Analyses were carried out in Stata 12.1 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.) and the SAS® Trajectory Procedure (Jones, Nagin, & Roeder, 2001) on the SAS® platform (v9.2).

2.7. Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and responsibility for the decision to submit for publication.

3. Results

A total of 851 Newcastle 85+ Study participants underwent both the MDHA and GPRR at baseline (wave 1); of these 840 had complete disability data, with 63.1% (*n* = 540) being female. Disability level increased from age 85 (wave 1) to 90 years (wave 4) for both men and women and was consistently and statistically significantly greater at each wave for women compared to men (Table 1). Compared to men, women were more likely to reside in a more deprived area (OR: 1.35, 95% CI: 1.04–1.76) and to have worked in intermediate occupations (OR: 2.58, 95% CI: 1.57–4.26). No gender differences were detected in the levels of education or disease count at baseline (Table 1). The retention profile of participants across the course of the study (to wave 4) is included in Table 2.

3.1. Disability trajectories

For both sexes, disability trajectories were best represented by a four-group model (model parameters shown in Supplementary Table 1). In women, the four trajectories (WT1–WT4) showed a gradual increase in the level of disability with advancing age and 21.8%, 43.6%, 21.9% and 12.7% were classified from WT1-WT4 respectively. Three trajectories were ascertained for men, showing monotonically increasing disability, with 44.3%, 29.7% and 17.0% being classified from MT2-MT4. However, trajectory one (MT1), comprising 9% if the male sample remained free of disability to at least aged 90 years. For both men and women, trajectory two contained the most participants. For men this was those people who experienced slight to mild disability (44.3%) and for women it

Table 2
Participant retention profile.

	Participant	Died	Withdrawn
Baseline			
Men	38.10 (320)	–	–
Women	61.90 (520)	–	–
Wave 2			
Men	73.13 (234)	19.69 (63)	7.19 (23)
Women	75.38 (391)	13.46 (70)	11.35 (59)
Wave 3			
Men	55.00 (176)	32.50 (104)	12.50 (40)
Women	58.46 (304)	23.65 (123)	17.88 (93)
Wave 4			
Men	36.88 (118)	48.75 (156)	14.38 (46)
Women	42.88 (223)	35.19 (183)	21.92 (114)

		Group size (%)	Disability trajectory	Mortality trajectory
MEN				
MT1	Disability free	9·0	No disability at age 85 and remaining free of disability to age 90 years.	Mortality static at each wave (23%)
MT2	Slight-mild disability	44·3	Very mild disability (difficulty with around 1 or 2 (I)ADL items) at age 85, plateauing by age 88 (to difficulty with around four (I)ADL items). No significant difference in baseline disability between MT2 and MT1 (p=0·321).The rate of increase in disability slowed over time (quadratic parameter: β_2= -0·113 (SE=0·052)).	Mortality increased at each wave, rising from 21% wave two (18 months) to 29% at wave four (60 months).
MT3	Mild disability progressing rapidly	29·7	Mild disability (difficulty with around 4 items) at age 85 which progressed rapidly to moderate/severe disability (difficulty with around 11 items) by age 90 years.	Mortality rose faster compared to MT1 and MT2, being 22% at wave 2 (18 months), similar to MT1 and MT2, but rising to 32% by wave 4 (60 months).
MT4	Severe persistent disability	17·0	Severe disability (difficulty with around 12/13 items) at age 85 with a steady increase to profound disability in nearly all items (16/17) by age 90.	Mortality was higher than previous trajectory groups being 43% at wave 2 (18 months) and increasing further to 57% by wave 4 (60 months).
WOMEN				
FT1	Slight-mild disability	21·8	Little disability (difficulty with around 1 item) at aged 85 but whose disability level increased gradually culminating in difficulty with around 4 items by age 90.	Mortality static at 12% over the study period.
FT2	Mild-moderate disability	43·6	Mild disability (difficulty with around 4 items) at age 85, which increased to moderate disability (difficulty with around 9 items) by age 90.	Mortality static, but at a higher rate than FT1 (around 22%).
FT3	Moderate to severe disability	21·9	Moderate disability (difficulty with eight items on average) at age 85 rising to severe disability (difficulty with 14 items by age 90. The rate of increase in disability slowed over time (quadratic parameter: β_2= -0·232 (SE=0·069)).	Rising mortality the study period from around 22% at wave 2 (18 months), and rising to 41% by wave 4 (60 months).
FT4	Severe persistent disability	12·7	Severe disability (difficulty with around 14 items) at age 85 rising to profound disability (difficulty in all items) by age 90.	Mortality was greatest among this group but remained static over time at around 58%.

