UNIVERSITY OF LIVERPOOL

Understanding health inequalities in multimorbidity and functional limitation of the ageing population in England

Thesis submitted in accordance with the requirements

of the University of Liverpool for the degree of Doctor

in Philosophy by:

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September 2019

Acknowledgements

First, I would like to acknowledge the School of Environmental Sciences for funding my PhD studies. The studentship was essential for the final completion of my research.

Secondly, being privileged to have a diverse and committed supervisory team was as important for my project as the financial backing. My greatest thanks go to Mark Green, Francisco Rowe, Yoav Ben-Shlomo, Karyn Morrissey and Hill Kulu. The level of patient support, practical advice and methodological guidance given was truly invaluable and much appreciated.

Thirdly, I am deeply grateful to my partner, Janet, and our children, Bridie and Lenka. Thank you for all your patience, thank you for all the trust and support without which I would never be able to complete. I am sorry for all these late evenings that you spent without your partner and your dad being around. I hope that all the sacrifice was worth it, that my research uncovered a couple of new facts that will be useful for the practical improvement of the society, and that it will lead to further career in the exciting and expanding field of multimorbidity.

Finally, I would like to acknowledge the memory of Betty, my mother-in-law from the north of Liverpool, whose extremely tough childhood literally embodied the complex circumstances described in this study. It was her unfair suffering and premature death in 2014, what made me interested in the subject of multimorbidity in the first place.

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Chapter 1

Introduction

The ageing process has a diverse impact on health and functional status which makes old populations heterogeneous (Lowsky et al., 2014). To capture this variability, researchers use several measures or indicators of the health status in old age. Among the most common measures are morbidity, physical functioning, cognitive functioning and disability (Santoni et al., 2015). This thesis investigates the variability of multimorbidity and functional limitations in the ageing population in England. Multimorbidity is the co-occurrence of two or more diseases within a person (Van den Akker, 1998). On average, every third person in the world has multimorbidity and the proportion of the population with multimorbidity is growing (Nguyen et al., 2019). Functional limitations are restrictions in performing fundamental physical and mental actions used in daily life (Verbrugge and Jette, 1993). The proportion of population with functional limitations is also growing (Guzman-Castillo et al., 2017). This thesis seeks to explore the extra-individual factors behind the growth in multimorbidity and functional limitation as well as their unequal distribution in the ageing population of England. Chapter 1 sets up the background for the topic, introduces the purpose and the aims of the thesis, its structure and the final outputs of the project.

1.1 Background

People are living longer lives but they have more diseases and disability. Societies have transitioned from an era dominated by communicable diseases to a world dominated by non-communicable diseases (Niessen et al., 2018).

They have become the leading cause of death in the world. In 2016 chronic diseases were responsible for 71% of the 57 million deaths globally and this proportion is increasing (World Health Organization, 2018). Among the major causes of death are cardiovascular diseases, cancers, chronic respiratory diseases and diabetes (World Health Organization, 2018). The role of non-communicable diseases now features prominently in both the High Income and the Low Income Countries (Garin et al., 2015; Niessen et al., 2018).

These trends have also been described as the global rise in *multimorbidity* which refers to the presence of two or more diseases within a person (Van den Akker, 1998; Global Burden of Disease Study 2013 Collaborators, 2015). Estimates of multimorbidity prevalence vary depending on the definition, the classification and number of studied conditions, the type of sample, age group, etc. A systematic review by Violan et al. (2014) focused on studies of primary care patients and found that the estimates ranged from 13% among young patients to 95% in a population aged 65 years and older. The prevalence of multimorbidity in general populations has been assessed between 13% and 72% (Fortin et al., 2012). Another review found the variation in general populations between 20% and 30% and 55% to 98% among elderly people (Marengoni et al., 2011). A rising prevalence has been documented in the United Kingdom (Reilly et al., 2015), the Netherlands (van Oostrom et al., 2016), Germany (Tetzlaff et al., 2018) and Canada (Canizares et al., 2018). The trend is unlikely to stop. The absolute number of people affected by multimorbidity in England is expected to double by 2035, and at least two thirds of the gain in life expectancy above 65 years will be spent with four or more chronic conditions (Kingston et al., 2018).

More older people with multimorbidity will mean more suffering as multimorbidity in the course of ageing often combines with functional limitation. Functional limitations refer to restrictions in performing fundamental physical and mental actions used in daily life (Verbrugge and Jette, 1993). The fundamental physical actions include body mobility, discrete motions and strengths, difficulties with seeing, hearing and communicating. Akin to multimorbidity, the number of people living with functional limitations

between 2015 and 2025 in England will increase by about 2-3% per year. While the lifespan will increase, a quarter of life expectancy at age 65 years will involve functional limitation (Guzman-Castillo et al., 2017).

Multimorbidity accompanied by functional limitation reduces quality of life (Kanesarajah et al., 2018). People living with multimorbidity combined with functional loss often experience pain, both physical and psychological. The impaired functioning and pain prevent them from conducting previous daily and social life. Typical for multimorbidity and loss of function is that physical and emotional difficulties compound. One illness gets aggravated by the effects or treatment of another (Sells et al., 2009). Such a series of escalating physical problems, often accompanied by psychological and social issues, has been referred to as "*cascading crises*" in individual lives or "probabilistic cascade" (Sells et al. 2009). Some symptoms may interfere in patients' ability to manage their care (Liddy, Blazhko and Mill, 2014). People with multimorbidity combined with functional limitation often talk about living in a state of endless uncertainty, in particular when it comes to their future health. The situation prevents them from planning future life, leading to feelings of powerlessness, low self-esteem and withdrawal from social interaction (Coventry et al., 2015; O'Brien et al., 2014). In addition, people with more complex multimorbidities struggle with following strict treatment regimes, take many different medicines (polypharmacy) and may face hospitalization as well as high medical charges, for example as co-payments for care, technical aids or home care (Calderón-Larrañaga et al., 2019).

All this makes life with multimorbidity time-consuming, as much for patients as for the health care systems. People with multimorbidity and functional loss use disproportionately more specialist services than people with a single health problem. The number of chronic diseases significantly predicts hospital usage (Lehnert et al., 2011). Higher utilization of health care services also adds to higher treatment costs compared to managing a single morbidity (Picco et al., 2016). Multimorbidity also predicts mortality. A study found that older adults

with multimorbidity were 44% more likely to die during follow-up than those with no or only one chronic disease (Calderón-Larrañaga et al., 2019).

The significance of the increasing multimorbidity and functional limitation for public health and welfare is elevated by the evidence suggesting an unequal distribution of this burden in populations (Northwood et al., 2017). In Britain, a compound nexus of young age, socio-economic deprivation and combined physical-mental multimorbidity has been identified (Barnett et al., 2012; Reilly et al., 2015; Cassel et al., 2018). While multimorbidity has been studied as a problem of the elderly, there is evidence that in absolute terms the majority of people with multimorbidity are younger than 65 years of age (Barnett et al., 2012; Sauver et al., 2015; Cassel et al., 2018). Younger age of the onset of multimorbidity is often related to living in poverty. Experiences of social deprivation also exacerbate the complexity of multimorbidity. In Scotland, the combination of physical and mental morbidities was two to threefold more prevalent in the deprived areas than in the affluent ones and among younger people it is more common than physical multimorbidity (McLean et al., 2014). The relationship between deprivation, young age and physical-mental multimorbidity was confirmed for a representative patient population in England (Cassel et al., 2018). The cluster is becoming common in the whole of the United Kingdom and increases at a faster rate in the poorer areas, as shown in a study for the period 2000-12 (Reilly et al. 2015).

1.2 The research purpose and aims

This thesis positions itself in the interdisciplinary efforts to understand the 'social drivers' of the increase in prevalence and inequalities in multimorbidity and functional limitation of ageing people in England. The purpose of the study is to enrich the growing discussions about the relationship between multimorbidity and functional decline and their societal context with new evidence and perspectives.

In a representative sample of people aged 50 years and older in England, collected in the period 2002-2015, this thesis aims to:

1. Explore the prevalence of multimorbidity and functional limitation and its variation by key socio-demographic characteristics.
2. Examine the association of key social determinants of health with multimorbidity and functional limitation.
3. Explain how childhood circumstances shape the risk of multimorbidity and functional limitation in old age.

1.3 Thesis structure

1.3.1 Chapter 1. Introduction

Chapter 1 introduces the general topic of the thesis and its societal relevance. It further presents the purpose and the aims of the thesis, its structure and the final outputs of the project.

1.3.2 Chapter 2. Literature review

The literature review documents the evolution of thinking about multimorbidity from the early predominantly medical perspectives to an integration of the knowledge about biological mechanisms with social theories of health. The review pays particular attention to the socio-theoretical aspects of the body of research. The review identifies and discusses a series of knowledge gaps in the studies of multimorbidity and functional limitation, which this thesis is trying to address.

1.3.3 Chapter 3. Trends in multimorbidity and functional limitation in the ageing population of England

The first analytical chapter builds on the emerging evidence of multimorbidity becoming more common and more socially stratified (Reilly et al., 2015; Van Oostrom et al., 2016; Tetzlaff et al., 2018; Canizares et al., 2018). The study focuses on changes in the multimorbidity and functional limitation of an ageing population in England over time. It explores trends in prevalence and distribution of prevalence by age, sex and socio-economic status at a population level. Two measures of multimorbidity are used comparatively. The first measure, referred to as *basic multimorbidity* in the study, is based on the count of single chronic diseases which the study argues is limited in its ability to identify the multimorbid individuals with higher care needs. The second measure, *complex multimorbidity*, defines a situation when three or more body systems are affected by chronic disease (Harrison et al., 2014).

The repeated cross-sectional analysis covers the period between 2002-03 and 2014-15, in total seven time points. At each time point, stratification analysis explores the differences in prevalence between age groups (5-year bands from age 50 to 85+), women and men and by quintiles of net household wealth. The potential health inequalities in multimorbidity and functional limitation and interaction effects between time and age and SES and age are verified in marginal effects logistic regression analysis.

1.3.4 Chapter 4. Social determinants of multimorbidity and functional limitation in the ageing population of England

After establishing robust inequalities in mutimorbid population by differences in the amount of household wealth, Chapter 4 builds on the theories of social determinants of health and health inequalities and includes more social determinants into the analysis. The extension addresses a lack of contextual data in studies of multimorbidity which typically focus on a few risk factors (Northwood et al., 2017). The study introduces material determinants

(household wealth, occupational level and subjective social status), psycho-social determinants (sense of control over individual life, loneliness, supportive children, supportive friends, supportive partner and participation in community organisations) and behavioural determinants (level of physical activity, consumption of alcohol and smoking). The analysis explores the association of the social determinants with the likelihood of multimorbidity, complex multimorbidity and multiple functional limitations.

Towards this aim, the study uses a population-averaged regression model, based on the Generalized Estimating Equations with autoregressive correlation structure. The model takes into account the within-individual correlation of outcomes over the period 2002-2015.

1.3.5 Chapter 5. Material, psychosocial and behavioural pathways to multimorbidity and functional limitation of old people

This explanatory study seeks to explain how the associations of the material, psychosocial and behavioural social determinants with multimorbidity and functional limitation develop over an individual life course. Instead of the usual single socio-economic proxy for childhood circumstances the chapter uses three latent measures: Social Class, Adverse Experiences and child's health. The study's aims are to establish if the effects of childhood circumstances on multimorbidity and functional limitation in old age are direct or indirect. Another aim is to assess the role of material, psycho-social and behavioural pathways in mediating effects of childhood circumstances on the individual differences in old age multimorbidity and functional limitation.

The key methods are Factor Analysis in the initial stage of the analysis, Structural Equation Model with latent factors and a complex mediation analysis with both parallel and serial mediators in the same model. Statistical inference is conducted via bias-corrected bootstrapping method.

1.3.6 Chapter 6. Conclusion

The final chapter recapitulates the knowledge gaps identified in the literature review. It summarizes the key research findings and discusses their contribution to the current knowledge in the field of multimorbidity. The limitations of the research are established, with suggestions about how the thesis could be improved. The chapter concludes with a series of ideas for possible extensions of the research that could build upon the achievements of this thesis.

1.4 Outputs

Chapter 3 *Trends in multimorbidity and functional limitation in the ageing population of England* is based upon Singer, Green, Rowe, Ben-Shlomo, Kulu and Morrissey (2019) Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England, 2002-2015, Journal of Comorbidity, https://doi.org/10.1177/2235042X19872030.

Chapter 3 differs from the published paper in Section 3.2.1. It contains a more detailed information about the core members included in the analyses and the weights used.

Chapter 4 *Social determinants of multimorbidity and functional limitation in the ageing population of England* originates from Singer, Green, Rowe, Ben-Shlomo & Morrissey (2019) Social determinants of multimorbidity and multiple functional limitations among the ageing population of England, 2002-2015, Social Science & Medicine – Population Health, doi:10.1016/j.ssmph.2019.100413.

Chapter 4 differs from the published version in Section 4.5.1. It has been expanded by explaining more about the number of core members, the data format and the principles behind the weighting.

Chapter 5 *Material, psychosocial and behavioural pathways to multimorbidity and functional limitation of old people* will be submitted to Social Science &

Medicine in February 2020. The co-authors are M. Green, F. Rowe, Y. Ben-Shlomo, K. Morrissey and H. Kulu.

Leo Singer developed the research aims of the thesis, designed the analytical chapters, performed the analyses and wrote the manuscripts. Mark Green and Francisco Rowe advised on the study design, scrutinized the analyses and helped interpret some of the findings. Yoav Ben-Shlomo helped to construct the health outcomes. All the co-authors were involved in revising the manuscript and gave final approval. Leo Singer has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

1.5 References

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Chapter 2

Literature review

This literature review introduces the development of studies in multimorbidity since its beginning (Feinstein, 1970). The review presents and discusses the fundamental issues of how multimorbidity and functional limitation are defined and measured. The lack of a unified approach to its measurement is demonstrated by the variety of prevalence estimates in the literature. This chapter presents current evidence on the growing trends in the prevalence of multimorbidity and functional limitation. The drivers of this trend are critically discussed and the sole explanation - the ageing of society - is questioned. The roles of societal factors such as health inequalities and social determinants of health are reviewed and placed in a historical context. The review argues that in order to understand the mechanisms through which societal factors influence multimorbidity and functional limitation of ageing populations, life course theories and models are needed. Research gaps that arise from the literature review are summarised and discussed at the end of the chapter.

2.1 Defining multimorbidity and functional limitation

The idea of a co-occurrence of health problems dates back to studies of alcoholism and associated mental disorders in the United States in the 1940s (Kushner 2014). The American clinical epidemiologist Alvan Feinstein first coined the term *comorbidity* in 1970, referring to "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (Feinstein 1970, pp. 456-7). As an example, Feinstein mentioned lung cancer as an index disease with comorbidities such as ulcers, coronary artery disease or diabetes mellitus. The

purpose of the article was to explain how, in clinical trials focused on a single disease, an unobserved comorbidity confounded the treatment effects on participants which led to biased practices in subsequent care management. In the same article Feinstein expanded his definition to "also include such 'non-disease' clinical entities as: pregnancy, deliberate dieting in an effort to lose weight and certain symptomatic reactions such as nausea, that may occur with various therapeutic manoeuvres" (Feinstein 1970, p. 457). This caveat opened the door to ambiguity in the understanding of comorbidity as it increasingly encapsulated a range of morbidities, conditions, symptoms and risk factors (Le Reste, 2013).

At its first stage, comorbidity research was dominated by psychiatry, later joined by neurology, general and internal medicine, surgery, cardiology and oncology (Catalá-López et al. 2018). The number of publications has increased exponentially since 1970, with two thirds of the articles published after 2010 (Catalá-López et al. 2018). The growing comorbidity research reflected the underlying processes of ageing and ailing societies in the West (Gruenberg, 1977; Crimmins and Beltrán-Sánchez, 2011). It was shaped and driven by the health care demands and policies of the period (Crimmins and Beltrán-Sánchez, 2011). A major topic in clinical and primary care studies of multimorbidity became the inadequacy of care management based on single-disease or index-disease regimens. The core of the problem lay in the general assumption that comorbidities in every patient were physiologically associated with the index disease and hence a treatment plan focused on the index disease could address all other morbidities. However multi-factorial medicine and growing availability of multi-variate analytical software allowed insights into complex biological pathways, overlapping clinical symptoms and their genesis (Krieger, 2011). Clinical studies increasingly agreed that the index-disease specific guidelines were appropriate only for situations when chronic diseases shared the same pathways (Van Weel and Schellevis, 2006).

The trend towards a pluralistic understanding of comorbidity where no disease assumed a dominant role was reinforced by a growing interest in comorbidity

from epidemiology and public health (Almirall and Fortin, 2013). A more consistent classification was proposed, whereby the term *multimorbidity* would be used in situations where no index disease was considered, and the term comorbidity would be reserved for situations in which one of the diseases is considered as index (Van den Akker et al., 1998).

A plurality of definitions refers to the situation of having simultaneously a multiple number of chronic and acute diseases (Johnston et al., 2019). Some authors define multimorbidity as the co-existence of "two or more diseases" (Van den Akker et al., 1998), "multiple diseases or medical conditions" (Huntley et al., 2016), "chronic diseases" (Diederichs et al., 2011) or "any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor" (Le Reste, 2013). Various additional terms, referring to the same health problem, can be found in the literature: polymorbidity, polypathology, pluripathology, multipathology, multicondition, multiple chronic conditions (Almirall and Fortin, 2013). A bibliometric analysis of the two most commonly used concepts has shown that while the number of articles using the term comorbidity still exceeds those using multimorbidity, the difference is getting smaller (Ramond-Roquin and Fortin, 2016).

Functional limitation is another aspect of health status that is a subject of this thesis. Functional limitation can be approached within the framework of the Disablement Process (Verbrugge and Jette, 1993). This widely used framework describes a pathway starting from disease, through impairments and functional limitations, leading to disability (Martin et al., 2017). Impairments are defined as dysfunctions and structural abnormalities in body systems, which can have impacts on physical, mental or social functioning (Verbrugge and Jette, 1993). Functional limitations refer to restrictions in performing fundamental physical and mental actions used in daily life (Verbrugge and Jette, 1993). The fundamental physical actions include body mobility, discrete motions and strengths, difficulties with seeing, hearing and communicating. The Disablement Process can be illustrated by arthritis (disease) leading to joint

stiffness and pain (an impairment). Joint stiffness and pain may in turn result in difficulty bending (functional limitation), which may ultimately result in a mobility disability (Martin et al., 2017).

The Disablement Process framework defines conceptually the relationship between multimorbidity and functional limitation as the first being the cause of the latter (Verbrugge and Jette, 1993; Santoni et al., 2015). Some conditions (e.g. high blood pressure) may have no effect on the physical functioning but other do, such as arthritis. Multimorbidity predicts increase in functional limitation of ageing and old people, which has implications for quality of life, need for health care, residential care and premature mortality (Sibritt, Byles and Regan, 2007; Ryan et al., 2015; Jindai et al., 2016). Combination of multimorbidity with functional impairments and limitations leads to situations where the total impact of multimorbidity on individuals' health surpasses the impact we would expect from the summed effect of single conditions (Schaefer, 2012; Calderón-Larrañaga, 2019).

2.2 Measuring multimorbidity and functional limitation

There is no consensus in the way researchers measure multimorbidity. The way it is measured in a population results from the choice of its definition and from deciding on other operationalizing criteria, such as the definition of disease entity and the number of diseases included in the analysis (Fortin et al., 2012; Johnston et al., 2019). The plurality in measurement complicates comparison of findings across populations and developing universal guidelines and interventions (Johnston et al., 2019).

2.2.1 Disease definition

The International Classification of Diseases (ICD) is the international standard for reporting diseases and related health conditions and the 11th version was

launched in 2018 (WHO Classifications, 2019). ICD is used primarily in hospitals. It allows for comparability of morbidity and mortality statistics between different countries, because it contains precise medical diagnoses given by trained professionals. The other common classification system is the International Classification of Primary Care (ICPC). The system records diagnosed conditions and undiagnosed symptoms, which are both commonly managed in primary care.

Regardless of the particular classificatory system, multimorbidity studies differ in how they define a disease entity. Some only treat a specific disease as an entity, while others use a group of conditions as an entity, for example myocardial infarction and chronic ischaemic heart disease (Diederichs et al., 2011). Some studies tried to ensure counting only distinct entities by considering only chronic diseases which affect distinct body systems. The Cumulative Illness Rating Scale (CIRS) is used to classify chronic diseases by body systems, for example cardiac, vascular or haematological systems (Hudon, Fortin and Soubhi, 2007). Constructing a CIRS scale requires using either ICD or ICPC system and rating severity of conditions which can only be done by a doctor or a trained nurse (Hudon et al., 2007). An alternative to the CIRS system is using the chapters within the ICD or ICPC classifications which are both based on body systems. Australian researchers Harrison et al. (2014) compared prevalence estimates of multimorbidity if classified as ICD, ICPC and CIRS chapters. They confirmed the validity of the measures and found no difference in estimates between the three systems.

The fact that ICD, ICPC and CIRS systems can be treated as commensurable means that researchers are no longer dependent on health records with measures of severity (CIRS). New opportunities open up to explore multimorbidity of distinct body systems as a specific case of multimorbidity using self-reported data and population-based surveys. This is relevant especially for multimorbidity of the elderly. The biology of ageing is characterised by a simultaneous breakdown or dysfunction of several distinct pathologies or body systems (Fabbri et al., 2015; Cesari et al., 2017). A study

found that the affected body systems of people aged 65+ were predictors of the total length of hospital stays and of the number of hospital admissions. Future research should consider measuring multimorbidity in the elderly by counting the body systems affected rather than the number of single diseases.

2.2.2 Number of diseases defining multimorbidity

While most studies define multimorbidity as the co-occurrence of two or more chronic diseases (2+), another common cut-off point is 3+ (Diederichs et al., 2011). Previous studies found that using a higher cut-off point reduces the prevalence estimates (Diederichs et al., 2011; Fortin et al. 2012). This means that more people have two diseases than three, having three diseases is more common than having four, etc. When multimorbidity was defined as 2+ disease entities, nearly half of the patients in primary care had multimorbidity, whereas using the 3+ cut-off reduced the prevalence to less than one in four (Harrison et al., 2014). Multimorbidity defined as 2+ leads to especially high estimates among the elderly. A paper reviewing multimorbidity of the elderly found that prevalence among those aged 65 or older ranged between 55% and 98% (Marengoni et al., 2011). Another study using the 2+ definition identified almost 91% as having multimorbidity and 66% when using 3+ among the 70-79 years old (Harrison et al., 2014).

The high estimates were considered to be unhelpful in identifying old patients with higher need (Fortin et al., 2012). Measuring multimorbidity of elderly people by the number of affected body systems might be more appropriate than just summing up the number of single diseases (Harrison et al., 2014). Counting a sum of single disease entities does not differentiate between the co-occurrence of problems developing within one body system and within two or more systems. The difference matters as multimorbidity may have a larger impact on overall health if it arises out of disparate conditions rather than closely related comorbidities. Piette and Kerr (2006) distinguished between *concordant* conditions, which are part of the same pathophysiology, and the unrelated

discordant conditions which do not share joint pathophysiology or underlying risk factor. For example, diabetes is concordant with hypertension and several vascular diseases but discordant with chronic back pain, asthma or cancer (Piette and Kerr, 2006). Treating discordant conditions is more complicated as chronic conditions in different body systems are likely to compete for treatment (Piette and Kerr, 2006).

Another consequence of merely summing up the diseases of elderly patients is that it may put them at risk of overdiagnoses and polypharmacy where some treatments act against the other (Cesari et al., 2017). A comparative use of both 2+ and 3+ definitions of multimorbidity has been recommended by Fortin et al. (2012) and Harrison et al. (2014).

2.2.3 Number of diseases studied

Diederichs et al. (2011) reviewed the number of diseases studied and found that the selection scope ranged from four to 102 diseases (with a mean number 18.5). The most common criteria for the choice of a certain number was high prevalence or high impact on patients (Diederichs et al. 2011, Harrison et al. 2014). It has been noted that the more diseases are analysed, the higher prevalence rates one gets (Van den Akker 2001; Diederichs et al., 2011; Fortin et al., 2012; Harrison et al., 2014). A review of 21 prevalence studies (both in primary care and among the general population) found much less variation in prevalence estimates between studies that analysed twelve or more diseases compared to studies with a smaller number (Fortin et al., 2012). The minimum of twelve diseases was recommended to achieve better commensurability of prevalence results between studies (Fortin et al.., 2012).

2.2.4 Patterns

The most frequently observed clusters of morbidity combinations are also referred to as patterns of multimorbidity (Agborsangaya et al., 2012; Prados-Torres et al., 2014; Ng, 2018). The goal of analysing patterns is to identify relevant

multimorbidity groups from a larger set of diseases (Marengoni et al., 2011; Violan et al., 2014). In a systematic review Violan et al. (2014) distinguished between two types of patterns: the most frequent combinations of specific diseases (pairs and triplets) and clusters of health conditions with the highest degree of association.

While the original research was limited to considering comorbid pairs and triplets of morbidities, methods such as cluster analysis, factor analysis and multiple correspondence analysis make it possible to consider how larger numbers of diseases tend to occur in conjunction with each other (Violan et al., 2014; Prados-Torres et al., 2014; Ng, 2018). With the use of these techniques it is possible to gain an overall picture of how diseases are associated in a particular population. Violan et al. (2014) and Prados-Torres et al. (2014) agreed that the three most common patterns are: cardiovascular and metabolic diseases (diabetes, hypertension, heart diseases, hyperlipidemia, obesity); mental health disorders (depression, anxiety, neurological disorders); and musculo-skeletal diseases (arthritis, arthopathy, osteoporosis, back-neck pain). Constructing patterns or clusters of multimorbidity requires good quality medical data with clear diagnostic differentiation between diseases and accompanying health conditions and symptoms (Ng, 2018).

2.2.5 Prevalence rate

In order to be able to compare the magnitude of multimorbidity in populations with differing sizes, the calculation of prevalence rates is necessary. Measurement of prevalence was at the beginning of population research in multimorbidity (Van den Akker, 1998).

Prevalence refers to the proportion of the population with multimorbidity at the time of measurement (Marengoni et al., 2011). The estimates of the prevalence vary, depending on the definition, the classification and number of studied diseases, whether the sample comes from a general population or primary care, age group, etc. In the first systematic review assessing both high-

income and low-income countries, the prevalence of multimorbidity in general populations was estimated at 33.1% (Nguyen et al., 2019). The average was 37.9% for the high-income countries and 29.7% for the low-income countries. Disease count, based on self-reported data, was the most common measure of multimorbidity (Nguyen et al., 2019).

A systematic review by Violan et al. (2014) focused on studies of primary care patients and found that the estimates ranged from 13% among young patients to 95% in a population aged 65 years and older. The prevalence of multimorbidity in general populations has been assessed between 13% and 72% (Fortin et al., 2012). Another review found the variation in general populations between 20% and 30% and for the elderly people between 55% and 98% (Marengoni et al., 2011).

Prevalence rates based on patient data from primary care tend to be higher than self-reported rates measured in the population which is due to a selection bias (Valderas et al., 2009, Mokraoui et al., 2016). The selection bias reflects the fact that people who visit primary care often have more diagnoses compared to those who avoid medical consultations (Valderas et al., 2009, Mokraoui et al., 2016). The variation in prevalence rates between studies makes it difficult to establish to what extent the differences between countries and between general and patient populations are real and to what extent they are caused by differences in methodological approaches (Fortin et al., 2012).

2.2.6 Measuring functional limitation

Measuring physical function and functional limitation in population research serves to enable comparing outcomes between population groups, for example levels of function between men and women, young and old, or according to some social characteristics (Lang, 2011). It can also help to predict outcomes or trajectories, for example disability, death and use of care or hospital admissions (Guralnik and Ferucci, 2003; Lang, 2011).

Functional limitation in older people can be measured either by standardized performance measures or by self-report (Guralnik and Ferucci, 2003). Direct measurement of physical performance requires a trained assessor to ensure validity. Commonly measured outcomes are grip strength, walk speed, tests of balance or "get up and go" tests (Lang, 2011). Self-reported measurement is gained from questionnaires and includes three aspects: Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs) and mobility. ADLs such as getting out of bed, toileting, bathing, dressing, grooming, and eating are frequently used. These measures can help to detect early onset of disability and are key factors for care management (Hopman-Rock et al., 2019). IADLs are used to measure skills for independent living and are more complex than ADLs. Ability to do housekeeping, shopping, bathing, to prepare food or use telephone are commonly assessed (Lang, 2011). Finally, self-reported measures of mobility include ability to walk quarter of a mile, walk 100 yards, climbing one or several flights of stairs and pulling or pushing objects (Lang, 2011).

2.2.7 Measuring multimorbidity and functional limitation in the thesis

Most reviewers recommend that decisions about the operationalizing criteria should be guided by the purpose of the study and available data (Johnston et al., 2019). This thesis explores multimorbidity and functional limitation in a representative population of people aged 50 years or older in England. As the ageing process is characteristic by the deterioration in physical and functional health, the cumulation of multimorbidity and functional limitations in the study population can be anticipated. Ageing is also marked by chronic dysregulation across multiple body systems, with multimorbidity and functional loss being the markers of the process (Fabbri et al., 2015). This thesis uses measures of multimorbidity and functional limitations that are appropriate for studying an ageing population.

Basic multimorbidity

Multimorbidity, defined as "the co-occurrence of two or more diseases within a person" (Van den Akker et al., 1998), will be called *basic* multimorbidity in the thesis. The summary count of single disease entities is the most common way of constructing a measure of multimorbidity in population-based studies which rely on self-reported data (Nguyen et al., 2019). This thesis constructs a binary measure of basic multimorbidity which identified persons in the ELSA survey who had two or more diseases out of the list of 25 diseases.

Complex multimorbidity

Summing up single disease entities cannot distinguish between the co-existence of problems developing within one body system and within two or more systems. Piette and Kerr (2006) distinguished between *concordant* conditions, which are part of the same pathophysiology, and the unrelated *discordant* conditions which do not share a joint pathophysiology or underlying risk factor. For example, diabetes is concordant with hypertension and several vascular diseases but discordant with chronic back pain, asthma or cancer (Piette and Kerr, 2006). Treating discordant conditions is more complicated as chronic conditions in different body systems are likely to compete for treatment (Piette and Kerr, 2006). Fortin et al. (2012) and Harrison et al. (2014) thought that this distinction had a broader relevance than just for clinicians managing multimorbidity. They proposed considering the difference between concordancy and discordancy in the process of defining multimorbidity itself. The concept of *complex multimorbidity* has been defined as "the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without an index chronic condition" (Harrison et al., 2014, p. 8).

The thesis will use complex multimorbidity as a comparative definition along with basic multimorbidity, in line with the recommendations made by Fortin et al. (2012) and Harrison et al. (2014). The body systems in the thesis were

represented by the chapters of the ICD (10th version). All 25 chronic diseases analysed in this thesis were classified to eight ICD-10 chapters.

Multiple functional limitations

To assess functional limitation this thesis will use a measure of multiple functional limitations. It is derived from the Disablement Process Framework (Verbrugge and Jette, 1993). The process defines a progression from disease, through impairments and functional limitations, to disability (Martin et al., 2017). The measure of multiple functional limitations merges measures of functional limitations – ADLs, IADLs and mobility - with measures of functional impairment (geriatric symptoms) into a summary outcome. The thesis also proposes the measure of having ten or more functional limitations as this might reflect the increase in limitations arising from multiple body systems as part of the ageing process (Jindai et al., 2016; Calderón-Larrañaga et al., 2019).

2.3 The growth of multimorbidity and functional limitation

The prevalence of multimorbidity and functional limitation is growing across populations of higher income countries. The occurrence of multiple diseases in the Netherlands doubled between 1985 and 2005. The proportion of patients with one and two chronic diseases remained stable, the proportion of those with three chronic diseases increased by approximately 60% and the prevalence of four or more chronic diseases increased by approximately 300% (Uijen and van de Lisdonk, 2009). An increasing trend among Dutch primary care patients between 2004 and 2011 was also noted by Van Oostrom et al. (2016). The trend was only partially explained by population aging, suggesting that other epidemiological and societal factors explained a substantial part of the increase.

Trends for functional limitations are contradictory. Prevalence of ADLs grew by 6% between 2000 and 2005 in the general population in the United States

(Fuller-Thomson et al., 2009). A study from Spain reported a concurrent growth in multimorbidity, ADLs and IADLs between 2001 and 2009 for both men and women (Palacios-Ceňa et al., 2013). Analysis of the same Health survey for the period 2009-2017 in contrast showed a slight decrease in ADLs and IADLs in Spain (Carmona-Torres et al., 2019). A slow decline in functional limitations was also reported from the Netherlands (Van Gool et al., 2011) and Sweden (Angleman et al., 2015).

Due to the significant societal implications, the growth of multimorbidity in populations generates attempts to explain it. The expansion of morbidity theory postulates that higher life expectancy due to the decline in infectious diseases leads to people living longer but in chronic illness (Gruenberg, 1977). Better disease management and treatment contribute to even more people surviving in ill health (Gruenberg, 1977; Crimmins and Beltrán-Sánchez, 2011; Muschik et al., 2017). The theory often features as an explanation of the increasing prevalence of multimorbidity in the Western societies (Fabbri et al., 2015; Kingston et al., 2018). For example, a population study from Germany found that the number of life years spent with multimorbidity rose at a faster pace than total life expectancy. The researchers pointed to the expansion of morbidity theory as an explanation (Tetzlaff et al., 2017).

The theory sometimes leads to interpretations that the growth is generated exclusively by people living longer lives. Solutions generated within this framework tend to focus on better clinical management and support for the elderly (Marengoni et al., 2011). The need to prevent or reduce the incidence of multimorbidity motivated researchers to start searching for the estimates of multimorbidity at younger age groups. The evidence began to challenge the assumptions of the expanded morbidity theory. A population-based study of the Adelaide region (Australia) revealed that over 40% of those who had multimorbidity were less than 60 years of age (Taylor et al., 2010). In a representative survey of the residents in Alberta (Canada), 70% of multimorbid population were younger than 65 years (Agborsangaya et al., 2012). Similar

results were reported from Scotland (Barnett et al., 2012) and the United States (Sauver et al., 2015).

Canizares et al. (2018) posed an important question whether the increase in multimorbidity documented by others could be explained by some current contingent factors (period effects) or whether the tendency can be observed across cohorts and for an extended period of time. The multi-cohort study of a general Canadian population provided the strongest evidence yet that the growth in multimorbidity is a consistent long-term trend affecting all age cohorts (Canizares et al., 2018). People are becoming multimorbid at increasingly younger age and especially those living in deprived areas. The age-cohort studies (Agborsangaya et al., 2012; Barnett et al., 2012; Sauver et al., 2015; Canizares et al., 2018) indicated that the growth in multiple diseases might be explained by more factors than the longer survival rates and medical advancements among the ageing population.

2.4 Health inequalities in multimorbidity and functional limitation

Multimorbidity is more common in poorer areas and manifests itself earlier in life among poorer people than more affluent people (Violan et al., 2014). The prevalence among young and middle-aged patients in the most deprived areas of Scotland was the same as the prevalence of 10-15 years older patients from the most affluent areas (Barnett et al., 2012). Experiences of social deprivation also exacerbate the complexity of multimorbidity. In Scotland, the combination of physical and mental morbidities was two to threefold more prevalent in the deprived areas than in the affluent ones. Among younger people the physical-mental multimorbidity is more prevalent than purely physical multimorbidity (McLean et al., 2014). The relationship between deprivation, young age and physical-mental multimorbidity was confirmed for a representative patient population in England (Cassel et al., 2018). The relationship is becoming increasingly common in the whole of the United Kingdom and increasing at a

faster rate in the poor areas, as shown in study for the period 2000-12 (Reilly et al., 2015). The limitation of this body of research is that it is all based on data from primary care and social deprivation was only measured by the Carstairs index or at an area level.

Multimorbidity is more common among women than men (Uijen and van de Lisdonk, 2008; Marengoni et al., 2011; Salisbury et al., 2011; Prados-Torres et al., 2015), but some studies did not observe the difference (Fortin et al., 2005; Sauver et al., 2015). Women have higher levels of multimorbidity than men in all ages but the difference vary by age group and type of morbidities. For example, in Scotland the difference was the largest between middle-aged men and women (45-54 years old). The combination of physical and mental conditions was more common among women (Agur et al., 2016). Similar gender disparities were found in a U.S. population-based study (Bobo et al., 2016), with the physical/mental multimorbidity 1.7 times more prevalent among females than males. The gender differences were greater for physical/mental multimorbidity than for the general multimorbidity.

Differences in race have been documented in the United States (Quiñones et al., 2011, 2019; Sauver et al., 2015). In a nationally representative sample during the period 1998-2014, Black middle-aged people (51-55 years old) had a higher initial degree of multimorbidity than White participants and their onset was four years earlier. In contrast, middle-aged adults of Hispanic origin started disease accumulation later than Black adults but at a faster rate than both (Quiñones et al., 2019). The interpretation of the racial differences was framed in terms of different risk factors affecting population groups. Observing residents in a county in the U.S. state of Minnesota in 2000-13 showed that compared to White participants, the incidence of multimorbidity was higher in Blacks but lower in Asians (Sauver et al., 2015). Importantly, all of these studies found that racial differences were not explained by any measures of socio-economic deprivation.

2.4.1 The persistence of health inequalities

The rise of modern capitalism, enabled by the industrial revolution, exacerbated the material gap between the rich and the poor. The concentration of this social divide in urban slums led to a whole array of health problems, including infectious epidemics and premature death. The fast trend gave birth to the first scientific inquiries into the scale and causation of what is today called health inequalities (Eyler, 1979). Edwin Chadwick's seminal *Report on Sanitary Condition of the Labouring Population of Great Britain*, published in 1842 was an early-Victorian synthesis of the existing medical knowledge about the effects of industrialization on the health of the working classes (Chadwick, 1843). Chadwick argued that the dire effects of England's urban environment on ill health were comparable to a war killing more people every year than any military conflict the country had ever fought (Chadwick, 1843).

The rise in living standards in the 20th Century and especially under welfare state reforms led to an improvement in health and life expectancy of whole populations and the working classes in particular (Krieger, 2011; Bartley, 2017). These improvements in Western countries translated into a gradual shift in the major causes of mortality and morbidity from acute infectious diseases to chronic non-communicable diseases, a process called "the epidemiologic transition" (Omran, 1971). The leading killers such as cholera, typhus or tuberculosis were replaced by chronic diseases, such as cardio-vascular diseases and cancers (Global Burden of Disease Study 2013 Collaborators, 2015). However, despite these pervasive changes, *the pattern of health inequalities* remained similar to that in the infectious era: people with lower status in society were more likely to be chronically ill and to die early than people above them in the social hierarchy (Cockerham, 2007). The simultaneous improvement in the general population health *and* the perseverance of class differences in health indicated to the existence of some hidden, structural forces at play. Link and Phelan (1995) postulated that this time-invariant association between socio-economic circumstances and health is a major reason why these circumstances should be understood as the "fundamental" cause of health inequalities.

2.4.2 Social determinants of health

Risky health behaviours which contribute to chronic diseases and multimorbidity, such as smoking, alcohol use, diet and physical inactivity, are not randomly distributed in the population. They cluster within individuals and within certain population groups (Poortinga, 2006; Sheiham, 2012). The risks are more prevalent among men, those who are economically inactive, people with low socio-economic status and low educational attainment (Bartley, 2017; Poortinga, 2006). The existence of this social pattern in risk behaviour shifted the focus from the level of individual risk factors to include more distant, "upstream" factors: *social determinants of health*. The social determinants of health refer to any extra-individual and non-medical factors influencing health, including health-related knowledge, attitude or behaviours (Bartley, 2017; Braveman, Egerter and Williams, 2011). The social determinants can take the form of various social, cultural, economic, and political conditions that influence the health of individuals and populations (De Maio, Mazzeo & Ritchie, 2013, Lucyk and McLaren, 2017). In contrast "downstream" factors are those located close to the health effects (both in space and time). They are influenced by the upstream social determinants (Braveman, Egerter and Williams, 2011; Short and Mollborn, 2015).