Fig. 1. Descriptions of disability trajectories for men and women.

was those who experienced mild to moderate disability (43.6%). A group with severe, persistent disability (initially dependent in 12 or more (I)ADLs) was evident for both sexes, though their mortality experience differed by sex with increasing mortality over time in men and static mortality in women. The four trajectories for men and women are described in detail in Fig. 1 and illustrated graphically in Fig. 2 (upper panel: men, lower panel: women). Supplementary Fig. 3 details the mortality trajectories by gender.

Combining mortality and those who withdrew to investigate the impact from two sources of attrition did not alter the number or shape of the trajectories.

3.2. The impact of SES on disability trajectories

We first examined the impact of the three SES measures individually (Table 3 model 1). Men and women with more education were less likely to belong to the more disabled trajectories with a stronger education gradient in women than men. Those with 12 or more years of education were less likely to belong to the most disabled trajectory compared to the least (Men: OR = 0.69, 95% CI 0.51–0.93; women: OR = 0.54, 95% CI 0.30–0.96) and women with the least education (0–9 years) were more likely to be in the most disabled (FT4) than the least disabled (FT1) trajectory (OR = 1.21, 95% CI 1.01–1.45). With regard to mid-life SES, identical patterns prevailed. Men and women who had been in managerial occupations were less likely to belong to the most disabled trajectory (Men: OR = 0.33, 95% CI 0.15–0.71; women: OR = 0.33, 95% CI 0.21–0.51) and women from manual occupations were more likely to be in the most disabled (FT4) than the least disabled (FT1) trajectory (OR = 1.35, 95% CI 1.05–1.74). Late-life socio-economic status (IMD) only impacted men, with those in the least deprived quartile of IMD being less likely to be in the most disabled trajectory (MT4) compared to the least disabled (MT1) (OR = 0.42, 95% CI 0.31–0.57).

When all socio-economic status indicators (i.e. early, mid and late life) were included in the model (model 2) only the effect of education remained significant and this effect persisted, though attenuated, after adjustment for potential confounders (disease burden, BMI, depressive symptomatology). Thus men and women with the most education remained less likely to be in the greatest, compared to the least, disabled trajectory (Men: OR = 0.80, 95% CI 0.65–0.98; women: OR = 0.59, 95% CI 0.42–0.83).

4. Discussion

We used group-based trajectory modelling to investigate whether distinct disability trajectories were present for very old men and women, and the effect of life course SES. Four distinct disability trajectories were evident for men and women, differentiated both by the initial level of disability and the pace of progression. Only in men did we detect a group (comprising 9%) who remained free of disability from age 85 to 90. Moreover, although the effects of SES in mid-life (occupationally based) and late-life (area deprivation) on trajectory membership were attenuated after adjustment for potential confounders, the effect of early-life SES (education) remained, with men and women with the more education (12+ years) being significantly less likely to be in the most disabled trajectories.

Despite the disability free trajectory being absent in women, there were similarities in the initial level and progression of the remaining trajectories between the sexes. Trajectories MT2 and MT3 for men (slight to mild disability and mild progressing to moderate respectively) were equivalent to the first two trajectories in women (FT1 and FT2), whilst the last trajectory for men (MT4: severe persistent disability) was between the final two trajectories for women (FT3, FT4), these being differentiated by initial disability level (moderate versus severe) but all showing the effect of reaching a plateau in disability level by age 90.

Our analytic technique, group-based trajectory modelling, accounted for non-random subject attrition (mortality) and this reaffirmed that mortality and disability are intricately linked. As the level of disability increased within a trajectory, mortality also increased with its functional form aligned with that of the disability trajectory, i.e. mortality was a function of disability severity. Although male mortality is known to exceed that of women of the same age, the probability of death occurring before participation in the next wave was almost identical for men and women in similar trajectories. For example men in MT3 and women in FT2 both had a 22% chance of dying prior to wave 2 (age 86.5 years). It may be possible that, as the more acutely fatal