The theory of the social determinants of health originated in the 1980s from debates about the limitations of focusing on individual risk factors in the prevention of disease. Critics argued that to understand why the ill health and risk behaviours were distributed in a non-random way, the focus needed to shift to the population level (Rose, 2001). These observations gave rise to the inter-disciplinary programme of health inequality studies. The Black report was the first major synthesis of current knowledge in the United Kingdom (Black, 1980). Interpreting the nature of health inequalities as multi-causal, it put forward three possible explanations of the relationships between social inequality and health.

First, it acknowledged the inequalities in the *material living conditions* as the central causal axis (Black, 1980). The report was based on census data for the

period from 1921 to 1971, which had no questions on income. That is why the material conditions were defined in terms of social class, car ownership and housing. Five categories of occupational status from the Registrar General were used as indicator of social class. The report observed a clear class gradient for most causes of death and mortality. Other factors such as work accidents, overcrowding or smoking were seen as closely related to the key importance of social class (Black, 1980). Inequalities were also found in the utilization of health care services, where members of the working classes were attending the primary care much less than those of higher occupational categories.

The second explanation was *cultural/behavioural* (Black, 1980). People in lower status occupations and with lower education levels were hypothesized to belong to a particular culture that encourages behaviours such as alcohol consumption, smoking, physical inactivity and unhealthy diet. On the contrary, people in managerial and professional occupations with higher education tended to show more health-promoting behaviour (Black, 1980). A common interpretation of these differences was based on theories of individual choice, where change towards health seeking had to come from the change in individual values. The other alternative, supported by the authors of the report, was to see behaviour embedded within a social structure that is associated and reinforced by social class (Black, 1980).

Third, the theory of *social selection*, according to which people with poor health in childhood and adolescence were more likely to end up in lower social classes and worse health as adults (Black, 1980). Social class is allocated the status of a dependent variable and health has a higher degree of causal significance. For example, the Registrar General's class I might have the lowest premature death rate because it was composed of the healthiest people in the population, while the reverse was true for class V. The term selection refers to the fact that over their life time people with worse health drift towards the bottom rungs of the social structure while the healthiest are upwardly mobile (Black, 1980).

2.4.3 Socio-economic gradient of health

The Black Report and subsequent studies, such as the Whitehall studies of the British civil servants, introduced the idea of the *socio-economic gradient* of health. It refers to the observed fact that health inequality increases in a gradual way with each step down the social hierarchy, regardless of the measure being occupational status or income (Bartley, 2017).

The first Whitehall Study in 1967 explored differences in mortality among 17,530 male employees of the highly stratified British Civil Service (Department of Medical Statistics and Epidemiology, 2008). The study demonstrated that the higher grade a person had in the hierarchy, the longer he might expect to live compared to people in lower positions. These disparities were independent of the possible risk factors, such as smoking. The observation of the gradient was even more interesting given the fact that the Civil Service did not employ the poorest and the richest members of society (Department of Medical Statistics and Epidemiology, 2008).

Twenty years later, the Whitehall II study shifted the focus from mortality to disparities in morbidity among 10,308 civil servants aged between 35 and 55 years (Marmot and Brunner, 2005). Two thirds were men and one third were women. Since the first wave in 1985-88, data had been collected every two to five years. The study revealed a similar socio-economic gradient for morbidity to the one identified earlier for mortality. The social gradient was observed for a range of different diseases: cancers, heart disease, lung disease, gastrointestinal disease, depression, suicide, back pain and general feelings of ill health (Marmot and Brunner, 2005). In addition to the material and behavioural factors observed by the Black Report (Black, 1980), the Whitehall II study postulated the existence of *psychosocial factors* influencing health inequality (Marmot and Brunner, 2005). For example, psychosocial working conditions such as job strain or job control influenced the risk of the coronary heart disease for men and lack of control at home for women (Chandola et al., 2004).

The social gradient in health has been repeatedly observed in other studies and in other countries (Cockerham, 2007; Krieger, 2011; Bartley, 2017). Longitudinal analyses demonstrated that the gradient remains persistent over time (Marmot and Brunner, 2005). The notion of the health gradient has gradually replaced an older notion of a clear health divide or health gap between the poorest and the richest (Bartley, 2017). The explanation of the existence of the gradient became the subject of debate among researchers (Krieger, 2011). What really puzzled them was the question why the disparities in health and mortality do reflect the stratification in social class in such a subtle way. Why does having a little more make a person a little healthier? (Bartley, 2017) To answer questions like these, a series of explanatory mechanisms were proposed, linking social conditions in early life with health outcomes in old age.

2.5 Life course models of health

The life course approach to chronic disease has been formalized and developed since the 1990s (Ben-Shlomo and Kuh, 2002). Life course epidemiology was defined as "*the study of long-term biological, behavioural and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations*" (Ben-Shlomo and Kuh, 2002, p. 285). It arose out of polemics among epidemiologists about the causation of chronic diseases. The 'biological programming' hypothesis claimed that the foetal developments and early infancy determined the future adult health outcomes (Barker, 1998). Others focused on adult factors, such as lifestyles (alcohol consumption, smoking, diet), physiological and psychosocial measurements (blood pressure, stress, psychological dispositions) or adult socio-economic status (income, occupation, etc.) Life course epidemiology attempted to provide a synthesis, built around the idea that chronic disease over individual life is shaped by biological, psychological and socio-economic factors. These factors act

simultaneously, *cumulatively* and *interactively* (Davey Smith and Lynch, 2004) and during the entire life span. Incorporating the conditions of antenatal and infant development with previous emphases on solely adult risk factors, the life course models helped to improve our causal explanation of diabetes, cardiovascular and respiratory diseases (Stone, Netuveli and Blane, 2014).

Crucially for understanding multimorbidity, life course epidemiology emphasizes that the role of *time* and *timing* is essential for explaining the links between societal structures, human agency and individual health consequences (Stone, Netuveli and Blane, 2014). The notion of the time lag between exposure and diagnosis or manifestation of a chronic disease is embedded in the etymology of the word *chronic* which refers to the Greek word *chronos*, 'time'. Life course models explicitly require temporal ordering of exposures and their mutual relationships (Kuh et al., 2003, Stone et al., 2014). A sequence of linked exposures is called a *pathway* or chain of risk. It raises disease risk if one harmful exposure to lead to another. The two original life course models are critical period and accumulation of risk models.

The *critical period model* (in the past called biological programming) refers to an exposure during a specific period which has lasting or long-term effects on the development of the individual (Ben-Shlomo and Kuh, 2002). For example, foetal growth retardation may lead to chronic problems in adult life, such as cardiovascular disease or diabetes (Haas and Oi, 2008). The *accumulation of risk model* postulates that factors increasing disease risk or protection from disease do accumulate over the life span (Ben-Shlomo and Kuh, 2002). For instance, a child from poor family is more likely to fail at school, leave school at an early age, take up unskilled work that is hazardous and badly paid and, when retired, spend the rest of their life in financial insecurity. This model is sometimes called the 'chain of risks model' as it suggests that early life advantage or disadvantage can set individuals on diverging paths (upward or downward), simply because one exposure leads to another. This has also been expressed in terms of a *probabilistic cascade*, referring to risks building up over time (Krieger, 2011).

Some authors took the pathway aspect from this model and formalized it into a distinct, *pathway model* (Niedzwiedz et al., 2012).

A typical challenge for life course methodology is the long period of time between an early-life exposure and a health outcome. The period increases the likelihood that any association may be due to confounding by a third factor (Stone, Netuveli and Blane, 2014). For example, an analysis establishing that smoking mediates the association between childhood adversity and adult anxiety and depression needs to take into account potential confounding effects of low education, alcohol consumption or social isolation (Sheikh, 2017). Controlling for potential confounding factors is key in order to conclude that smoking "alone" is the pathway between childhood adversity and anxiety/depression in adulthood (Sheikh, 2017). The estimated strength of the association between exposure and outcome may be biased or entirely missed if a wrong time period is chosen for analysis (Stone, Netuveli and Blane, 2014).

Among the social pathways (mediating mechanisms) linking lower social class position to ill health are economic deprivation, lack of educational opportunities and exposures resulting from neighbourhood environmental characteristics such as violence, pollution, lack of green spaces, etc. (Krieger et al., 2011). Social class position is strongly associated with access (or lack of) to social and public resources, health care, social networks, institutional resources, and inter-generational resources (Krieger, 2011; Bartley, 2017). Another pathway involves differences in the nature of the social and work environments, and includes the differences in stress levels from adverse labour market experiences, including unemployment, underemployment, and exposure to stressful work (Kawachi and Berkman, 2001). These specific pathways linking social class to health may change over time. New causal paths might emerge, others might be removed, yet as long as the society continues to have a social class structure, these health disparities will be perpetuated (Link and Phelan, 1995; Bartley, 2017; Krieger, 2011).

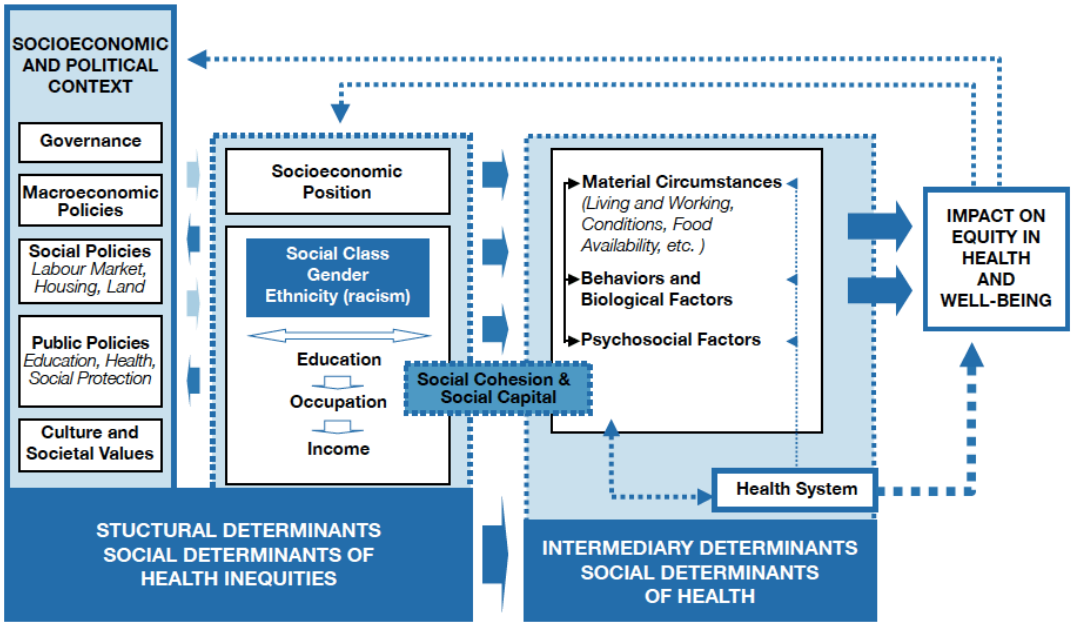

Figure 2. 1 Solar and Unwin's framework (2010) adopted by the Commission on Social Determinants of Health of the World Health Organisation. In this model the intermediary determinants represent the same processes as that this thesis defines as pathways. Source:

2.5.1 Life course approach to multimorbidity and functional limitation

Whilst there is a wealth of longitudinal and life course studies of various health outcomes, research on multimorbidity lags behind. Health professionals are sometimes interested in predicting development of multimorbidity, especially for conditions that constitute the highest treatment burden and contribute to future health care costs (Marengoni et al., 2011). Specific diseases have different mean age of onset and order of appearance and some are associated with an increased risk of developing other morbidities (Ruel et al., 2014). For instance, a study found that having type 2 diabetes as the first disease was strongly related to subsequent rise in the number of diseases as well as to the rise in prevalence from 32% to 80% in the period of 16 years (Pouplier et al., 2018).

People develop multimorbidity at different rates. Findings from ten General Practices in England documented five different trajectories: people with no recorded chronic diseases (40%), those who developed their first chronic morbidity over 3 years (10%), a developing multimorbidity group (37%), a group with increasing number of morbidities (12%), and 1% were a multi-chronic

group with many chronic morbidities (Strauss et al., 2014). A population-based study of middle-aged women in Australia identified five distinct trajectories over a nine-year period, two of which were cumulative. Rates of growth were related to individual and social factors. Being overweight or obese, having low education and low income were key risk factors for belonging to a trajectory where conditions accumulated over time. Smoking, alcohol consumption and physical inactivity were other risk factors for the development of some trajectories (Jackson et al., 2015). Trajectories of accumulation of multimorbidity conditional on race were modelled in the United States and found racial differences both in the time of onset and in the rate of developing multimorbidity (Sauver et al. 2015; Quiñones et al., 2019).

The aforementioned studies explored multimorbidity over a limited period of time in adulthood and old age. This literature review identified only two studies that examined the influence of childhood circumstances on multimorbidity and functional limitation in adult or old age. Pavela and Latham (2015) used the Health and Retirement Study in the U.S. After controlling for adult SES and adult health behaviours (obesity, smoking, visiting a doctor visit in the past 2 years, having health insurance), the study found no effect of childhood SES but the effect of childhood health did persist. They characterized the model as the accumulation of risk where the socio-economic circumstances from early life followed a pathway model while the childhood health effects reflected a critical period model. Haas and Oi (2018) analysed variation in multimorbidity and functional limitations across 13 European countries. They found that the relationship between childhood illness with multimorbidity and functional limitations in later life persisted in the presence of adult socioeconomic circumstances and health behaviours. The effects of childhood social class were attenuated by socio-economic circumstances in adulthood.

2.6 Research gaps

This literature review has discussed the fundamental issues and problems of how multimorbidity and functional limitation are defined and measured. The chapter presented evidence of growing prevalence in multimorbidity and functional limitation and raised the question whether the trend can be explained solely by the ageing of populations. The review suggested that population studies of multimorbidity and functional limitation could benefit from the knowledge of health inequalities, social determinants and life course models of health, accumulated by researchers in other fields of inquiry. A series of research gaps gradually emerged from the literature review.

2.6.1 Taking into account the biology of ageing

The first limitation in the current understanding of multimorbidity of the elderly is the lack of consideration of the effects of the biological process of ageing. The process is characteristic by a simultaneous breakdown in several distinct body systems (Fabbri et al., 2015; Cesari et al., 2017). The number of affected body systems of old people can predict hospital stays and hospital admissions (Condelius et al., 2008). Outside the research in primary care based on health records (the CIRS system), there is currently a lack of studies measuring multimorbidity in the elderly by counting the body systems rather than single diseases.

The thesis responds to this problem by measuring multimorbidity differently from counting single diseases. Compared to basic multimorbidity, complex multimorbidity, as a more discriminating definition, should lead to selecting population with discordant chronic conditions (Piette and Kerr, 2006) and with higher health care need (Harrison et al., 2014; Cesari et al., 2017). Biology of ageing also leads to an increase in functional limitations arising from distinct body systems (Jindai et al., 2016; Calderón-Larrañaga et al., 2019). The thesis proposes the measure of having ten or more functional limitations to reflect this process of breakdown at old age.

2.6.2 Inequalities in the onset of multimorbidity and functional limitation

This literature review has presented growing evidence of socio-economic inequalities in multimorbidity, both in terms of prevalence and in terms of its onset in life (Barnett et al., 2012; Violan et al., 2014). Life in social deprivation also leads to higher complexity of multimorbidity. A study found that discordant multimorbidity – affecting several body systems that is harder to treat (Piette and Kerr, 2006) - was more prevalent in the deprived areas of Scotland than in the affluent ones. Discordant multimorbidity is more prevalent among younger people than older people (McLean et al., 2014). The clustering of social deprivation, young age and discordant multimorbidity was also observed in England (Cassel et al., 2018). The prevalence of this cluster is increasing in the whole of the United Kingdom and the growth is faster rate in the poorer areas (Reilly et al., 2015).

The body of research on inequality in multimorbidity is limited in three ways. The data originates from the primary care sources and estimates for the general population are missing. Secondly, multimorbidity has only been measured using the count of single diseases. Given the complex nature of the nexus between deprivation, young age and discordancy of multimorbidity, an alternative measure, taking into account the discordancy of multimorbidity (McLean et al., 2014), could uncover a more accurate distribution of multimorbidity across the socio-economic gradient. Thirdly, social deprivation was only measured by the Carstairs index and by the Index of Multiple Deprivation. Using area-based indices may lead to classifying some individuals as deprived when they are not and vice versa (Fischbacher, 2014).

2.6.3 The role of the social determinants

The integrative framework of the material, psychosocial and behavioural determinants and the related Solar and Unwin's framework (Figure 1) are the theoretical drivers of this literature review. They help to illuminate the gaps in the body of research. Current studies pay insufficient attention to the

contextual factors of multimorbidity (Bayliss et al., 2014). Researchers use socio-demographic, socio-economic, psychological or behavioural characteristics in isolation from each other (Northwood et al., 2017; Pathirana and Jackson, 2018). A review of 22 articles found that the most frequently studied determinants were the health care system (13 articles) and health behaviours (8). Psychosocial factors (6) and material circumstances (1) were examined less often (Northwood et al., 2017). Studies which include social determinants within the context of multimorbidity do so without any theoretical framework that would explain the choice of the contextual factors and their relevance (Bayliss et al., 2014; Northwood et al., 2017; Pathirana and Jackson, 2018).

Building on the Black Report (Black, 1980) and Whitehall II study (Marmot and Brunner, 2005), the three most influential explanations of health inequality, the material, psychosocial and behavioural, were integrated into a unified framework (Moor, Spallek and Richter, 2017). These hypotheses are no more conceived as mutually exclusive but rather complimentary and their effects assessed in one model (Van Oort, van Lenthe and Mackenbach, 2005; Robertson et al., 2015). A systematic review found eleven studies which jointly examined the contributions of material, psycho-social and behavioural pathways to inequalities in self-reported health (Moor, Spallek and Richter, 2017). While results varied between studies, material pathways had the largest effect (11% to 76% of explained variance), followed by the psycho-social (4% to 49%) and the behavioural factors (7% to 45%). These studies were cross-sectional, so the influence of reverse causation could not be excluded.

This thesis builds on the theoretical legacy of the Black Report (Black, 1980) and the Whitehall Study II (Marmot and Brunner, 2005) and it applies the integrated framework of the material, psychosocial and behavioural determinants to the area of multimorbidity and functional limitation.

2.6.4 Taking a life course approach

Some quantitative researchers characterized multimorbidity as a multi-causal phenomenon (Schäfer et al., 2012; Jackson et al. 2015). Multi-causality refers to the fact that chronic disease is caused by more than one causal mechanism, and every causal mechanism involves the joint action of several component causes (Krieger, 2011). Another major characteristic of multimorbidity is the time lag between exposure and diagnosis or manifestation of a chronic disease. It is a gradual accumulation of mundane experiences, wearing down the body systems rather than rare exceptional events that is characteristic of the period leading to onset of multimorbidity (Hertzman and Boyce 2010). Whilst it is commonly accepted that it often takes the whole lifetime for multimorbidity to accumulate, life course investigations are only beginning (Northwood et al., 2017; Pathirana and Jackson, 2018).

This review presented a few studies which examined trajectories of change in multimorbidity across a period of time (Quiňones et al. 2011, 2019; Strauss et al., 2014; Jackson et al., 2015; Sauver et al., 2015). Considering the multi-causal and temporal character of multimorbidity, these studies are unable to explore life course pathways to multimorbidity due to their limited choice of social determinants and the narrow window of time.

This literature review found only one study that formally tested pathways from childhood to old age in a mediation model of multimorbidity (Ferraro, Schafer and Wilkinson, 2016). Using data from the National Survey of Midlife Development in the U.S., childhood was conceptualized into three domains: SES (measured with 3 items), family composition (3 items) and abuse (measured as a scale). The hypothesized adult pathways were divided into three domains: socio-economic status (SES) (an index composed of years of education, household income and financial strain), lifestyle risk (based on obesity, smoking, drinking) and psychological resources (items for family and friend support, family and friend strain, a scale of social integration and the level of personal control). The study demonstrated that the childhood social class and parental abuse were associated with fewer adult social resources and more

lifestyle risks. These pathways, especially smoking and obesity, in turn affected the risk of adult multimorbidity. The study operationalized the multi-causality of multimorbidity and the time period from childhood to adulthood. Reconsidering multimorbidity as a multi-causal process with a long period of accumulation that interacts with external, social developments in individual lives can also inform the choice of timing of preventative interventions, making them more focused and efficient (Stone, Netuveli and Blane, 2014, Green and Popham 2017). This approach will be followed later in this thesis.

2.7 Summary

This chapter reviewed the literature on multimorbidity and functional limitation, starting from the early predominantly medical perspectives and progressing to integrate the knowledge about biological mechanisms with social theories of health. The literature review identified several gaps in the current state of knowledge that this thesis sought to address. The first limitation is methodological. Studies based on general populations with self-reported information on health tend to define multimorbidity as two or more diseases. This measure does not capture the multimorbidity of disparate body systems, which is an important marker of ageing (Fabbri et al., 2015). Second, little is known about socio-economic inequalities in the prevalence of multimorbidity and functional limitation in general populations and their effect on ageing. A few studies that highlighted health inequalities and earlier onset of multimorbidity in deprived areas used primary care records (Barnett et al., 2012; McLean et al., 2014). Third, while ageing on its own cannot explain the rising trends in multimorbidity, the theory of social determinants of health has not become part of multimorbidity research yet. Contextual characteristics are rather being chosen due to data availability and in isolation from each other (Northwood et al., 2017, Pathirana and Jackson, 2018). Fourth, the role of childhood and pathway mechanisms on multimorbidity at old age remains

unknown. Elucidating the preceding factors would benefit attempts to prevent and reduce the burden of multimorbidity in society.

2.8 References

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Chapter 3

Trends in multimorbidity and functional limitation in the ageing population of England

Abstract

This study aimed to estimate the prevalence of three measures of multimorbidity among people aged 50 years or older in England. Beside the basic measure of two or more diseases within a person, we added a measure of three or more affected body systems (complex multimorbidity) and a measure of ten or more functional limitations. We found that the three health outcomes became more prevalent between 2002 and 2015. They were more common among females than males and were becoming more common among younger age groups. While in 2002 the prevalence of basic multimorbidity exceeded 50% for the 70-74 age group upwards, in 2015 it crossed the same threshold in the 65-69 age group. The distribution of multimorbidity and multiple functional limitations were stratified by the amount of household wealth. Multiple functional limitations reflected the largest differences between the most and the least affluent groups (5.9-fold in 2014/15), followed by the measure of complex multimorbidity (2.8-fold in 2014/15) and basic multimorbidity (1.9-fold) in 2014/15. While age acted as a levelling factor for the wealth differences in basic multimorbidity, it had no such effect on the two other outcomes. Our study observed social polarization among the multimorbid ageing population in England with complex multimorbidity and multiple functional limitations increasing faster and reflecting stronger inequality than basic multimorbidity.

3.1 Introduction

Multimorbidity, when defined as the co-occurrence of two or more diseases within a person, is rising globally (Van den Akker et al., 1998; Garin et al., 2015; The Academy of Medical Sciences, 2018). The prevalence of multimorbidity among people aged 65 years or older in England is projected to rise from 54% in 2015 to 67.8% in 2035 (Kingston et al., 2018). People will live longer but in worse health. The extra years lived with multimorbidity will lead to higher utilisation of primary and secondary healthcare (Marengoni et al., 2011; Kingston et al., 2018). However, the definition of multimorbidity as two or more diseases has been criticized for leading to prevalence estimates in the elderly population which are too high (55% to 98% between studies) to be able to predict patients with higher need (Fortin et al., 2012; Harrison et al., 2014). Practitioners need a measure of multimorbidity that can reflect the biology of ageing and identify elderly populations with higher healthcare needs.

Harrison et al. (2014, p. 8) introduced the concept of *complex multimorbidity,* defined as "the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without an index chronic condition". Compared to the basic definition of two or more conditions, the construct of complex multimorbidity leads to lower prevalence estimates and it has been proposed that it might better identify patients with higher needs (Fortin et al., 2012; Harrison et al., 2014). We argue that complex multimorbidity might also be better at reflecting the biology of ageing since it characterizes a simultaneous breakdown or dysfunction of several distinct pathologies or body systems (Fabbri et al., 2015; Cesari et al., 2017). The affected body systems of people aged 65 or older were found to be predictors of the total number of hospital stays and of the number of hospital admissions (Condelius et al., 2008).

The process of ageing manifests itself not just in the number of morbidities an individual has, but also in physical functioning. A measure of multiple functional limitations was included as our third health outcome. Its purpose is

to identify the impact of multimorbidity on the combined functioning of ageing people. Some conditions (e.g. high blood pressure) may have no effect on physical functioning but others do, such as arthritis. Multimorbidity predicts a decline in physical functioning among ageing people (Ryan et al., 2015; Jindai et al., 2016), which has implications for quality of life, need for health care and residential care, and premature mortality (Sibritt et al., 2007; Ryan et al., 2015; Jindai et al., 2016). Measuring functional limitation also responds to the fact that the proportion of old people with impairments and limitations in several body systems increases with age (Jindai et al., 2015; Burden of Disease Network Project, 2004).

Socio-economic status (SES) is a major determinant of health inequalities. Studies which explored the association between multimorbidity and SES focused on area deprivation (Barnett et al., 2012; McLean, 2014; Morrissey, Espuny and Williamson, 2015), income (Agborsangaya et al., 2012), occupational status (Van den Akker et al., 2000) and education (Agborsangaya et al., 2012; Schiøtz et al., 2017). Regardless of the type of measure, multimorbidity is more common among people with lower SES, even when controlling for age and sex. However, all of these studies focus on the simple definition of multimorbidity that may hide the nuances of relationships and the true underlying scale of inequalities.

Our study is the first population-level analysis that differentiates the prevalence of multimorbidity by complexity and degree of functional limitation as well as their variation by key modifying factors. The study has two aims: (1) to compare temporal trends in the prevalence of basic multimorbidity, complex multimorbidity and multiple functional limitations in an ageing population in England; and (2) to examine the variation in their prevalence by age, sex and socio-economic status.

3.2 Methods

3.2.1 Data and study population

We used data from the English Longitudinal Study of Ageing (ELSA) which is a panel study with a range of social, economic, psychological, cognitive and health data. It is based on a representative sample of people living in England aged 50 plus years. It commenced in 2002 and is followed up every two years. The data used in this analysis was collected via personal interviews and the study response rate at wave 7 was 61% (Clemens et al., 2017). The baseline sample consisted of 12,099 members. This analysis uses data from the core sample members who were recruited at either the first wave or at any of the refreshment samples at waves 3, 4, 6 and 7 (Steptoe et al., 2013). The number of core members in each wave varied: 12,099 in wave 1; 8,780 in wave 2; 8,811 in wave 3; 9,896 in wave 4; 9,090 in wave 5; 9,169 in wave 6 and 8,253 in wave 7.

We conducted a repeated cross-sectional analysis, treating each wave separately. Respecting the multi-stage sampling process, the data in each wave were declared a complex survey data using Stata *svyset* command. This allowed to adjust each wave for the effects of clustering (household level), strata (the geographic region) and changing age structure (cross-sectional weights) by using specific variables provided by ELSA. The weights include a scaling factor in order to make sure that the original sample and refreshment samples are equally proportional with respect to age in the general population (Banks et al., 2017).

3.2.2 Measures of health

ELSA records data on a range of physical and mental health conditions. Twenty five of these variables were consistently recorded at each wave and are used to measure multiple health conditions in this study (Table 3.1). This includes the most common conditions among the elderly (diabetes, hypertension, stroke, cancer and depression), as found by a systematic literature review (Sinnige et al., 2013).

Participants were asked whether they still had the condition diagnosed by a doctor that they had reported previously and if not whether they could report a new condition. We have grouped health data into three categories: individual morbidities, groups representing body systems and functional limitations (Table 3.1). Adapting Verbrugge and Jette's Disablement Process Framework (1994), instances of impairment (dysfunction and abnormalities in body systems) and disability (difficulty with daily activities) were included within the category of 'functional limitations' (restrictions in basic physical and mental actions).

Table 3. 1 Health data used to measure basic multimorbidity, complex multimorbidity and multiple functional limitations

	Morbidities	Body systems		Functional limitations
1	High blood pressure	1. **Eye disorders**		**General mobility**
2	Angina	1.1. Glaucoma	1	Walking 100 yards
3	Congested heart failure	1.2. Macular degeneration	2	Sitting for 2 hrs
4	Heart murmur	1.4. Cataracts	3	Getting up from chair
5	Abnormal heart rhythm	2. **Circulatory disorders**	4	Climbing several flights of stairs
6	Heart attack	2.1. High blood pressure	5	Climbing one flight of stairs
7	Diabetes	2.2. Angina	6	Stooping, kneeling or crouching
8	Stroke	2.3. Heart attack	7	Reaching arms above shoulders
9	Lung disease	2.4. Congestive heart failure	8	Pulling or pushing a chair
10	Asthma	2.5. Heart murmur	9	Lifting/carrying weights over 10 pounds
11	Arthritis	2.6. Abnormal heart rhythm	10	Picking up a 5p coin
12	Osteoporosis	2.7. Stroke		**Activities of daily living**
13	Cancer	3. **Endocrine, nutritional and metabolic**	11	Dressing, including putting on shoes and socks
14	Parkinson's disease	3.1 Diabetic eye disease	12	Walking across a room
15	Dementia	3.2. Diabetes	13	Bathing or showering
16	Alzheimer's disease	4. **Musculoskeletal and connective system**	14	Eating, such as cutting up your food
17	Hallucinations	4.1. Osteoporosis	15	Getting in or out of bed
18	Anxiety	4.2. Arthritis	16	Using the toilet, including getting up or down
19	Depression	5. **Respiratory**	17	Using a map to figure out how to get around
20	Emotional problems	5.1. Lung disease	18	Preparing a hot meal
21	Mood swings	5.2. Asthma	19	Shopping for groceries
22	Glaucoma	6. **Neoplasms**	20	Making telephone calls
23	Diabetic eye disease	6.1. Cancers	21	Taking medications
24	Macular degeneration	7. **Nervous disorders**	22	Doing work around the house or garden

25	Cataracts	7.1. Parkinson's disease	23	Managing money (paying bills, track of expenses)
		7.2. Alzheimer's disease		**Symptoms**
		7.3. Hallucinations	24	Difficulty walking 0.25 mile
		8. **Mental and behavioural**	25	Pain in general
		8.1. Anxiety	26	Problems with eyesight
		8.2. Depression	27	Problems with hearing
		8.3. Emotional problems	28	Balance on level surface
		8.4. Mood swings	29	Dizzy walking on level surface

Measure 1: Basic multimorbidity

We created a binary variable which identified people at each wave who had two or more morbidities as listed in Table 1. The list includes a few symptoms such as hallucinations which do not represent a condition but can be used as a proxy for schizophrenia or another condition, for example alcohol dependency (Chaudhury, 2010). In a similar way, emotional problems and mood swings are used as indicators of either mild anxiety and depression or possibly manic depressive tendencies (Valiengo et al., 2016) but the clinician has chosen to not use the more formal diagnostic label, for whatever reason. The information on whether an individual has or has not got a chronic disease was composed of the data fed forward from the previous wave of observation and from the information on the newly reported cases of disease.

Measure 2: Complex multimorbidity

Following the definition of complex multimorbidity by Harrison et al., (2014), we identified individuals with three or more body systems affected by disease as having complex multimorbidity. Body systems were defined and represented by the chapters of the International Classification of Diseases 10th Revision (ICD-10) system (Table 3.1).

Measure 3: Multiple functional limitations

The third health outcome was based on the combination of general mobility variables, Activities of Daily Living (ADL) variables, and data on symptoms of

chronic conditions (Table 3.1). ADL is used to measure functional capacity and it concerns the abilities necessary for basic functioning, as well as functions necessary for living in a community (Chatterji et al., 2015). Most studies have explored prevalence and effects of either single impairments and functional limitations or their combinations in ADL or IADL (Jindai et al., 2016), but we decided to examine their combined burden by summing all of them up including the symptoms. Difficulties with walking were captured with three distinct variables (having difficulty walking 0.25 mile, walking 100 yards and walking across a room) which, if combined, reflect the degree of severity. For example, a person who has got all three difficulties is more functionally limited than a person with only one of them. The total number of functional limitations per individual was summed up. Based on the exhaustive list of 29 limitations, the frequencies of multiple functional limitations were high, reflecting the older age of participants. In order to identify the participants with the highest level of disability we decided to set a cut-off point of ten or more functional limitations within the same person.

3.2.3 Covariates

Age

Age was categorized into 5-year bands, from 50-54 up to 80-84 years of age. The age of persons aged 85 and older was collapsed in one category 85+ due to small sample size.

Sex

Sex is an important determinant of health. Previous studies have shown that while women in most countries have a longer life expectancy than men, they are more likely to be affected by a number of chronic diseases (Marengoni et al., 2011; Abad-Diez et al., 2015; Agur et al., 2016).

Socio-economic status (SES)

SES was measured using quintiles of net total household wealth. Household wealth embodies access to financial resources accumulated during life and therefore reflects social status at later life (Demakakos et al., 2015; Nazroo, 2017). The net household wealth is defined as the sum of savings, investments, physical wealth and housing wealth after financial debt and mortgage debt has been subtracted). It is based on 22 distinct components of wealth and debt (Banks et al., 2017). The wealth intervals in £s between 2002-15 are presented in Appendix B (Table B.4). While the median value of households increased in 2002-15 from £100,000 to £190,000, most change was due to the outlier values in the poorest and the richest quintiles.

3.3 Statistical analysis

Descriptive analyses of the study population included summary statistics to explore general patterns. Data were weighted for non-response, stratification and clustering effects. The variation in the size of the age groups decreased over time for age groups of older people, but the pattern nevertheless justified the need for age standardization between waves (Appendix A). The prevalence was standardized to the age distribution of the population at wave 1 in 2002, to allow for more robust comparison of trends over time. Standardization also helps our results to remain representative of national patterns improving their generalisability.

We have conducted repeated cross-sectional analyses of prevalence at a population level. Prevalence estimates were stratified by age group, sex and wealth quintiles, in order to observe the distribution of outcomes by selected covariates. We then checked for consistency and interaction effects of time*SES and age*SES by merging the waves of measurement into a panel dataset. This allowed us to compare the estimates from cross-sectional analyses with two multilevel logistic regression models, taking into account temporal correlation

within individuals. The results were plotted graphically using marginal effects at representative values. All analyses were conducted in Stata version 13.

3.4 Results

3.4.1 General characteristics of the study population

The general characteristics of the studied population are shown in Table 3.2. The number of participants varied between 11,391 (2002/03) and 8,249 (2014/15). The median age in 2002/03 was 64 (IQR 56-73) and it increased to 67 years in 2014/15 (IQR 61-75). The proportion of the oldest old people, aged 85 or more, was between 5.2% in 2002/03 and 5.7% in 2014/15. The proportion of women was higher than the proportion of men (53.1%) on average during the period 2002-15.

Table 3. 2 Overview of the study population by age, sex and year

	2002/03	2004/05	2006/07	2008/09	2010/11	2012/13	2014/15
Age (years)	n (%, weighted)	n (%, weighted)	n (%, weighted)	n (%, weighted)	n (%, weighted)	n (%, weighted)	n (%, weighted)
50-54	1,981 (19.4)	744 (9.6)	1,388 (14.3)	1,043 (13.3)	215 (3.1)	635 (17.7)	564 (19.5)
55-59	2,185 (17.9)	1,853 (21.4)	1,658 (21)	1,861 (22.7)	1,753 (23.7)	1,427 (17.8)	917 (16.7)
60-64	1,688 (14.8)	1,477 (16.1)	1,421 (16.7)	2,013 (17.7)	1,976 (20.3)	1,725 (16.7)	1,499 (16.7)
65-69	1,710 (13.6)	1,397 (15)	1,176 (13.7)	1,497 (13.3)	1,534 (15.6)	1,726 (15.2)	1,652 (15.3)
70-74	1,471 (12.3)	1,211 (12.7)	1,130 (11.7)	1,455 (11.5)	1,389 (13)	1,274 (11.1)	1,281 (15.6)
75-79	1,094 (10.2)	977 (11.2)	908 (9.8)	904 (9.4)	1,025 (10.4)	1,170 (9.1)	1,134 (11.4)
80-84	806 (6.8)	698 (8.2)	623 (7.2)	609 (6.4)	646 (7.1)	642 (6.7)	657 (9.2)
85-100	456 (5.2)	423 (5.7)	506 (5.75)	513 (5.7)	552 (6.2)	570 (5.5)	545 (5.7)
Total	11,391	8,780	8,811	9,896	9,090	9,169	8,249
Male % (95% CI)	46.3 (45.7-47)	46.1 (45.4-46.8)	46.8 (46.1-47.6)	47 (46.2-47.8)	46.9 (46.1-47.7)	47.4 (46.5-48.4)	47.6 (46.4-48.7)
Female % (95% CI)	53.7 (53-54.3)	53.9 (53.2-54.6)	53.2 (52.4-53.9)	53 (52.2-53.7)	53.1 (52.3-53.9)	52.6 (51.6-53.5)	52.4 (51.3-53.6)
Age (median, IQR)	64 (56-73)	66 (58-74)	64 (57-74)	65 (58-73)	66 (60-74)	66 (60-75)	67 (61-75)

3.4.2 Trends in the prevalence of our measures of multimorbidity

Figure 3.1 summarizes trends in the prevalence of basic multimorbidity, complex multimorbidity and 10+ multiple functional limitations. The prevalence of basic multimorbidity grew from 41.6 percent in 2002/03 to 46.6

percent in 2014/15. The prevalence of complex multimorbidity grew from 12.2 percent in 2002/03 to 21.1 percent in 2014/15. This is a larger change relative to the baseline estimate than the growth of basic multimorbidity. The prevalence of 10+ multiple functional limitations rose from 9.6 percent in 2002/03 to 14.3 percent in 2014/15 which is larger than the growth of basic multimorbidity. Given our knowledge of the nature of functional limitation as a consequence of multimorbidity (Ryan et al., 2015, Jindai, 2016), we would expect a larger relative change in this outcome than in either of the multimorbidities. Hence we examined developments for each component subgroup (General mobility, ADLs and symptoms) separately and found a similar flat trend for each of them (Appendix D, Figure D.1).

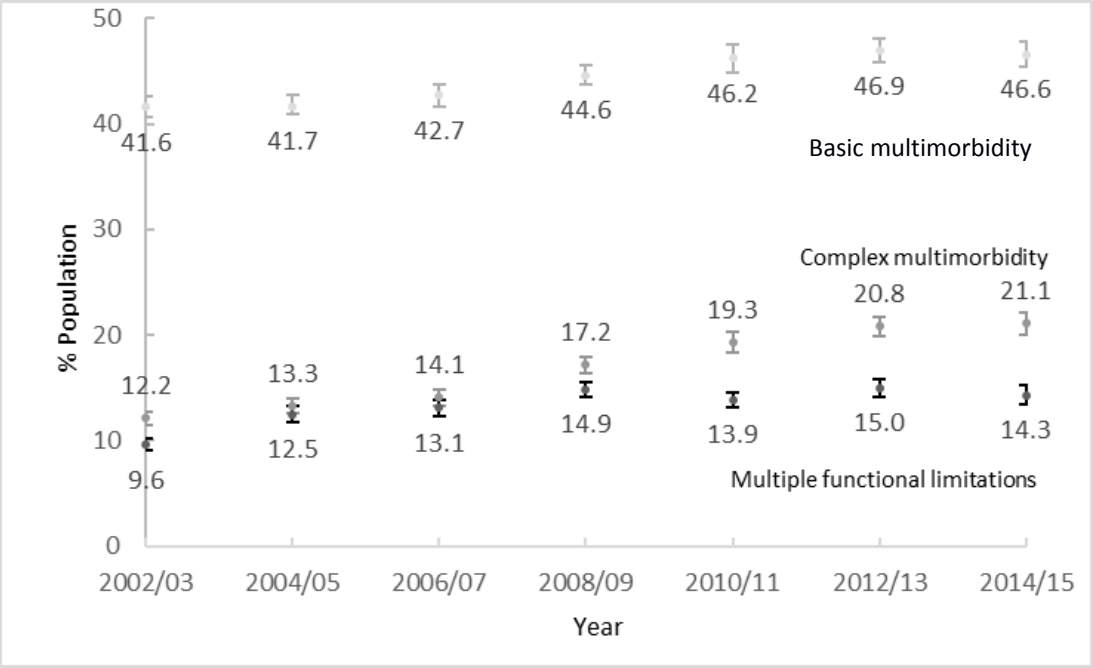

Figure 3. 1 Age-standardized prevalence of basic multimorbidity, complex multimorbidity and 10+ multiple functional limitations for England, 2002-15 (95% CIs).