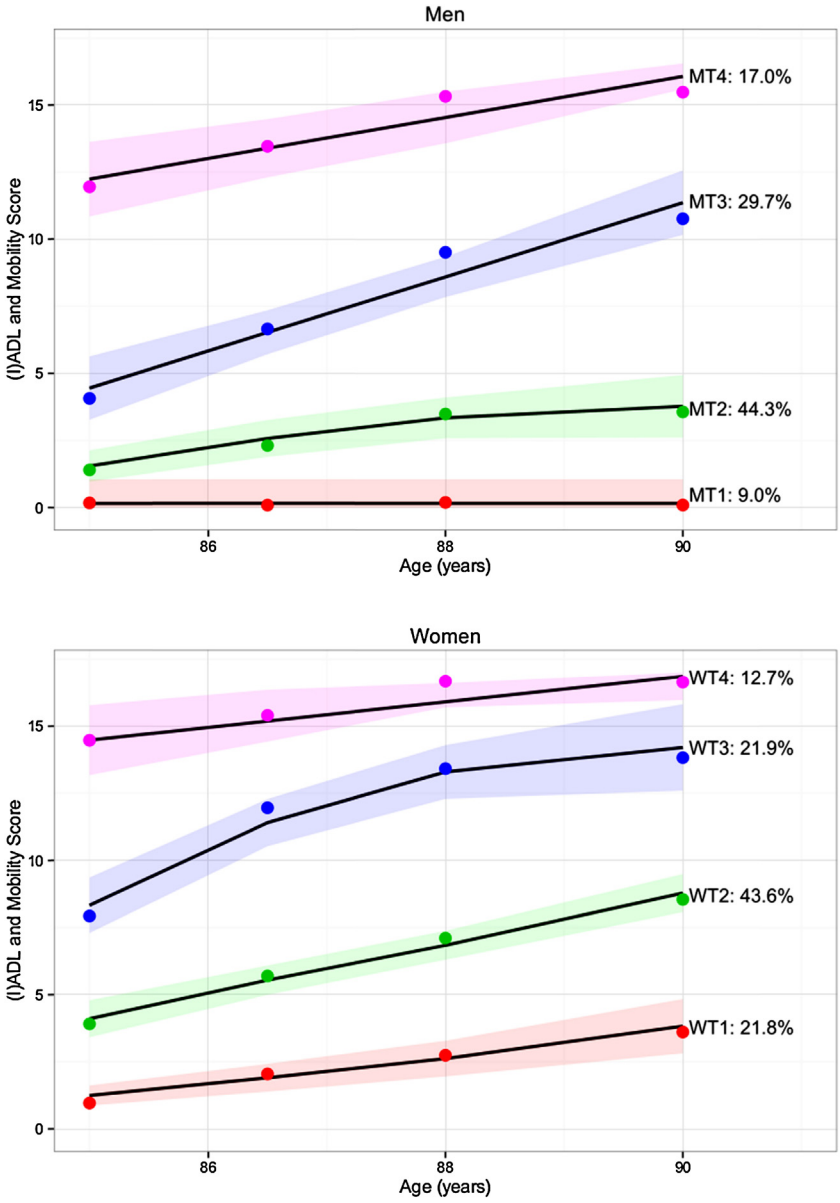

Fig. 2. Disability trajectories*.

conditions become less common, and men suffer long-term disabling conditions, that their mortality experience begins to resemble that of women. This would explain, at least in part, the more rapid increase in male compared to female life expectancy and the subsequent narrowing of the gender gap.

There are two main limitations to our study. Firstly, although the time interval between disability measures was only 18 months for the first three study waves, we may have missed some disability transitions which could have resulted in fluctuating trajectories. However such fluctuations may be noise around an otherwise steady downward progression. Secondly, our study relied on proxy measures of disadvantage earlier in life (education and occupation) in contrast to cohort studies which follow individuals from birth and which can collect contemporaneous data to measure disadvantage. Education and occupation are unlikely to be subject to recall bias but they cannot capture the whole picture of early-life disadvantage.

Strengths of our study include: the large number of individual ADL items constituting the disability score, thus providing a greater spectrum of disability; validation of the self-report ADL items with the objectively measured TUG; comprehensive follow-up of the study participants with little attrition other than death; and the study design of a single birth cohort of a total population (community dwelling: inclusive of those living in care homes (nursing/residential) who are socio-demographically nationally representative (Collerton et al., 2009; Jagger et al., 2011).

There is little research examining disability trajectories, and even less that focuses on the very old including those living in institutional care. Using similar techniques to ours to account for decedents but with fewer measures of ADL limitations, a study of the very old in China also identified a group of consistently non-disabled men between the ages of 80 and 90 (Zimmer et al., 2012), lending credence that this able group of men may exist in other populations regardless of geographical location. On the other hand older people surviving with persistent severe disability, as ours, have been identified in the US, although this study was restricted to community-dwelling older people aged 70 or more years interviewed monthly, not accounting for mortality (Gill, Gahbauer, Han, & Allore, 2010). Disability has been found to be a dynamic

Table 3
Multinomial logistic regression of the impact of SES variables on the trajectory of disability by gender–Odds Ratio (95% CI).