Figure 3.2 shows the distribution of the three health outcomes by sex over time. The comparison between sexes shows that regardless of the measure of multimorbidity or specific time point, on average a higher proportion of women have multimorbidity than men. The difference in the change of prevalence

between sexes over time was only marginal with the only exception being in complex multimorbidity. The prevalence for males more than doubled at the end of the followed period while the prevalence of complex multimorbidity for females grew only 1.6 times.

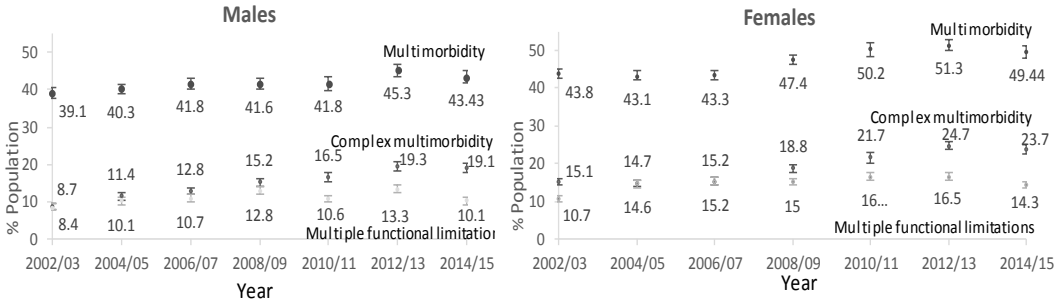

Figure 3. 2 Age-standardized prevalence of basic multimorbidity, complex multimorbidity and multiple functional limitations by sex for England, 2002-15 (95% CIs).

3.4.3 Prevalence of the three measures of multimorbidity by age group

We further explored how the prevalence varied within age bands for each measure. The prevalence of both types of multimorbidity and of 10+ multiple functional limitations at each time point increased with age (Appendix B, Tables B.1-B.3). The difference in prevalence of multimorbidity between the youngest (aged 50 to 54) and the oldest group (aged 85+) ranged between threefold in wave 2012/13 and fourfold in wave 2004/05 (Table B.1). The majority of participants were multimorbid when and after reaching the 70-75 age group. From 2012/13, this threshold shifted to the 65-69 age band.

The difference in the prevalence of complex multimorbidity between the youngest and the oldest group ranged between 4.6 times in 2010/11 and 8.8 times in wave 2004/05 (Table B.2). The variation in prevalence levels by age is larger in the complex than basic multimorbidity. The difference in the prevalence of 10+ functional limitations between the youngest and the oldest group ranged between 3.9 times in wave 2010/11 and 7.2 times in 2014/15 (Table B.3).

Prevalence of both complex multimorbidity and 10+ multiple functional limitations remained under 50% within each age group.

3.4.4 Stratification of prevalence by socio-economic status

Regardless of the outcome, clear differences between the socio-economic groups were observed (Figure 3.3). Prevalence of basic multimorbidity, complex multimorbidity and 10+ multiple functional limitations was graded by each wealth quintile with people in the poorest quintile having the highest prevalence and people in the wealthiest quintile having the lowest. The measure of 10+ functional limitations captured the largest relative differences between the most and the least affluent groups (5.9-fold in 2014/15), followed by the measure of complex multimorbidity (2.8-fold in 2014/15). The relative difference was the smallest for basic multimorbidity (1.9-fold) in 2014/15. The interaction between time and household wealth was tested in a logistic marginal effects model and the results agreed with the stratified distribution of the prevalence (Appendix C, Figure C.1)

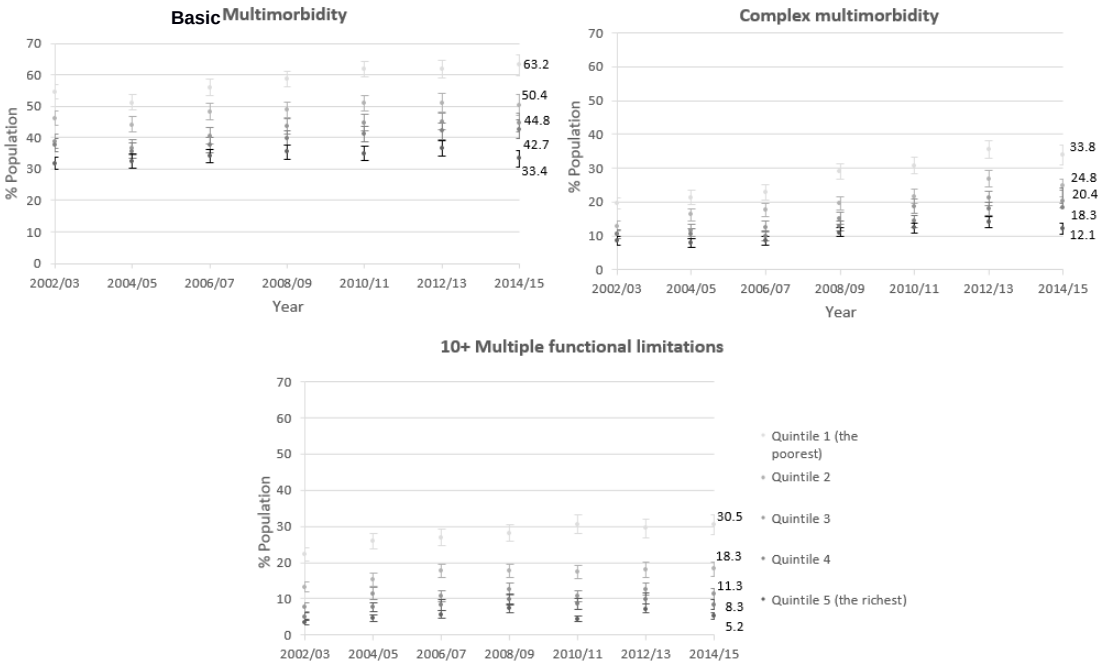

Figure 3. 3 Age-standardized prevalence of basic multimorbidity, complex multimorbidity and multiple functional limitations by quintiles of household wealth for England, 2002-2015 (95% C.I.s).

We further stratified each age band by quintiles of household wealth in order to observe differences in prevalence of our measures (Figure 3.4). In order to avoid data clutter, we report only results for the observation in 2014/15. We found the largest variation in the youngest age group (50-54 years of age). The prevalence of basic multimorbidity in the poorest quintile was 4.1-times higher than in the richest quintile in the youngest age group. People aged 50-54 years in the poorest quintile had levels of multimorbidity equivalent to people 15-20 years older in the most affluent quintile. The prevalence of complex multimorbidity and 10+ multiple functional limitations in the poorest category was 18.7-times and 14-times higher than in the wealthiest category in the youngest age group. People aged 50-54 years in the poorest quintile had levels of complex multimorbidity equivalent to people 20 years older and levels of 10+ multiple functional limitations equivalent to those 30 years older in the most affluent quintile.

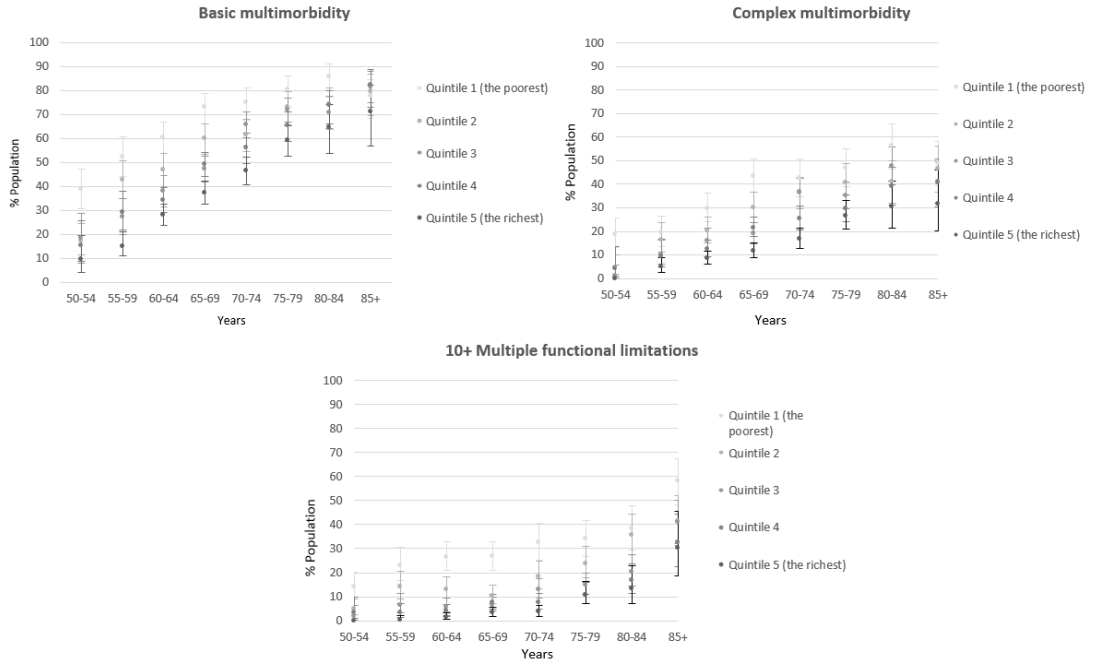

Figure 3. 4 Prevalence of basic multimorbidity, complex multimorbidity and 10+ multiple functional limitations by age band and wealth quintile for England, 2014/15 (95% C.I.s).

The patterns in Figure 3.4 indicated that the effect of age on the prevalence estimates varies by socio-economic status. The interaction effect for the whole period 2002-15 was further explored in a logistic regression model. The marginal effects (Appendix C, Figure C.2) show changes in the probability of an outcome as the values of the household wealth variable change between quintiles. The additional effect of change in wealth quintile on the probability of having multimorbidity in 2014/15 was the strongest in the lowest wealth quintile up to the age 80-84. An overall pattern for all quintiles represents a socio-economic gradient up to the age of 75-80. For older age groups the effects overlap and no pattern is discernible any more. The pattern changes for people with 10+ functional limitations. The graded differences in effects between quintiles are more pronounced and they remain distinct even in the oldest age category. This confirms the distribution for 2014/15 identified in Figure 3.4.

3.5 Discussion

3.5.1 Key results

Our study found that the prevalence of basic multimorbidity, complex multimorbidity and 10+ multiple functional limitations in the ageing population of England increased between 2002/03 and 2014/15. We standardised our analysis to remove differences in age structure over time but in absolute terms this increase will be even larger due to the ageing poulation. Also the addition of refreshment samples (age 50–53) at waves 3, 4, 6 and 7 has potentially resulted in an underestimation of the prevalence. The distribution of these health outcomes at population level was influenced by sex as they were more common among women than among men. Age was another determinant of the distribution. Our health outcomes were becoming more common in younger age groups during the observed period. The age when the majority of an age

group became multimorbid shifted from the 70-74 age group to the 65-69 age group (Appendix B, Table B.1). Out of the three measures, the prevalence of complex multimorbidity had the steepest growth, followed by 10+ multiple functional limitations and basic multimorbidity. Furthermore, the prevalence of multimorbidity, complex multimorbidity and 10+ multiple functional limitations was socially stratified. People with less household wealth had higher levels of multiple health problems than people from the more affluent wealth quintiles. The disparity in wealth was larger for complex multimorbidity and 10+ functional limitations than for basic multimorbidity.

We also discovered that socio-economic status and age mutually interacted. The differences in the prevalence of basic multimorbidity between the wealth quintiles were the largest in the youngest age group and they narrowed down as people aged (Figure 3.4). The differences in the prevalence of complex multimorbidity and especially multiple functional limitations between the poorest and wealthiest quintile remained large for all age groups (Figure 3.4).

The pattern of health inequality based on cross-sectional stratification analyses in Figures 3.3 and 3.4 were confirmed after data were reshaped into a panel design where time interacted with wealth (Appendix C, Figure C.1) and age interacted with wealth (Appendix C, Figure C.2).

3.5.2 Interpretation

The rising prevalence of multimorbidity consistent across three different conceptualisations between 2002/03 and 2014/15 supports projections of a growing trend (Kingston et al., 2018). Prevalence in general is shaped by both the rate at which new cases are occurring and the average duration of disease. Our analysis was a repeated cross-sectional and as such it examined neither the incidence nor the duration of multimorbidity and cannot quantify their relative contribution to the increased prevalence.

Household wealth, an indicator of socio-economic status, was negatively associated with multimorbidity and 10+ functional limitations. This is

consistent with previous studies reporting socio-economic gradient in multimorbidity (Van den Akker et al., 2000; Agborsangaya et al., 2012; Barnett et al., 2012; Charlton et al., 2013; McLean, 2014; Morrissey et al., 2015; Schiøtz et al., 2017). Our study observed that the gap between the wealth quintiles was larger for participants with complex multimorbidity and largest for people with ten or more functional limitations. Lack of household wealth was related to higher complexity of multimorbidity and corresponding limitations and vice versa. This is consistent with the findings of a study examining growth in functional limitations and socio-economic factors (Calderón-Larrañaga et al., 2018). It seems plausible that this gradient in complexity might be explained by problems with the self-management of multimorbidity. Patients whose everyday lives are overwhelmed by acute social problems are less able to manage the complex treatment burden and find adequate social support (O'Brien et al., 2014). This would suggest that the true impact of inequalities is under-estimated if multimorbidity is defined as the presence of two or more conditions or, similarly, if the cut-off measure for number of functional limitations is set too low.

Ageing with multimorbidity and functional limitation was differentiated by SES. We observed an excess of multiple health problems in the youngest age cohort with lowest SES. People aged 50-54 years in the poorest quintile had levels of complex multimorbidity comparable to those 20 years older in the most affluent quintile and level of 10+ functional limitations comparable to those 30 years older in the top wealth quintile. This suggests an earlier onset of multimorbidity, and especially of complex multimorbidity and multiple functional limitations, for people with lower socio-economic status. Earlier origins of basic multimorbidity in Scotland were observed by Barnett et al. (2012), McLean (2014) and Canizares et al. (2019). The differences in prevalence between wealth quintiles were largest in the youngest age group but they narrowed down as people aged. Similar levelling effects of ageing on basic multimorbidity prevalence have been reported previously (Barnett et al., 2012). The differences in the prevalence of complex multimorbidity and especially

multiple functional limitations between the poorest and the wealthiest quintile remained large for all age groups. This suggests that accumulated financial resources at older age can act as a protective factor against increased disease complexity. One pathway in which this accumulated financial resources may protect against increased disease complexity is via financial advantage translating into an actual healthy behaviour. For example, Link and Phelan (1995) postulate that individuals from higher social class backgrounds are capable to use resources such as power, money, knowledge, prestige or social contacts to either protect themselves from the health risks or compensate for their existing disease burden.

3.6 Limitations

Our exploratory study focused on the assessment of the burden of multimorbidity, complex multimorbidity and multiple functional limitations at the population level. Using a repeated cross-sectional design does not allow any explanatory inferences to be drawn regarding individual trends or causal relationships between covariates and outcome variables.

The estimates of prevalence might be under-estimated as they are based on self-reported information on health problems. A previous study found that prevalence based on self-reports was lower than if data were obtained from medical examinations (Schramm et al., 2008). A combination of data sources was suggested as the best way of providing the most reliable results (Fortin et al., 2012).

This study could be expanded if we had shown an association between the two multimorbidity measures and the measure of ten or more functional limitations. Such an analysis might be interesting especially as both complex multimorbidity and multiple functional limitations represent problems affecting multiple body systems.

3.7 Conclusion

To our knowledge, this paper is the first study to examine trends in the prevalence of multimorbidity as measured through three types of conceptualisations of multimorbidity. We uncovered processes of clear polarization within the ageing population of England. Alongside a stable proportion of people who were free of any chronic disease and a declining proportion of those with one disease, we observed that the increase in complexity overtakes the rise in basic multimorbidity and multiple functional limitations. Another axis of differentiation is by socio-economic status where the higher household wealth is related to lower prevalence. At the same time this process introduces health inequality within age groups. Complex multimorbidity and multiple functional limitations are increasing faster and capture stronger inequality than the measure of basic multimorbidity. Using different measures of multimorbidity can contribute to identifing population groups with higher health care needs and to a better allocation of health care resources. Reporting the patterns of body systems affected by chronic conditions may help health care planners identify services which should be co-located, for an optimal care of these patients (Harrison et al., 2016). The complex multimorbidity measure would also allow identification of patients who may need help in coordinating care between multiple health care providers.

Policies aiming to prevent and reduce the growth in multimorbidity should be approaching the older population as diverse and take into account the multiple polarizations we have described. It would be meaningful to focus the preventive efforts on younger age groups where social inequality appears to be more intertwined with chronic complexity and functional limitation than in older age. The contribution of these younger cohorts as they age into the older population, along with growing numbers of the very old, could significantly increase health and social care costs in the future.

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Appendix A.

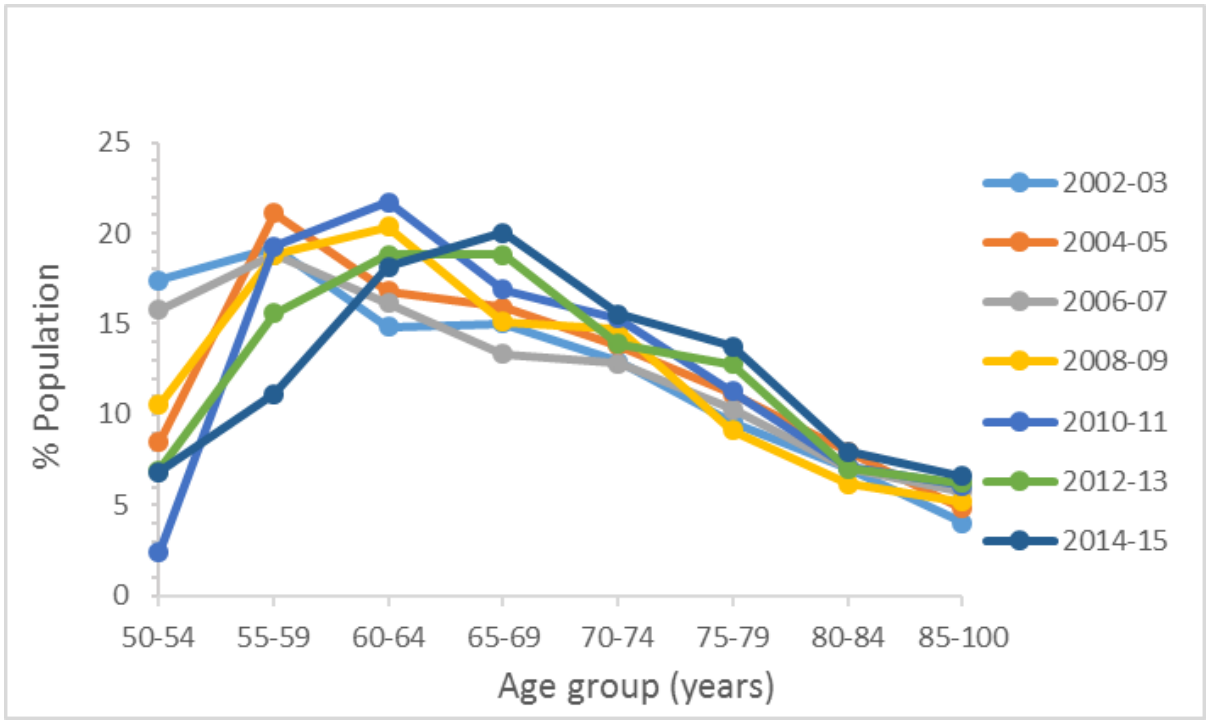

Table A.1 Age structure 2002-2015

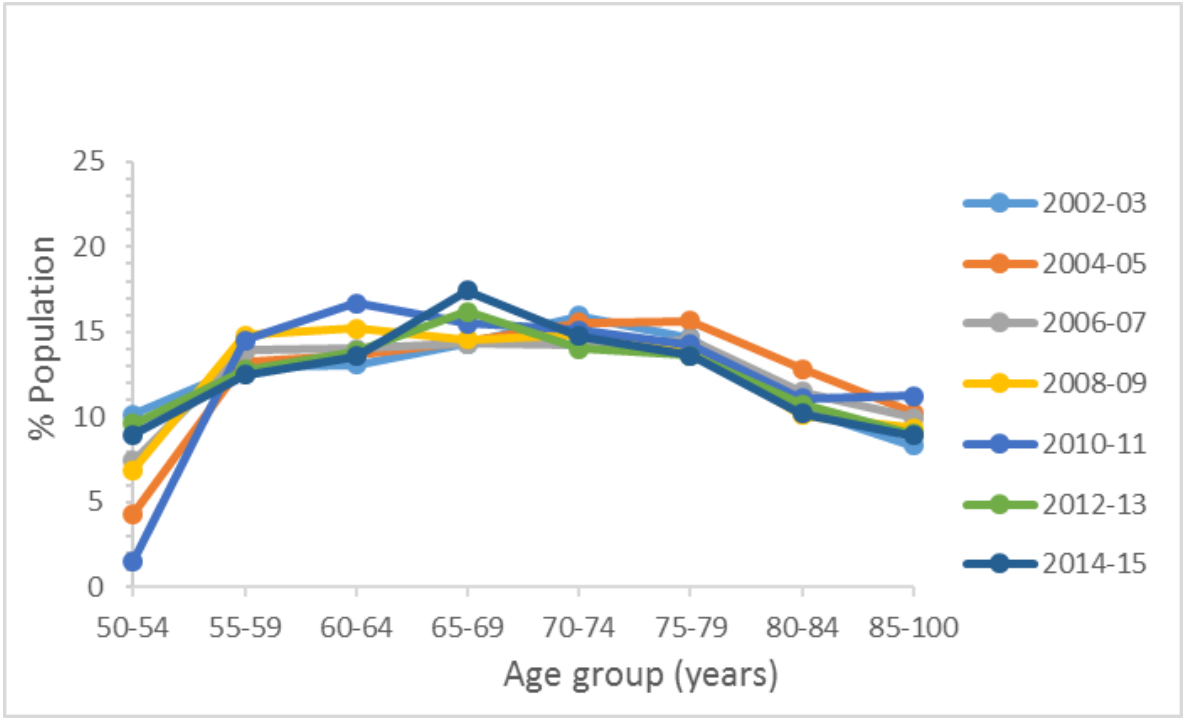

Table A.2 Distribution of multimorbidity by age group and time

Appendix B.

Table B.1 Prevalence of basic multimorbidity by age

	2002/03		2004/05		2006/07		2008/09		2010/11		2012/13		2014/15	
Age (years)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)
50-54	481	21.8 (19.9-23.8)	158	18.8 (16.1-21.7)	279	22.5 (20.3-24.9)	303	23.3 (20.7-26)	69	24.7 (19.4-30.9)	422	26.3 (22.8-30.1)	375	23.6 (20.1-27.5)
55-59	616	30.3 (28.3-32.4)	485	25.8 (23.7-28)	523	28.9 (26.7-31.2)	652	29.3 (27.1-31.5)	645	30.3 (28.1-32.7)	563	35 (32.1-37.9)	521	38.3 (34.8-41.8)
60-64	619	36.8 (34.3-39.3)	501	35.5 (33-38)	528	36.5 (33.9-39.2)	668	38.5 (36.3-40.8)	743	40.7 (38.4-43)	611	40.3 (37.9-42.8)	568	45.6 (43-48.3)
65-69	678	43.8 (41.5-46.2)	530	40.3 (37.7-42.9)	538	45.4 (42.5-48.4)	640	49.2 (46.6-51.8)	689	49.3 (46.6-51.9)	713	51.8 (49.3-54.3)	729	57.3 (54.9-59.8)
70-74	755	54 (51.4-56.7)	570	50.9 (48.1-53.8)	534	52.9 (49.8-55.9)	652	57.8 (55.1-60.4)	671	57.3 (54.5-60)	617	61.3 (58.5-64)	616	66.2 (63.4-68.9)
75-79	696	59.8 (56.8-62.7)	574	58.3 (55.2-61.4)	548	64.6 (61.3-67.8)	623	67.4 (64.1-70.5)	634	67.7 (64.7-70.6)	600	72.4 (69.6-75)	570	75.8 (73.1-78.4)
80-84	496	64.3 (60.8-67.6)	471	65 (61.3-68.5)	433	69.6 (65.7-73.3)	445	70.7 (66.6-74.5)	493	77.3 (73.6-80.5)	474	78 (74.5-81.1)	426	79.2 (75.6-82.3)
85-100	396	68.9 (64.2-73.1)	376	74.7 (70-78.9)	375	75.3 (70.5-79.6)	412	74.1 (69.6-78.1)	501	82.8 (79-86.1)	397	77.7 (73.6-81.3)	372	80.2 (76.1-83.7)
Total	4,739	41.6 (40.6-42.6)	3,664	41.7 (40.6-42.9)	3,759	43.4 (42.3-44.5)	4,396	44.8 (43.8-45.9)	4,446	49.5 (48.4-50.6)	4,398	48.5 (47.3-49.8)	4,178	51.2 (49.9-52.6)
Mean age (SD)		68.9 (10.5)		70.7 (10.3)		70.1 (11.1)		69.8 (10.3)		70.8 (9.5)		70.8 (9.6)		71.4 (9.2)
Median age (IQR)		69 (60-77)		71 (62-78)		70 (61-78)		69 (62-77)		70 (63-78)		71 (64-78)		71 (65-78)

* Number of persons with BMM

Table B.2 Prevalence of complex multimorbidity by age

	2002/03		2004/05		2006/07		2008/09		2010/11		2012/13		2014/15	
Age (years)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)	n *	Prevalence (95 % CI)
50-54	90	4.1 (3.3-5.1)	32	3.8 (2.6-5.5)	77	6.2 (5-7.6)	77	5.9 (4.6-7.5)	25	8.9 (5.8-13.3)	131	8.2 (6.2-10.8)	113	7.1 (5.2-9.6)
55-59	122	6 (5.1-7)	109	5.7 (4.8-6.9)	144	8 (6.7-9.5)	196	8.8 (7.5-10.2)	180	8.5 (7.2-9.9)	230	14.3 (12.3-16.5)	163	12 (9.7-14.6)
60-64	142	8.4 (7.2-9.9)	140	9.9 (8.4-11.6)	164	11.4 (9.8-13.2)	240	13.8 (12.3-15.5)	261	14.3 (12.7-16)	260	17.2 (15.4-19.2)	200	16.1 (14.2-18.1)
65-69	168	10.8 (9.4-12.4)	182	13.9 (12.1-15.8)	158	13.4 (11.5-15.5)	240	18.4 (16.4-20.6)	287	20.6 (18.5-22.8)	325	23.6 (21.6-25.8)	293	24 (20.9-25.4)
70-74	233	16.7 (14.8-18.7)	208	18.5 (16.4-20.9)	184	18.2 (15.9-20.8)	265	23.5 (21.3-25.9)	298	25.4 (23-28)	302	30 (27.4-32.7)	282	30.3 (27.7-33.1)
75-79	245	21 (18.7-23.6)	224	22.8 (20.2-25.6)	195	23 (20.3-25.9)	288	31.1 (27.9-35.7)	309	33 (30-36.1)	325	39.2 (36.3-42.2)	266	35.5 (32.6-38.5)
80-84	223	28.9 (25.9-32)	210	29 (25.7-32.6)	176	28.3 (24.7-32.1)	199	31.6 (28.1-34.3)	255	40 (36-44)	275	45.2 (41.2-49.2)	236	43.8 (39.8-47.9)
85-100	178	31 (26.6-35.7)	168	33.4 (28.8-38.4)	151	30.4 (26.3-34.9)	194	34.9 (30.5-39.5)	250	41.3 (36.9-45.7)	214	41.9 (37.4-46.5)	203	43.6 (39.1-48.3)
Total	1400	12.3 (11.7-12.9)	1,272	14.5 (13.7-15.3)	1,250	14.4 (13.7-15.2)	1,698	17.3 (16.5-18.1)	1,865	20.8 (19.9-21.7)	2,062	22.8 (21.8-23.7)	1,756	21.5 (20.5-22.6)
Mean age (SD)		71.9 (10.6)		73 (9.9)		71.6 (11.2)		71.5 (10.2)		72.5 (9.4)		72 (9.5)		73 (9.1)
Median age (IQR)		72 (64-80)		74 (66-81)		72 (63-80)		71 (63-80)		73 (65-80)		72 (65-79)		73 (66-80)

* Number of persons with CMM

Table B.3 Prevalence of 10+functional limitations by age

	2002/03		2004/05		2006/07		2008/09		2010/11		2012/13		2014/15
Age (years)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)	n*	Prevalence (95 % CI)
50-54	104	4.7 (3.9-5.7)	55	6.6 (4.9-8.7)	83	6.7 (5.5-8.2)	128	9.8 (8.1-11.9)	30	10.8 (7.3-15.6)	157	9.8 (7.5-12.6)	110	6.9 (5.1-9.3)
55-59	149	7.3 (6.3-8.5)	150	7.9 (6.8-9.3)	157	9.2 (7.8-10.8)	200	10.2 (8.8-11.7)	189	8.9 (7.5-10.5)	213	13.2 (11.3-15.4)	138	10.1 (8.1-12.5)
60-64	136	8.1 (6.8-9.5)	153	10.9 (9.4-12.6)	165	11.4 (9.8-13.3)	228	11.5 (10.1-13.2)	160	8.8 (7.5-10.2)	174	11.5 (10-13.2)	129	10.4 (8.8-12.2)
65-69	138	8.8 (7.6-10.3)	124	9.4 (8-11.1)	157	12.1 (10.3-14.1)	179	13.8 (12.1-15.7)	174	12.5 (10.7-14.4)	184	13.4 (11.7-15.2)	141	11.1 (9.5-12.9)
70-74	145	10.3 (8.8-12.1)	149	13.4 (11.5-15.5)	147	14.5 (12.5-16.8)	175	15.5 (13.6-17.6)	176	15 (13.1-17.2)	160	15.9 (13.8-18.2)	139	15 (12.9-17.3)
75-79	160	13.7 (11.7-16)	162	16.4 (14.1-19)	157	18.6 (16-21.4)	175	20.9 (18.3-23.9)	183	19.6 (17.2-22.3)	153	18.5 (16.2-21)	158	21 (18.5-23.8)
80-84	147	19 (16.4-21.9)	192	26.6 (23.3-30.1)	162	26 (22.4-29.8)	193	27.9 (24.2-31.9)	178	28 (24.4-31.8)	158	26 (22.5-29.9)	163	30.3 (26.7-34.2)
85-100	191	33.2 (28.7-37.9)	221	43.9 (38.8-49)	216	43.4 (38.6-48.3)	218	39.1 (34.5-44)	254	42 (37.6-46.7)	206	40.2 (35.8-44.8)	231	49.8 (45-54.6)
Total	1169	10.3 (9.6-10.9)	1,207	13.7 (12.9-14.6)	1,240	14.3 (13.5-15.1)	1496	15.3 (14.5-16.1)	1,346	15 (14.2-15.8)	1,405	15.5 (14.7-16.4)	1,210	14.8 (14-15.7)
Mean age (SD)		70.7 (12)		72.6 (11.8)		72.3 (12.6)		71.2 (12.1)		73.2 (10.6)		72 (11)		74.3 (10.6)
Median age (IQR)		70 (61-80)		73 (62-81)		72 (62-82)		70 (61-80)		73 (64-82)		72 (63-81)		75 (66-83)

* Number of persons with 10+ functional limitations

Table B.4 Household wealth bands in £s by year

Household wealth (£s i	2002/03		2004/05		2006/07		2008/09		2010/11		2012/13		2014/15	
	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Quintile 1	-108,000	0	-130	27,5	-160	37,5	-450	56	-80	65	-20	65	-220	70
Quintile 2	3,000	75	29,5	129	37,5	150	56,5	150	66	150	66	150	71,1	160
Quintile 3	75,250	125	129,3	185	151	200	150,5	200	150,5	208	151	210	161	240
Quintile 4	126,000	200	185,4	265	201	300	200,2	300	208,7	300	211	320	241	350
Quintile 5	200,500	2,486	266,7	2,000	301	4,440	301	3,500	304	4,000	321	4,500	351	4,000
Median (IQR*)	100 (33-180)		155 (75-245)		175 (89-261)		175 (91-265)		180 (100-285)		180 (95-290)		190 (100-310)	
* Interquartile range														

Appendix C.

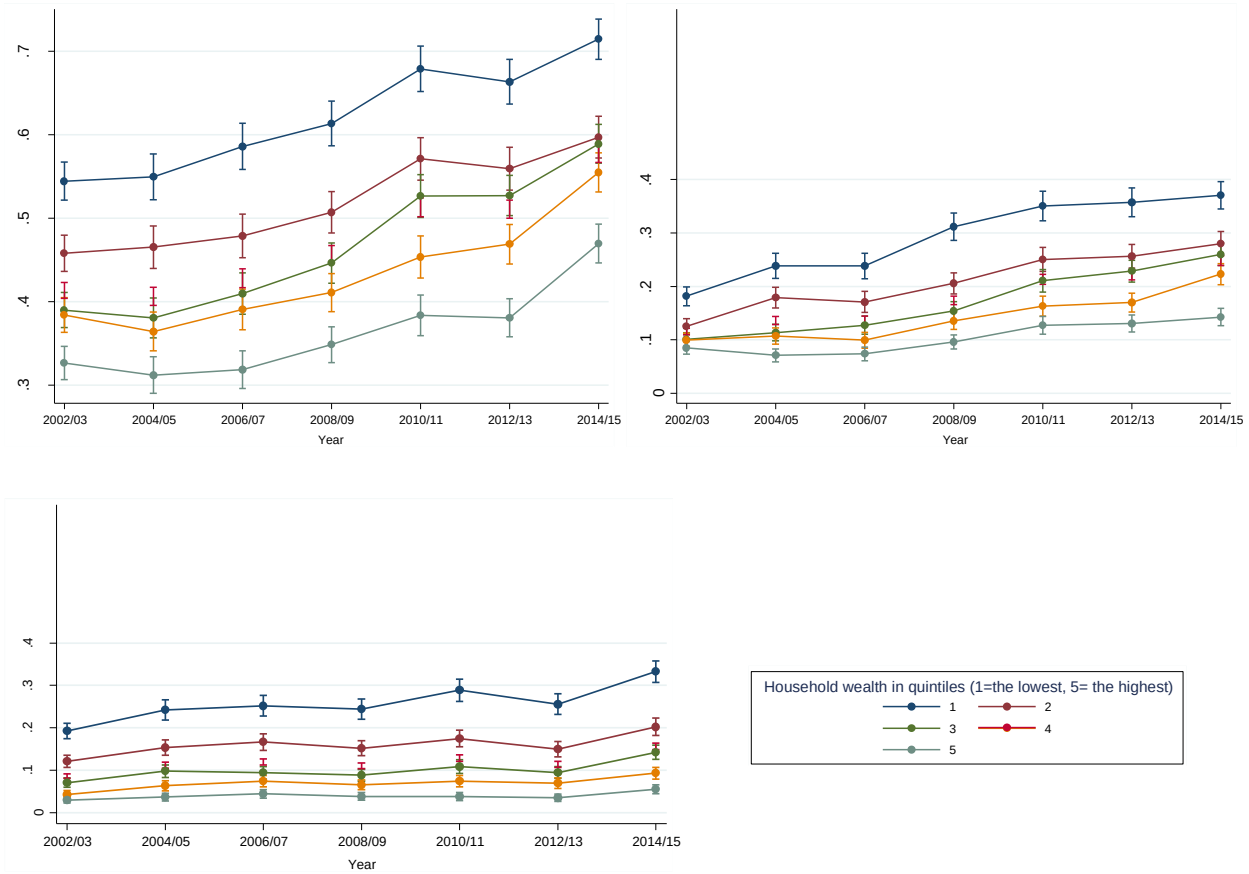

Figure C.1 Marginal interaction effects of time and wealth on the probability of basic multimorbidity, complex multimorbidity and 10+ functional limitations (95% CIs) in the period 2002-2015.

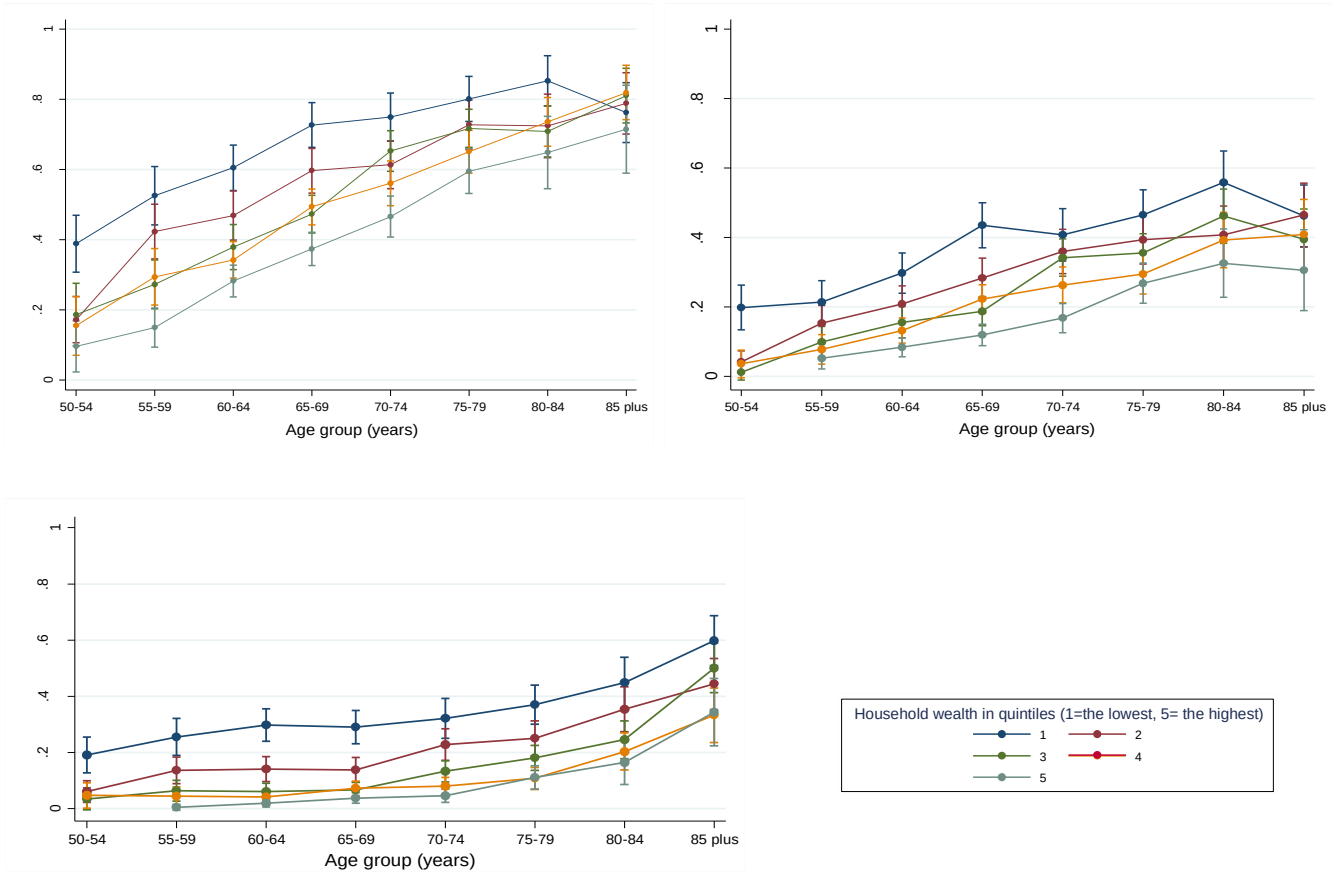

Figure C.2 Marginal interaction effects of age and wealth on the probability of basic multimorbidity, complex multimorbidity and 10+ functional limitations (95% CIs) in 2014/15

Appendix D.