	Men			Women		
	MT2 vs. MT1	MT3 vs. MT1	MT4 vs. MT1	MT2 vs. MT1	MT3 vs. MT1	MT4 vs. MT1
Model 1[b]						
Education (no. of years)						
0–9	1.02 (0.82–1.27)	1.21 (0.32–4.58)	1.23 (0.26–5.82)	0.98 (0.38–2.53)	1.01 (0.52–1.96)	1.21 (1.01–1.45)[a]
10–11		Referent			Referent	
12+	0.92 (0.54–1.57)	0.99 (0.21–4.67)	0.69 (0.51–0.93)[a]	0.93 (0.31–2.79)	0.73 (0.54–0.98)[a]	0.54 (0.30–0.96)[a]
Occupational class						
Routine and manual	0.88 (0.39–1.99)	1.03 (0.41–2.59)	1.01 (0.38–2.68)	1.00 (0.45–2.22)	1.02 (0.68–1.53)	1.35 (1.05–1.74)[a]
Intermediate		Referent			Referent	
Managerial	1.21 (0.45–3.25)	0.84 (0.21–3.36)	0.33 (0.15–0.71)[a]	0.96 (0.21–4.39)	0.82 (0.34–1.98)	0.33 (0.21–0.51)[a]
Deprivation (IMD)						
> 75th centile	0.84 (0.21–3.36)	0.98 (0.51–1.88)	1.19 (0.87–1.63)	1.05 (0.81–1.36)	1.06 (0.72–1.56)	1.15 (0.81–1.63)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	0.87 (0.11–6.88)	0.99 (0.51–1.92)	0.42 (0.31–0.57)[a]	1.02 (0.79–1.32)	0.84 (0.51–1.38)	0.82 (0.56–1.20)
Model 2[c]						
Education (no. of years)						
0–9	0.99 (0.51–1.92)	0.99 (0.48–2.04)	1.09 (0.84–1.41)	1.04 (0.41–2.64)	1.03 (0.46–2.31)	1.12 (0.81–1.55)
10–11		Referent			Referent	
12+	0.92 (0.73–1.16)	0.88 (0.62–1.25)	0.71 (0.55–0.92)[a]	1.02 (0.51–2.04)	0.62 (0.32–1.20)	0.55 (0.41–0.74)[a]
Occupational class						
Routine and manual	0.98 (0.42–2.29)	1.12 (0.64–1.96)	1.14 (0.79–1.65)	1.05 (0.59–1.87)	1.03 (0.51–2.08)	1.11 (0.63–1.96)
Intermediate		Referent			Referent	
Managerial	0.91 (0.31–2.67)	0.90 (0.42–1.93)	0.82 (0.29–2.32)	0.85 (0.21–3.44)	0.89 (0.45–1.76)	0.74 (0.39–1.40)
Deprivation (IMD)						
> 75th centile	1.05 (0.52–2.12)	1.06 (0.68–1.65)	1.06 (0.78–1.44)	1.01 (0.42–2.43)	1.05 (0.11–10.02)	1.06 (0.41–2.74)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	1.03 (0.42–2.53)	0.92 (0.52–1.63)	0.86 (0.62–1.19)	1.11 (0.35–3.49)	0.97 (0.59–1.59)	0.91 (0.61–1.36)
Model 3[d]						
Education (no. of years)						
0–9	1.00 (0.53–1.89)	0.99 (0.69–1.42)	1.12 (0.57–2.20)	0.97 (0.35–2.69)	1.01 (0.42–2.43)	1.09 (0.63–1.89)
10–11		Referent			Referent	
12+	0.87 (0.21–3.60)	0.82 (0.54–1.25)	0.80 (0.65–0.98)[a]	0.93 (0.49–1.77)	0.86 (0.54–1.37)	0.59 (0.42–0.83)[a]
Occupational class						
Routine and manual	1.15 (0.32–4.13)	1.08 (0.41–2.84)	1.18 (0.39–3.57)	1.06 (0.88–1.28)	1.10 (0.72–1.68)	1.09 (0.76–1.56)
Intermediate		Referent			Referent	
Managerial	1.09 (0.49–2.42)	0.93 (0.42–2.06)	0.87 (0.56–1.35)	0.90 (0.51–1.59)	0.87 (0.67–1.13)	0.86 (0.64–1.16)
Deprivation (IMD)						
>75th centile	1.03 (0.47–2.26)	1.02 (0.52–2.00)	1.05 (0.43–2.56)	1.00 (0.21–4.76)	1.02 (0.35–2.97)	1.15 (0.87–1.52)
25th ≤ centile ≤ 75th		Referent			Referent	
<25th centile	0.98 (0.35–2.74)	0.98 (0.46–2.09)	0.93 (0.67–1.29)	0.93 (0.19–4.55)	0.93 (0.16–5.41)	0.89 (0.28–2.83)