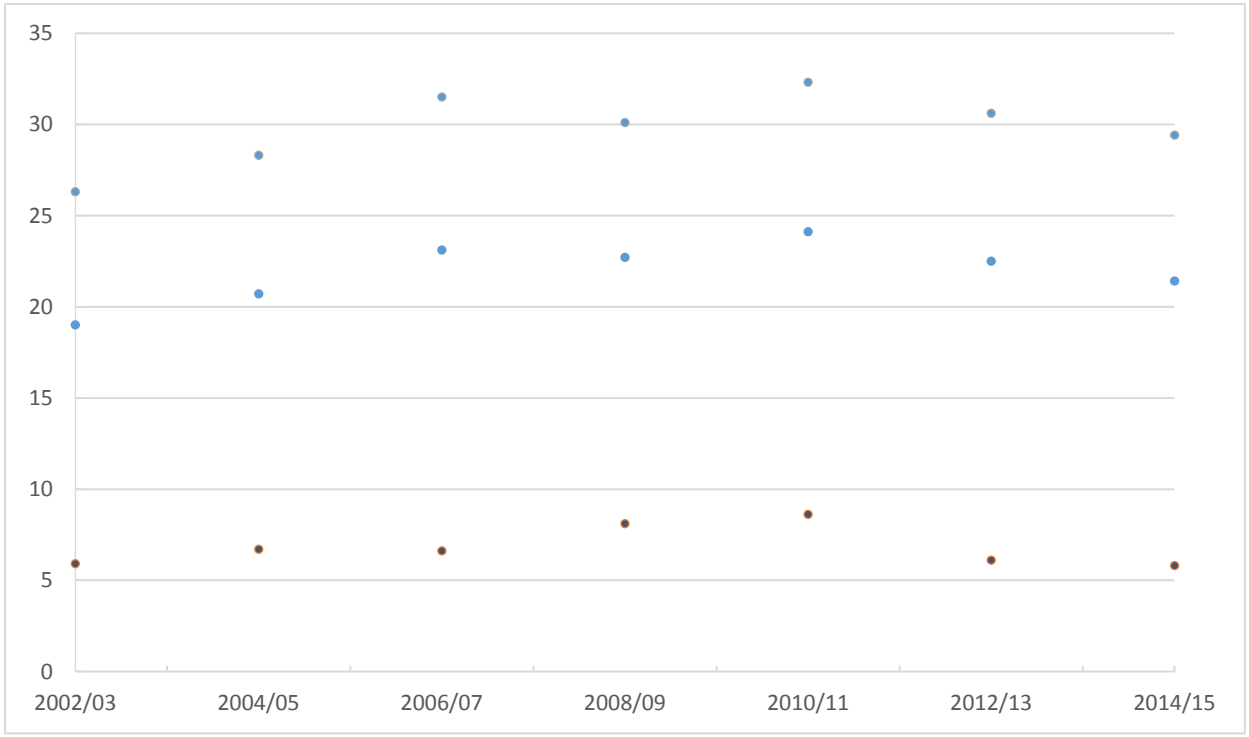

Figure D.1 Prevalence of functional limitations in Activities of Daily Living, general mobility and symptoms for England in 2002-15 (95% CIs).

Chapter 4

Social determinants of multimorbidity and functional limitation in the ageing population of England

Abstract

This study explores longitudinal relationships between material, psycho-social and behavioural social determinants of health and multimorbidity of people aged 50 years or older in England. We used data from the English Longitudinal Study of Ageing collected biannually between 2002 and 2015. Apart from the basic measure of multimorbidity (two or more diseases within a person) we constructed two distinct measures in order to take into account the biology of ageing (complex multimorbidity and multiple functional limitations).

We found that the likelihood of multimorbidity and multiple functional limitations was consistently associated with the levels of household wealth, sense of control over one's life, physical activity and loneliness. Larger health inequalities were observed when health was measured as complex multimorbidity and multiple functional limitations than basic multimorbidity. We did not find a dose-response relationship between alcohol consumption, smoking and multimorbidity but rather evidence of people in ill health actively moderating their health behaviour.

We suggest that materialist models of multimorbidity at older age can not, on their own, explain the health inequalities as behavioural and psycho-social factors play an important role. Policies aiming to reduce the risk of multimorbidity and functional limitation should address the issue at these three levels simultaneously, using the existing national infrastructure of General Practices.

4.1 Introduction

Multimorbidity, the co-occurrence of two or more diseases within a person, affects over a quarter of primary care patients older than 18 years of age in England (Cassell et al., 2018). Individuals with multimorbidity have higher rates of GP consultations, prescriptions, and hospitalisations compared to people without multimorbidity (Salisbury et al., 2011; Cassell et al., 2018). Multimorbidity also leads to lower health-related quality of life (Bayliss et al., 2012; Peters et al., 2018) and decline in physical functioning (Jindai et al., 2018). Multimorbidity among people older than 65 years in England is set to rise with prevalence projected to increase from 54% in 2015 to 67.8% in 2035 (Kingston et al., 2018). People will live longer lives in worse health and this will increase the utilization of health services and the costs of health care (Cassell et al., 2018, Kingston et al., 2018).

While current studies of multimorbidity focus on the impact of biomedical and socio-demographic characteristics on patients' individual risk (Northwood et al., 2017), we also need to understand the extra-individual factors contributing to the increase of multiple health problems in the ageing population. Only a few studies examined simultaneously longitudinal trends in multimorbidity and their relationship with extra-individual factors such as society and environment (Schäfer et al., 2012, Jackson et al., 2015, Dhalwani et al., 2017 and Mounce et al., 2018). None of them referred to any theoretical framework that would justify the choice of the contextual characteristics. This leads to the risk of omitting relevant factors which might explain more of the outcome variance and to exaggerating effects of the observed characteristics (Frohlich, Corin and Potvin, 2001). Choosing an appropriate measure should be backed by theory too. For instance, education and income reflect different mechanisms through which socio-economic status operates (Demakakos et al., 2008). We argue that multimorbidity should be studied with the help of the theories of *social determinants of health* (SDoH). These refer to the social, cultural, economic,

and political conditions that influence the health of individuals and populations (De Maio, Mazzeo & Ritchie, 2013, Lucyk and McLaren, 2017).

Further, we suggest that measuring multiple health problems of older people should be consistent with our knowledge of biological ageing. The concept of multimorbidity should reflect the build-up of damage within cells (Kirkwood, 2008, Austad, 2009, Barnes, 2015) that accumulates during the life course and leads to a chronic dysregulation of multiple body systems (Fabbri et al., 2015, Li et al., 2015). Accumulation of diseases is a milestone for this system dysregulation, loss of resilience and accelerated ageing (Fabbri et al., 2015). The role of body systems in development of multimorbidity is beginning to receive some attention (Sturmberg et al., 2017, Yarnall et al., 2017).

Our study seeks to address these gaps in the understanding of multimorbidity among ageing people. Alongside the basic definition of multimorbidity (Van den Akker et al., 1998) we propose two measures which in our view better reflect the biological process of ageing: *complex multimorbidity* (Harrison, Britt & Henderson, 2014) and *multiple functional limitations*. These outcomes should not be omitted when studying multimorbidity as they have implications for quality of life, need for health care and residential care, and premature mortality of old people (Zulman, Pal & Wagner, 2015, Jindai et al., 2016). Our approach is also novel in that it brings together new measures of multimorbidity with social theory of SDoH in a longitudinal design. The aim of our study is to explore the association of material, psycho-social and behavioural determinants to the probability of developing basic multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England over a 14 year period.

4.2 Theoretical framework

Our starting point is the centrality of dysfunction in several body systems that is conducive to multiple impairment, limitation and disease. We postulate that

if we can identify diverse social determinants that simultaneously affect an individual, changes could be observed across a number of body systems that will be involved in generating compound health outcomes. Here we follow the Generalized Health Impact model of White et al. (2013) that showed how a combination of social determinants (stress, poverty or quality of housing) generated a range of host responses encompassing more than one health condition. This model informed our approach to the choice of social determinants and for measuring multimorbidity.

4.3 Measuring multimorbidity

Multimorbidity has been measured by a range of methods. In primary care settings, indices based on diagnostic or pharmaceutical data have been used such as the Charlson Index, Adjusted Clinical Groups System or Cumulative Illness Index Rating Scale (Diederichs, Berger & Bartels, 2011, Huntley at al., 2012). Multimorbidity estimates in general populations are based on a simple unweighted enumeration of the number of diseases. The most common definition is "the co-occurrence of two or more diseases within a person" (Van den Akker et al., 1998) but different cut-off points have been used too (Marengoni et al., 2011). In our study this measure will be called *basic multimorbidity* in order to distinguish it from two other measures. The limitation of the concept of basic multimorbidity is that it leads to very high estimates among old people (55% to 98% between studies) which may be less informative than other definitions (Marengoni et al., 2011). Neither does it differentiate between co-occurrence developing within one body system and two or more systems. Multimorbidity may have a larger impact on overall health if it arises out of disparate conditions (such as physical and mental health) rather than closely related comorbidities (Piette and Kerr, 2006).

The construct of complex multimorbidity addresses these issues. It has been defined as "the co-occurrence of three or more chronic conditions affecting

three or more different body systems within one person without an index chronic condition" (Harrison et al., 2014, p. 8). Individuals with chronic conditions in 3+ body systems may require more complex care, as chronic conditions in different body systems are likely to compete for treatment, while conditions within the same system are more likely to be complementary (Piette and Kerr, 2006). With regard to the theories of ageing based on dysregulation of body systems described earlier, we argue that complex multimorbidity might be a more appropriate measure for ageing people than basic multimorbidity.

The third measure of multiple functional limitations reflects the knowledge that the proportion of old people with physical impairments and limitations in multiple body systems increases with age (Burden of Disease Network Project, 2004, Jindai et al., 2016). Functional limitations are defined as restrictions in performing vital situation-free physical actions needed in everyday life (Verbrugge and Jette, 1994). Most studies have explored prevalence and effects of single impairments or functional limitations but we know less about the relationships between combined burden of impairments and functional limitations and social determinants (Burden of Disease Network Project, 2004).

4.4 Social determinants

The theoretical approach to health inequalities and the role of SDoH in the UK was shaped by the publication of the Black Report in 1980 that concluded that material conditions were the major determinant of health and premature mortality (Black, 1992). This led to discussions between proponents of the materialist explanations and those who claimed that health inequalities are result of culturally mediated choices and behaviours (Bartley, 2004, Cockerham, 2007). The debate has been enriched by a third perspective, the role of psycho-social factors highlighted in the Whitehall II Study (Marmot et al., 1991). The current approach is to understand these hypotheses as complimentary rather than mutually exclusive and to assess their effects in one model with three

groups of determinants (Van Oort, van Lenthe and Mackenbach, 2005, Robertson et al., 2015).

Material determinants refer to the distribution of income and wealth in society and to resources that allow people to secure goods and services needed for a healthy life, e.g. housing, healthcare (Bartley, 2004, Cockerham, 2007). Studies of ageing population in England and the UK found disparities by socio-economic status (SES) for a range of health outcomes (Nazroo et al., 2017). The few longitudinal studies of multimorbidity showed associations with low education, low household income, difficulties managing on income and total household wealth (Schäfer et al., 2012, Jackson et al., 2015, Mounce et al., 2018). A lower level of education, manual occupation and poor social network predicted a higher number of functional limitations in the Swedish population older than 60 years of age (et al., 2018). Subjective social status (SSS) has been referred to as a subjective measure of SES as it reflects individual's *perceived* standing in a social hierarchy and hence can be included in the group of material determinants (Singh-Manoux, Marmot and Adler, 2005). SSS also captures feelings and perceptions of anxiety, stress and the sense of inequality (Charonis et al., 2017). To our knowledge there are no studies of how SSS is related to multimorbidity and only one study has examined its association with functional decline (Chen et al., 2012).

Psycho-social determinants, such as leisure and social activities and social networks and contacts, are increasingly more relevant to older people's idea of healthy ageing (Bowling, 2008, Cosco et al., 2013). Social networks affect health via pathways such as provision of social support, social influence, social engagement and attachment, and access to resources and goods (Berkman, 2000). Living as a couple, in a family, having a large social network and having a sense of control over one's life were all protective factors reducing the risk of multimorbidity (Marengoni et al., 2011, Melis et al., 2014). Older multimorbid people with a supportive social network have longer survival time compared to those without social support (Olaya et al., 2017). Loneliness has been found positively associated with multimorbidity in England, although the relationship

was stronger for people younger than 44 than for people older than 65 (Stickley and Koyanagi, 2018). The stress-buffering hypothesis suggests that social relationships can provide resources that buffer the effect of stress on health (Uchino, 2009, Gellert et al., 2018). The direct effects' model says that social networks can facilitate positive health behaviours and access to health care by providing resources such as material assistance or transportation (Olaya et al., 2017).

Behavioural determinants describe different types of consumption and leisure activities that directly affect health and are, to some extent, subject to individual choice and decision-making (Bartley, 2004). While sociology of health described an interplay between human agency and social structure (Cockerham, 2007), health behaviours are still treated in isolation from other social determinants (Moor, Spallek and Richter, 2016). Dhalwani et al. (2017) reported a social gradient between multimorbidity and physical activity, fruit and alcohol consumption, smoking tobacco and Body Mass Index.

Each type of social determinant can work through any or several of the body systems (Blane et al., 2013). For instance, occupation can affect respiratory, endocrine or cardiovascular system through toxins at work (Agency for Toxic Substances & Disease Registry, 2018) or nervous system and immune system through stress (Marmot et al., 1991). Smoking tobacco can affect nervous, respiratory, cardiovascular or digestive systems through both inhaled carcinogens and lower self-esteem (Bartley, 2004). These examples illustrate our assumption that the combined long-term impact of material, psycho-social and behavioural determinants should be sufficiently wide to be observable across a range of body systems through our measures of complex multimorbidity and multiple functional limitations.

4.5 Material and methods

4.5.1 Data

The English Longitudinal Study of Ageing (ELSA) is a multidisciplinary panel study of a representative sample of men and women aged 50 years and over living in England. ELSA explores the dynamics between ageing and demographic, socio-economic, psychological and health factors. The study began in 2002 with 12,099 participants and the sample is re-examined every two years. It was replenished at waves 3, 4, 6 and 7 with new participants to maintain the size and representativeness of the study (Steptoe et al., 2013). We used data from the core sample members who are individuals aged 50 or older who were recruited at the first wave or at any of the refreshment samples. The numbers of core members were: 12,099 in wave 1; 8,780 in wave 2; 8,811 in wave 3; 9,896 in wave 4; 9,090 in wave 5; 9,169 in wave 6 and 8,253 in wave 7.

Data on core members from waves 1 to 7 were merged into a panel dataset. In order to give additional effect to those who dropped out of the analysis, we used longitudinal weights. In each wave, every individual who took part in all preceding waves was assigned a longitudinal weight by ELSA. Those who missed on one or more waves had been given a weight with a missing value by ELSA. In order to include a maximum number of core members in the analysis, we gave these individuals a weight that was equal to their longitudinal weight in the last wave they had participated.

4.5.2 Dependent variables: measures of health

We used data on 25 physical and mental health conditions that were consistently recorded at each wave (Table 4.1). The data were grouped into three categories: individual morbidities, groups representing body systems and functional limitations, a decision based on Verbrugge and Jette's Disablement Process Framework (1994). We decided to enlarge their category 'functional

limitations' by including instances of impairment (dysfunction and abnormalities in body systems) and disability (difficulty with daily activities) (Table 4. 1).

Table 4. 1 Health data used to measure basic multimorbidity, complex multimorbidity and multiple functional limitations

	Morbidities	Body systems		Functional limitations
1	High blood pressure	1. **Eye disorders**		**General mobility**
2	Angina	1.1. Glaucoma	1	Walking 100 yards
3	Congested heart failure	1.2. Macular degeneration	2	Sitting for 2 hrs
4	Heart murmur	1.4. Cataracts	3	Getting up from chair
5	Abnormal heart rhythm	2. **Circulatory disorders**	4	Climbing several flights of stairs
6	Heart attack	2.1. High blood pressure	5	Climbing one flight of stairs
7	Diabetes	2.2. Angina	6	Stooping, kneeling or crouching
8	Stroke	2.3. Heart attack	7	Reaching arms above shoulders
9	Lung disease	2.4. Congestive heart failure	8	Pulling or pushing a chair
10	Asthma	2.5. Heart murmur	9	Lifting/carrying weights over 10 pounds
11	Arthritis	2.6. Abnormal heart rhythm	10	Picking up a 5p coin
12	Osteoporosis	2.7. Stroke		**Activities of daily living**
13	Cancer	3. **Endocrine, nutritional and metabolic**	11	Dressing, including putting on shoes and socks
14	Parkinson's disease	3.1 Diabetic eye disease	12	Walking across a room
15	Dementia	3.2. Diabetes	13	Bathing or showering
16	Alzheimer's disease	4. **Musculoskeletal and connective system**	14	Eating, such as cutting up your food
17	Hallucinations	4.1. Osteoporosis	15	Getting in or out of bed
18	Anxiety	4.2. Arthritis	16	Using the toilet, including getting up or down
19	Depression	5. **Respiratory**	17	Using a map to figure out how to get around
20	Emotional problems	5.1. Lung disease	18	Preparing a hot meal
21	Mood swings	5.2. Asthma	19	Shopping for groceries
22	Glaucoma	6. **Neoplasms**	20	Making telephone calls
23	Diabetic eye disease	6.1. Cancers	21	Taking medications
24	Macular degeneration	7. **Nervous disorders**	22	Doing work around the house or garden
25	Cataracts	7.1. Parkinson's disease	23	Managing money (paying bills, track of expenses)
		7.2. Alzheimer's disease		**Symptoms**
		7.3. Hallucinations	24	Difficulty walking 0.25 mile
		8. **Mental and behavioural**	25	Pain in general
		8.1. Anxiety	26	Problems with eyesight
		8.2. Depression	27	Problems with hearing
		8.3. Emotional problems	28	Balance on level surface
		8.4. Mood swings	29	Dizzy walking on level surface

Measure 1: Multimorbidity (MM)

A binary variable was created in order to identify participants at each wave who had two or more morbidities. At each wave this variable was composed of the data fed forward from the previous wave and the data on newly reported morbidities.

Measure 2: Complex multimorbidity (CMM)

Individuals with three or more body systems affected by disease were considered as having CMM. Body systems were represented by the Chapters of the International Classification of Diseases 10th Revision (ICD-10) (Table 1). A patient with CMM had one or more chronic conditions within each of three or more different ICD-10 Chapters.

Measure 3: Multiple functional limitations (MFLs)

We derived the measure of MFLs from the combination of general mobility variables, Activities of Daily Living (ADL) variables, and data on symptoms of chronic conditions (Table 1). ADL is a common measure of the abilities necessary for basic functioning and for living in a community (Chatterji, Byles & Cutler et al., *2015)*. We counted the number of functional limitations per individual. The frequencies of MFLs per individual were high, reflecting the older age of participants and the large list of 30 limitations. Therefore we decided to specify the measure of MFLs as the presence of 10 or more functional limitations within the same person. This cut-off point allowed us to identify a group of participants with a total high functional limitation, compared to a cut-off point of three or five limitations.

4.5.3 Explanatory variables

Material SDoH were represented by four variables: net household wealth (high, medium, low), subjective social status (high, medium, low), the last occupation (managerial/professional, intermediate, semi/routine) and education (A-level or higher, O-level or equivalent and less than O-level). Psycho-social SDoH reflected aspects of social engagement, social support and individual sense of control. Social engagement was measured through individual participation in community organizations. A person was defined as very active if they took part in 3 or more community organizations and active if they participated in 1 or 2. Perception of loneliness was a binary variable (yes/no). Social support was represented by the variables supportive children (very/some, a little/not at all, no children), supportive friends (very/some, a little/not at all, no friends) and supportive partner (very/some, a little/not at all, no partner). Behavioural SDoH were represented by the variables physical activity (vigorous, moderate, mild, none), alcohol consumption (never, monthly or less, weekly, daily) and tobacco smoking (never, ex-smoker, current smoker). Confounding variables were: wave (with values 1 to 7), age (categorized in 5-year bands and 90+ years age band) and a binary variable for sex.