[a] Statistically significant.
[b] Model 1 – each SES covariate considered alone with no-adjustment.
[c] Model 2 – each covariate adjusted for other SES covariates.
[d] Model 3 – each covariate adjusted for other SES covariates plus BMI, disease burden and depressive symptomatology.

process over short periods of time and we have shown that this dynamism relaxes long term to form distinct trajectories. The number of trajectories we found is broadly consistent with other literature in younger ages and they are developmentally similar (Gill, Gahbauer, Lin, Han, & Allore, 2013; Han et al., 2013; Hardy, Dubin, Holford, & Gill, 2005). Our analyses revealed a disability-free trajectory in men but not women, and a persistently-disabled trajectory in women but not men; these gender differences suggest that analysis of men and women together might mask gender specific trajectories.

The impact of SES on future health and functional status is widely researched in the younger old but there is a dearth of information in the very old. We have shown that early-life SES (education) still determines disability trajectories after age 85. Though mid (occupation) late-life SES (deprivation) gave similar pictures when assessed individually, only education remained significant when all SES variables were included and confounders adjusted for. Consistent with other research, having more education was significantly associated with less disabled trajectories at aged 85, irrespective of gender (Freedman & Martin, 1999; Hayward & Gorman, 2004; Taylor, 2010). Our results lend credibility to the cumulative disadvantage hypothesis whereby those disadvantaged by less education in early life are potentially exposed to a greater degree of social inequality thereafter, and suggest that this inequality reaches right through the life course, influencing disability pathways beyond age 85. Conversely, we found no evidence that biological forces move to neutralise the impact of SES disparities in the very old (i.e. the age as leveler theory) and that disability in very late life is not simply explained by a person's disease profile. This suggests that future cohorts of very old people may be less disabled since they will have enjoyed more years of education.

While it is an interesting finding that we discovered 9% of men remained disability free over the course of the study, it is important to note that all other participants showed increasing levels of disability over time. If these trajectories remain static over the course of the next fifteen years (to 2030) and with the increases in the very old population (aged 85 and over: 47.3% for men and 38.6% for women) we will see increases in the region of 50,000 people (in the UK) who belong to the most disabled trajectories (WT3/MT3–WT3/MT4). This will have important implications for policy makers and health care providers to ensure services have the capacity to cope with this increase. However, further exploration of the trajectories in terms of their disease, syndromes and

psychosocial profile could yield important information (in terms of etiology and identification of risk factors) and increase our understanding of the disability process, leading to potential interventions that could positively augment the disability trajectories themselves.

5. Conclusion

In summary, four trajectories of disability are able to describe both men and women in our cohort of very old people. Of these trajectories, we detected a disability-free trajectory only in men. We found that early life SES (education) was associated with trajectory affiliation at age 85, with those less educated more likely to be in the most disabled trajectory, even after adjusting for multiple confounding variables. Our findings add strength to the theory that SES accumulates over the life course (cumulative disadvantage theory) and that disability at later ages is not simply a result of age related biological decline. Furthermore, it suggests that future cohorts of the very old with more education could enjoy less severe disability trajectories as they age.

Conflict of interest statement

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.archger.2015.02.006.

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APPENDIX E

E1 Polychoric Correlations - Maximum Likelihood Estimation

If two variables x_1^* and x_2^* are categorised from an assumed underlying, continuous format (in this case the measurement of disability as a continuum), then these variables are assumed to follow a normal distribution with correlations ρ , thus:

$$\begin{pmatrix} x_1^* \\ x_2^* \end{pmatrix} \sim N\left(0, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}\right), \; -1 \le \rho \le 1 \qquad (7)$$

If, from the assumed, underlying continuous distribution, the variable is categorised at points $\alpha_{i,k}$ then:

$$\alpha_{1,0} = -\infty < \alpha_{1,1} < \alpha_{1,2} < \ldots < \alpha_{1,K} = \infty, \; \alpha_{2,0} = -\infty < \alpha_{2,1} < \ldots < \alpha_{2,K_1} < \alpha_{2,K} = \infty \qquad (8)$$

It then follows that when $x_i = k$ then $\alpha_{i,k-1} < x_i^* < \alpha_{i,k}$, *for* $i = 1,2$. As such, it is then possible to calculate, via maximum likelihood, the theoretical proportions that populate the cells of a contingency table, thus:

$$L(\rho) = \prod_{i=1}^{N} \pi(x_{i,1}, x_{i,2}; \rho, \alpha) \Rightarrow LnL(\rho) = \sum_{i=1}^{N} \ln \pi(x_{i,1}, x_{i,2}; \rho, \alpha) \qquad (9)$$

The maximum likelihood is then calculated over ρ and the $\alpha's$ to determine an estimate for rho i.e. the Polychoric correlation (Pearson and Pearson, 1922).
The process can be summarised in three steps:

i) The cut-off points (α) are estimated for the underlying assumed continuous distribution of the recorded ordinal variable.

ii) Estimates of ρ are calculated conditional on α .

iii) Pairwise estimates of the correlations are placed into a matrix to form the matrix of correlations.

The accurate calculation of the correlation matrix via Polychoric methods is then able to be submitted to a standard Principal Components Analysis.

E2 Principal Component Analysis

Given that PCA is grounded in the ability to diagonalise a correlation matrix, the method is represented, thus:

Let **U** represent an eigenvalue matrix, **D** the corresponding eigenvector matrix and **M** a matrix of correlations from a dataset, then eigenvalue decomposition means:

$$\mathbf{U} = \mathbf{D}'\mathbf{M}\mathbf{D} \tag{10}$$

The calculation of the eigenvalue matrix is found by the solution to the characteristic equation:

$$\left|\mathbf{M} - \lambda\mathbf{I}\right| = 0 \tag{11}$$

Correspond eigenvectors are then calculated (given known eigenvalues from (5)) based on solutions to:

$$(\mathbf{M} - \lambda\mathbf{I})\underline{\mathbf{v}} = \underline{0} \tag{12}$$

The number of eigenvectors equals the number of eigenvalues and it follows that an eigenvector matrix and corresponding eigenvalue matrix can be shaped into equation 4.

This leads to an interesting results for the eigenvalue matrix; namely that the product of the eigenvalue matrix with its transpose yields the identity matrix, thus:

$$\mathbf{D}'\mathbf{D} = \mathbf{I} \tag{13}$$

This property (the product of the eigenvalue matrix with its transpose give the identity matrix) encapsulates the objective of PCA. That is, that the original correlation matrix has been captured in a different form that exhibits the property of orthogonality.

It follows from 4 that (after re-arrangement) that:

$$\mathbf{M} = \mathbf{D}\mathbf{U}\mathbf{D}' \tag{14}$$

This shows that the correlation matrix can be represented as a product of the eigenvalue and eigenvector matrices and as such it is then possible to ascertain the component loadings.

Equation 8 can be further expanded as:

$$\mathbf{M} = \mathbf{D}\sqrt{\mathbf{U}}\sqrt{\mathbf{U}}\mathbf{D}' = (\mathbf{D}\sqrt{\mathbf{U}})(\sqrt{\mathbf{U}}\mathbf{D}') \tag{15}$$

And if $\mathbf{T} = \mathbf{D}\sqrt{\mathbf{U}} \Rightarrow \mathbf{T}' = \sqrt{\mathbf{U}}\mathbf{D}'$ then:

$$\mathbf{M} = \mathbf{T}\mathbf{T}' \tag{16}$$

This outcome is one of the fundamental assertions of PCA and is known as **fundamental equation of factor analysis** (of which PCA is a branch of factor

analysis) (Kestelman, 1952). This asserts that the original correlation matrix can be expressed as a product of the component loading matrix (**T**) and it's transpose. After the establishment of the component loadings, the component scores (**S**) can be calculated as:

$$\mathbf{S} = \mathbf{M}^{-1}\mathbf{T} \qquad (17)$$

APPENDIX F

F1 Further multi-state model scenarios

A second multistate model that has been used is known as a bivariate model and is outlined in figure F1.

Figure F1 : Bivariate model

These type of models have been used to analyse data that have been collected over time (both prospectively and retrospectively) and examples include osteoporotic related fractures in older women (Riggs *et al.*, 1990) and the metastatic occurrences of cancer in bones (Chen *et al.*, 2005). This model allows for the simultaneous events to take place and in the case of the two studies mentioned, it is clear that an individual can have more than one fracture at a given point in time (with the flexibility of only having one). Similarly, an individual with a cancer diagnosis could be unfortunate enough to have a further diagnosis of more than one skeletal metastatic tumour. The tractability of this multistate model allows one to investigate covariate effects on movement into the various states. This is highlighted by Chen *et al.* where they investigated the effect of fluoridation treatment on osteoporotic fracture rates in older women.

A third model relates to outcomes that have competing interests related to cause of death. The basic structure of the model is outlined in figure F2.

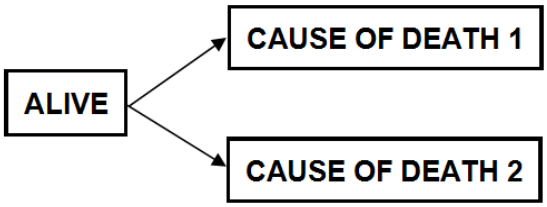

Figure F2: Competing risks model with death from 2 causes

Within this model the only non-absorbing state is that when an individual is alive. Therefore the only path a person can travel is that from a state which alive to one which is dead. This type of model has been used extensively within the literature where death can be looked at via cause-specific outcomes instead of all-cause

mortality that is used in standard survival modelling (Blanche *et al.*, 2015; Castillo *et al.*, 2015; Jepsen *et al.*, 2015).

APPENDIX G

G1 - Multistate model maximum likelihood

If we generalise the 3-state model to a model with *N* states over a standard temporal metric then the final response at time *N* can be either a censored observation or death. Under the Markov assumption its input to the likelihood, conditional on the opening observation, is:

$$L = P(X_{t2} = x_{t2},...,x_{tM} = x_{tM} \mid X_{t1} = x_{t1}) = L_2 \times ... \times L_M \qquad (18)$$

The contributions of $L_k : k \in \{2,...,N\}$ and an observation at time t_k whereby the states possible at t_k are $k \in \{2,...,N-1\}$ being 1 or 2 then:

$$L_k = P(X_{t_k} = x_{t_k} \mid X_{t_{k-1}} = x_{t_{k-1}}) \qquad (19)$$

And if the state at time t_N is *p* and *p* is a known death state, then:

$$L_N = P(X_{t_M} = 1 \mid X_{t_{M-1}} = x_{t_{M-1}}) q_{13} + P(X_{t_M} = 2 \mid X_{t_{M-1}}) q_{23} \qquad (20)$$

In other words we accept that the state at time t_N is not known and then death is an instant experience thereafter. However, if we have no information on whether an individual is dead at this time then we assume they are alive but in an unknown state (a censored observation) then the contribution to likelihood becomes:

$$L_N = P(X_{t_N} = 1 \mid X_{t_{N-1}} = x_{t_{N-1}}) + P(X_{t_N} = 2 \mid X_{t_{N-1}} = x_{t_{N-1}}) \qquad (21)$$

APPENDIX H

H1 - GBTM Maximum likelihood

If we consider a set of repeated observations on an individual *i* over *T* interviews (or recording schedules) then we have the sequence $Y_i = \{y_{i1}, y_{i2}, ..., y_{iT}\}$ and we let $P(Y_i)$ represent he probability of observing Y_i. The probability of observing this sequence will depend upon the nature of the data and how they are distributed. For the purposes of this thesis we will restrict this to a censored normal distribution (for reasons outlined in section 4.5). The primary objective of the procedure is to estimate a set of parameters that will maximise $P(Y_i)$. Standard growth curve modelling will describe how the observations evolve via the use of temporal polynomial functions (in age or time) on the population mean and a covariance matrix is used to augment the development of individuals. However, this technique only allows for variation from one mean trajectory. Contrary to this, GBTM allows the investigation of a finite set of trajectories for which the degree of the polynomial describing each trajectory is afforded the flexibility to vary. The probability of belonging to a particular trajectory can now be denoted $P^j(Y_i)$ where *j* refers to the trajectory group; in addition π_j refers to the probability of random member drawn from the population belonging to trajectory *j*. An important caveat of this technique is the unobserved trajectory membership of individuals and as such, this influences the construction of the likelihood function. The function is constructed by the accumulation of *J* conditional likelihood functions, $P^j(Y_i)$ which describe the unconditional probability of the observed data, Y_i, thus:

$$P(Y_i) = \sum_j^J \pi_j P^j(Y_i) \qquad (22)$$

In essence this model describes the unconditional probability of a set of repeated observations of a given individual, *i*. It is formed through summation over *J* trajectories and the product of the probability of *Y(i)* given affiliation with trajectory *j* and the probability of affiliation with trajectory *j*. As this summation is over a finite number of possible trajectories that exist within the population then the name, 'finite mixture model' is assigned.

An assumption of this technique is made regarding sequential observations; in that they are conditionally independent i.e. an observation at time *t* is not influenced by an

observation at time *t-1*. While this may seem to be an unlikely occurrence, it is also an assumption invoked in standard growth curve modelling where serial observations are independent conditional on the random effect. However, where the conditional independence assumption for the standard random effect model is at the level of the individual, with GBTM it is at the trajectory level. This conditional independence for a given *j* and observations attributed to individual *i* over *T* observations yields:

$$P^j(Y_i) = \prod^T p^j(y_{it}) \tag{23}$$

In this equation $p^j(y_{it})$ represents the probability density function of y_{it} given affiliation with trajectory *j*. Extending this to a complete sample of *N* participants we form the product of individual likelihoods, thus:

$$L = \prod^N P(Y_i) \tag{24}$$

H2 - GBTM distribution specific likelihood

Equation 22 can be adapted and specified in terms of the distribution to which it serves. In this case, we consider a censored normal distribution (for reasons outlined in section 4.5). To make the change from the generalised form of the model to the specific, there are two assumptions that must be made. The first surrounds the form that $p^j(y_{it})$ will take to account for the shape of the distribution, accounting for censored, normally distributed data. The second involves the specification of a link function that connects the evolution of the behaviour under investigation to a temporal parameter (age or time). This link is created via the use of a latent variable, y^*_{it}, that connects the behaviour of an individual with time (or with increasing age). This variable can be thought of as capturing the behaviour of an individual at a particular point in time and can be expressed as:

$$y^*_{it} = \beta^j_0 + \beta^j_1 Age_{it} + \beta^j_2 Age^2_{it} + \ldots + \beta^j_n Age^n_{it} + \varepsilon_{it} \tag{25}$$

Within this equation the β parameters are there to dictate the shape of any detected trajectories and the error term, ε, should be distributed normally with a mean of zero and constant standard deviation. In addition, y^*_{it}, is connected to its censored complement and S_{min} and S_{max} represents the lower and upper ends of a censored normal distribution, thus:

$$\begin{aligned} y_{it} &= S_{\min} && \text{if } y^*_{it} < S_{\min} \\ y_{it} &= y^*_{it} && \text{if } S_{\min} \le y^*_{it} \le S_{\max} \\ y_{it} &= S_{\max} && \text{if } y^*_{it} > S_{\max} \end{aligned} \tag{26}$$

The current software that analyses group based trajectories does not allow polynomials in age greater than of quartic degree and for the purposes of this thesis we restrict this to cubic polynomials in age (or time). If we let $\beta^j X_{it}$ represent $\beta_0^j + \beta_1^j Age_{it} + \beta_2^j Age_{it}^2 + \beta_3^j Age_{it}^3$ then equation 1.4 can be rewritten as $y_{it}^* = \beta X_{it} + \varepsilon_{it}$ and as it is assumed that ε_{it} is normally distributed with a mean of zero and constant standard deviation then by deduction y_{it}^* is also normally distributed but with a mean of $\beta^j X_{it}$ conditional on age, with a constant standard deviation. The censored normal attribution arises as the distribution is apparent however the censored complement y_{it} is similarly defined by a normal distribution. Explicitly, $p_j(y_{it})$ can therefore be defined as:

$$p^j(y_{it} = S_{\min}) = \Phi\left(\frac{S_{\min} - \beta^j x_{it}}{\sigma}\right) \tag{27}$$

$$p^j(y_{it}) = \frac{1}{\sigma}\theta\left(\frac{y_{it} - \beta^j x_{it}}{\sigma}\right) \quad for\ S_{\min} \le y_{it} \le S_{\max} \tag{28}$$

$$p^j(y_{it} = S_{\max}) = 1 - \Phi\left(\frac{S_{\max} - \beta^j x_{it}}{\sigma}\right) \tag{29}$$

Where θ and Φ describe the cumulative distribution function and the density function of a normal random variable, respectively. Within this framework we yield a mean of $\beta^j X_{it}$ and constant standard deviation σ. Furthermore, to specify the likelihood, a substitution of equations 1.6, 1.7 and 1.8 into equation 1.2 for y_{it} will yield the necessary likelihood function.

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