4.6 Calculation

All explanatory and outcome variables were time-varying. We chose to use the population-averaged regression method rather than subject-specific regression. This is more appropriate as our focus is on the differences in the risk of multimorbidity between population groups and not between individuals (Muller and MacLehose, 2014). We used the Generalized Estimating Equations (GEE) model which extends standard regression analysis by taking into account correlation between repeated measurements. The GEE models estimate the average occurrence of an outcome for a group over time. The advantage of GEE is that they use robust estimation of standard errors to allow for clustering

(correlation) between individuals. The standard errors are derived from the observed variability in the data rather than variability predicted by the model (Twisk, 2013). The GEE method adjusts for within-subject correlation by assuming an a priori correlation structure for the repeated measurements of the outcome variables. Correlation matrices for each of the three outcomes showed a decrease in correlation coefficients with increasing time between the measurements, which justified the choice of an autoregressive correlation structure (Twisk, 2013). Confounding factors of time (wave of measurement), age (varying between waves) and sex were taken into account in our regression models where both the explanatory factors and confounders were included as covariates. The associations were measured in odds ratios as our outcome variables were all binary and it is a common measure of health inequalities in large population-based studies (Di Lorenzo et al., 2014). In order to give additional effect to those who dropped out of the analysis, we used longitudinal weights. They calculated the inverse predicted probability of response among respondents who responded to all previous waves and multiplied that weight by the previous wave's longitudinal weight (Banks et al., 2018). Analyses were conducted in Stata version 13.

4.7 Results

The general characteristics of the studied population are presented in Table 4.2. The number of participants decreased from 10,331 (wave 1) to 7,130 (wave 7). The retained population are those who remained in the study and took part in the self-completion interviews. The mean age was 66 years (SD 10.9). The proportion of women was 55.3%. All longitudinal studies are subject to problems with non-response and attrition and these problems are starker in studies of ageing where rates of attrition tend to be higher (Banks et al. 2016). In our study respondents who took part in all waves of measurements were different to those who dropped out or refused to fill in the self-completion

interview. The retained cohort was slightly older (mean age 67 years compared to 66.2 years), more female (56.2% versus 54.9%) and more affluent (23.3% in the top wealth tertile compared to 21.6%). The core cohort was also more active, with a third conducting vigorous PA compared to 27% of those who dropped out at one or more occasions. A quarter of them was very active in their community compared to 17%. The problem of the differences between the two populations was less relevant for our analysis because we focused on all core members rather than just those who took part in all waves of measurements.

Table 4. 2 Descriptive sample characteristics

	N	%		N	%
Measurement occasions	56,202		Sense of control		
Basic MM	26,179	46.6	High	15,513	27.6
Complex MM	9,663	17.19	Some	35,708	63.54
MFL10+	6,345	11.29	Low	3,608	6.42
Mean age (SD)	66(10.9)		Partner support		
Age group (years)			A lot/some	37,399	66.54
50-54	5,576	9.92	A little/not at all	1,549	2.76
55-59	10,074	17.92	No partner	16,953	30.16
60-64	10,434	18.57			
65-69	9,569	17.03	Children support		
70-74	8,166	14.53	A lot/some	43,693	77.74
75-79	6,233	11.09	A little/not at all	4,230	7.53
80-84	3,791	6.75	No children	7,895	14.05
85-89	1,789	3.18			
90 plus	570	3.18	Friends' support		
			A lot/some	42,705	75.98
Females	31,106	55.3	A little/not at all	9,076	16.15
			No friends	3,946	7.02
Physical Activity					
Vigorous	16,327	29.05	Loneliness		
Moderate	27,124	48.26	Yes	6,720	11.96
Mild	8,319	14.8			
No	4,416	7.86	Household wealth		
			Top	12,244	21.79
Alcohol consumption			Medium	32,358	57.57
Never	6,635	11.81	Low	10,490	18.66
Monthly or less	15,661	27.87			
Weekly	14,111	25.11	SSS		
Daily	18,661	33.2	Top	9,080	16.16
			Medium	38,025	67.66
Smoking			Low	6,756	12.02
Never	21,041	37.44			
Ex-smoker	27,526	48.98	Occupational level		
Smoker	7,564	13.46	Managers/professionals	18,555	33.01
			Intermediate	13,895	24.72
Participation			Semi/routine	22,334	39.74
Very active	11,162	19.86			
Active	26,940	47.93	Educational level		
Not active	15,142	26.94	High	18,418	32.77
			Medium	14,436	25.69
			Low	23,088	41.08

The probability of people aged 50 or older in England to develop multimorbidity, complex multimorbidity and 10 or more functional limitations has increased between 2002 and 2014-15 (Table 4.3). Compared to 2002/03, the odds of having multimorbidity in 2014/15 were 2.33 times larger (95% CI 2.14–2.54), the odds of having complex multimorbidity 2.57 times larger (95% CI 2.29-2.88) and the odds of having MFLs 2.28 times larger (95% CI 1.97-2.65). The probability of having multimorbidity increases with age across the three measures. The increase peaked in multimorbidity at the age 85-89 years and in complex multimorbidity at the age 80-84 years. Females were more likely to have basic MM (OR 1.31, 95% CI 1.21 – 1.41), complex MM (OR 1.26, 95% CI 1.14 – 1.38) and MFLs (OR 1.24, 95% CI 1.1 – 1.4).

Table 4. 3 Basic multimorbidity, complex multimorbidity and functional limitation by year of measurement, age and sex

	Basic MM		**Complex MM**		**MFLs**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
Year						
2002/03	1		1		1	
2004/05	0.87	0.82-0.92	1.06	0.96-1.17	1.38	1.22-1.57
2006/07	1.07	1.01-1.13	1.17	1.05-1.29	1.70	1.50-1.93
2008/09	1.42	1.33-1.52	1.79	1.62-1.99	1.43	1.24-1.63
2010/11	1.61	1.51-1.73	2.07	1.86-2.29	1.60	1.39-1.83
2012/13	1.69	1.56-1.82	2.26	2.03-2.52	1.47	1.26-1.69
2014/15	2.33	2.14-2.54	2.57	2.29-2.88	2.28	1.97-2.65
Age group (years)						
50-54	1		1		1	
55-59	1.23	1.11-1.37	1.36	1.09-1.68	1.17	0.94-1.44
60-64	1.61	1.43-1.81	1.97	1.57-2.48	1.27	1.01-1.61
65-69	2.16	1.90-2.45	2.63	2.08-3.33	1.29	1.04-1.66
70-74	2.95	2.59-3.38	3.52	2.76-4.48	1.50	1.15-1.93
75-79	4.14	3.59-4.79	4.37	3.41-5.60	1.72	1.31-2.24
80-84	4.98	4.24-5.86	5.41	4.19-7.01	2.11	1.61-2.79

85-89	5.89	4.81-7.23	4.56	3.42-6.00	2.73	2.03-3.67
90 plus	4.70	3.40-6.51	3.33	2.33-4.75	3.44	2.38-4.97
Females	1.31	1.21-1.41	1.26	1.14-1.38	1.24	1.11-1.41

4.7.1 Material determinants

We observed a health gradient across the three levels of household wealth in basic multimorbidity, complex multimorbidity and multiple functional limitations (Table 4.4). Compared to the population group with the highest wealth, those with the lowest wealth had 47% higher odds of basic MM, 73% higher odds of complex MM and 91% higher odds of 10+ functional limitations (Table 4). Low subjective social status was associated with higher odds of having all three outcomes compared to reporting high SSS, with odds ratios at 1.14 (95% CI 1.04-1.24), 1.2 (95% CI 1.07-1.35) and 1.35 (95% CI 1.15-1.59) respectively. People in routine or semi-routine occupations had higher odds of having basic multimorbidity and MFLs than people in the managerial and professional group, with odds ratios at 1.07 (95% CI 1.04-1.24) and 1.2 (95% CI 1.04-1.38) respectively. People with basic education had higher odds of having MFLs than people with at least A-levels (OR 1.1, 95% CI 1-1.21).

Table 4. 4 Basic multimorbidity, complex multimorbidity, functional limitation and material determinants

	Basic MM		**Complex MM**		**MFLs**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
Household wealth						
High	1		1		1	
Medium	1.13	1.10-1.19	1.20	1.09-1.31	1.28	1.12-1.47
Low	1.47	1.34-1.61	1.73	1.52-1.96	1.91	1.60-2.27
Subjective social status						
High	1		1		1	

Medium	1.04	0.98-1.10	1.11	1.00-1.20	1.09	0.97-1.24
Low	1.14	1.04-1.24	1.21	1.07-1.35	1.35	1.15-1.59
Occupation						
Manager/prof.	1		1		1	
Intermediate	0.93	0.85-1.01	0.92	0.81-1.03	1.03	0.88-1.20
Semi/routine	1.07	1.04-1.24	1.03	0.92-1.15	1.19	1.04-1.38
Education						
A-level+	1		1		1	
o-Level or equiv.	0.93	0.86-1.00	0.92	0.81-1.03	0.88	0.76-1.02
Less than o-Level	1.02	0.97-1.07	1.04	0.92-1.16	1.1	1.00-1.21

4.7.2 Psycho-social determinants

Relationships between the predictors of social support and our outcomes were limited (Table 4.5). We observed that on average people without friends had 14% higher odds of basic multimorbidity than people whose friends were very supportive or supportive to some degree. Similarly people with no partner had odds of having basic multimorbidity and multiple functional limitations higher than those who reported having supportive partner, with OR 1.15 (95% CI 1.06-1.26) and 1.13 (95% CI 1.02-1.26) respectively. The perception of loneliness was positively associated with all three outcomes: for basic MM OR 1.18 (95% CI 1.10-1.26), for complex multimorbidity OR 1.21 (95% CI 1.11-1.32) and for MFLs OR 1.31 (95% CI 1.18-1.46). The relationship between the sense of control and the probability of having each of our health outcomes was graded by the degree of the perceived control. The odds ratios were higher for MFLs than for the other two outcomes. Participation in community was not associated with multimorbidity and complex multimorbidity (Table 4.5). The odds of having MFLs increased the less people participated, with those not active in community having 26% higher odds (95% CI 1.10-1.45) than those who were very active.

Table 4. 5 Basic multimorbidity, complex multimorbidity, functional limitation and psycho-social determinants

	Basic MM		Complex MM		MFLs	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
Participation						
Very active	1		1		1	
Active	0.97	0.92-1.03	1.03	0.95-1.12	1.12	1.01-1.27
Not active	1.04	0.96-1.12	1.01	0.91-1.12	1.27	1.11-1.46
Sense of control						
High	1		1		1	
Some	1.21	1.16-1.27	1.28	1.20-1.37	1.82	1.64-2.01
Low	1.57	1.41-1.74	1.70	1.51-1.91	3.31	2.84-3.84
Supportive children						
Very/some	1		1		1	
A little/not at all	1.02	0.94-1.11	1.02	0.90-1.15	1.15	1.00-1.32
No children	0.96	0.86-1.07	0.98	0.86-1.11	0.93	0.79-1.08
Supportive friends						
Very/some	1		1		1	
A little/not at all	0.99	0.94-1.06	0.96	0.89-1.04	1.03	0.93-1.13
No friends	1.14	1.02-1.26	1.07	0.95-1.2	1.09	0.95-1.25
Supportive partner						
Very/some	1		1		1	
A little/not at all	0.93	0.81-1.07	0.98	0.81-1.18	0.99	0.79-1.22
No partner	1.15	1.06-1.26	1.03	0.94-1.14	1.13	1.02-1.26
Loneliness						
Yes	1.19	1.11-1.28	1.22	1.12-1.33	1.31	1.18-1.46

4.7.3 Behavioural determinants

The relationship between physical activity and the probability of having each of our health measures was graded by the level of intensity of physical activity (Table 4.6). Compared to those who exercised vigorously, people who were physically inactive had 1.6 times larger odds of having basic MM (95% CI 1.21 –

1.41), twice larger odds of having complex MM (95% CI 1.78-2.27) and 8 times larger odds of having MFLs (95% CI 7.01-9.69). The frequency of alcohol consumption was associated with our health outcomes but not in the expected way. The probability of developing each of our health outcomes increased with decreasing frequency of drinking (Table 6). The history of smoking was related to the health outcomes. Ex-smokers had higher odds ratios compared to people who never smoked: 1.27 (95% CI 1.17 – 1.37) for basic MM, OR 1.29 (95% CI 1.17 – 1.42) for complex MM and OR 1.3 (95% CI 1.15 – 1.48) for multiple functional limitations.

Table 4. 6 Basic multimorbidity, complex multimorbidity, functional limitation and behavioural determinants

	Basic MM		**Complex MM**		**MFLs**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
Physical activity						
Vigorous	1		1		1	
Moderate	1.22	1.16-1.28	1.32	1.22-1.42	1.81	1.59-2.03
Mild	1.57	1.46-1.68	1.92	1.75-2.12	4.20	3.61-4.85
None	1.60	1.45-1.76	2.01	1.78-2.27	8.19	7.01-9.69
Alcohol consumption						
Don't drink	1		1		1	
Monthly or less	0.90	0.83-0.99	0.79	0.71-0.87	0.73	0.65-0.83
Weekly	0.82	0.75-0.91	0.68	0.61-0.77	0.55	0.47-0.63
Daily	0.81	0.73-0.88	0.65	0.58-0.74	0.51	0.44-0.59
Smoking						
Never	1		1		1	
Ex-smoker	1.27	1.17-1.37	1.29	1.17-1.42	1.30	1.15-1.48
Current	1.03	0.91-1.14	1.04	0.90-1.21	1.43	1.20-1.70

4.8 Discussion

4.8.1 Main results

We have explored the longitudinal association between material, psycho-social and behavioural determinants and three multimorbidity outcomes in an English population of people aged 50 years or older. We found a consistent association between the outcome measures and the levels of household wealth, the sense of control over one's life, physical activity and loneliness. The relationship with smoking and alcohol consumption was not linear but complex, showing signs of reverse causation. Multiple functional limitation and complex multimorbidity captured larger inequalities than basic multimorbidity.

4.8.2 Interpretation

We have presented evidence that a variety of material, psycho-social and behavioural determinants are to varying extents related to basic multimorbidity, complex multimorbidity and multiple functional limitations. We found consistent inequalities in multimorbidity and functional limitation across the levels of household wealth, the sense of control over one's life, physical activity and loneliness. These inequalities appeared larger when measured as multiple functional limitation and complex multimorbidity than basic multimorbidity. Our results suggest that solely materialist models of multimorbidity at older age are insufficient, as behavioural and psycho-social factors play an important role. Behavioural patterns in smoking and alcohol consumption suggest that while health inequality accumulates during the life course, psycho-social resources and active human agency also contribute to shaping the individual health trajectories.

Among material determinants the strongest health disparities were captured by household wealth. Compared to the population group with the highest wealth, those with the lowest wealth had 47% higher odds of basic MM, 73% higher odds of complex MM and 91% higher odds of multiple functional limitations.

The stark disparities support the evidence that the amount of available household wealth or assets constrains individuals' consumption choices on quality of housing, usable outdoor space, type of residential area or quality of health care (Joseph Rowntree Foundation, 2014). Savings also act as a buffer against unexpected loss of income due to ill health in later life thus reducing the exposure to stress. We observed that individuals with the lowest subjective social status had 14% larger odds of having basic MM, 20% larger odds of having complex MM and 35% larger odds of having multiple functional limitations than those with the top SSS. These differences might reflect two-way effects: a very low subjective perception of one's status contributes to worse health but having more complex issues (with simultaneously affected body systems and limited in everyday lives) additionally reinforces the negative rating of individual status (O'Brien, Wyke and Watt, 2014).

Occupational status was weakly associated with basic MM and MFLs and educational qualifications were weakly related to MFLs. In comparison to the measure of household wealth which reflects a process of life-long accumulation, the indicators of education and occupation reflect periods of time from a more distant past. This might explain stronger and more consistent effect of household wealth and suggest that it is a better indicator of an older person's status (Adena and Myck, 2014, McGovern and Nazroo, 2015).

Psycho-social determinants produced mixed results. We found a clear gradient between individuals with the strongest and the weakest sense of control over their lives. The more people felt in charge of their lives the less likely they were to develop ill health. Low control beliefs can affect health in several ways. They may lead to anxiety and aggression which facilitates chronic stress response, smoking and drinking. Feeling low control over destiny can also lead to passive responses such as low self-esteem which induce depression (Whitehead et al., 2016). Loneliness was the other factor consistently related to all of our measures. The feeling of being socially isolated is relatively common among the elderly because some relationships are lost as people get older (Singh and Misra, 2009).

Participation in community groups was a protective factor against the probability of developing 10 or more functional limitations but not protective from multimorbidity. Participating in at least three community groups presupposes certain level of health and physical functioning which acts as a clear barrier for those with at least 10 functional limitations. This health selection process might explain why we can see a social gradient for functional limitations but not for multimorbidities. Other measures of social support showed either no significant relationship or a limited relationship. We found an association with friendship among people with basic MM and MFLs. The effects of support on health of older people depend on the source of support and the quality of relationship. For example relationships with friends can be beneficial to one's health while relationship with family members not (Huxhold, Miche & Schüz, 2014).

In the group of behavioural determinants we found a dose-response relationship between all levels of physical activity and the probability of all three health outcomes. This confirms that the lack of physical activity is an important factor increasing the probability of chronic and complex health problems and limitations in the ageing population (Cimarras-Otal et al., 2014, Dhalwani et al., 2017). Increasing frequency of alcohol consumption seems to have protective effect on the odds of multimorbidity and functional limitation. We suggest that our findings can be explained by reverse causality. Holdsworth, Mendonça, Pikhart et al., (2016) found that older people with good or improving self-reported health were increasing their drinking over time while people with bad or worsening health were moderating their drinking.

The relationship between smoking and both types of multimorbidity is ambiguous. Compared to people who never smoked, ex-smokers were more likely to develop any of the three outcomes but there was no relationship between current smokers and those who never smoked for basic or complex MM. Cross-tabulating smoking, age and prevalence of multimorbidity, we found that ex-smokers were more prevalent among older age groups with higher morbidities and current smokers were younger and healthier. The

explanation of similar findings by Nazroo, Zaninotto and Gjonca (2008) is that when people become ill they might stop smoking. The results for alcohol consumption and smoking exemplify how people in later life continue making active choices within their social context (Elder, 1994).

Multiple functional limitation and complex multimorbidity captured larger inequalities than basic multimorbidity. Working with the basic measure of multimorbidity might limit our ability to see the social heterogeneity of an ageing population. But apart from improving the measure we also need to try to explain why different measures lead to different inequalities. Functional limitation and decline in the elderly is a consequence of chronic disease, with greater effect among people with a higher number of morbidities (Ryan et al., 2015, Jindai et al., 2016). Complex multimorbidity results from dysfunction in three or more body systems. Both outcomes demand complex and long-term care but we know that patients' responses are socially differentiated (Bartley, 2004, Cockerham, 2007). People from higher social backgrounds are capable of using resources such as power, money, knowledge, prestige or social support to protect themselves from health risks or mitigate the consequences of multimorbidity (Link and Phelan, 1995). Taking into account this socially patterned human agency might help to explain why inequalities in complex multimorbidity and multiple functional limitations are stronger than in basic MM.

4.9 Limitations

There are several limitations to our study related to methodology and the scope of analyses. Our study was exploratory and based on using the GEE method with population-averaged data. It allowed us to observe the averaged distribution of certain characteristics between individuals. However this study design does not enable building explanatory analyses or drawing conclusions on both within-individual and between-individual variance or change in outcomes.

Recent studies reported that social determinants do not only influence health simultaneously but also influence each other (Short and Mollborn, 2015, Moor, Spallek and Richter, 2016). For instance, social support can mitigate the effect of stress on people with low social status (Gellert et al., 2018). We have not examined these interaction effects but they could lead to modification of some effects.

We constrained our classification to a generic count of single diseases, ICD-10 chapters and functional limitations without identifying the most frequent combinations. These have been studied either as pairs and triplets or as clusters with the highest degree of association and due to their synergistic effects are of special interest to clinicians (Ng et al., 2018). Unpacking the associational heterogeneity might shed some light on the relationships between these patterns of multimorbidity and specific determinants or groups of determinants.

4.10 Conclusions

Our study was the first study to comprehensively explore materialist, psycho-social and behavioural determinants of health in relation to multimorbidity and multiple functional limitations. Policies aiming to reduce the risk of multimorbidity and functional limitation should address the issue at several levels, as a socio-economic and behavioural intervention. Pension reform policy introducing changes to retirement age which are uniform for all population groups should take into account the evidence of the social gradient in the risk of multimorbidity and functional decline. Behavioural and therapeutic approaches in the community can help to compensate for social isolation, reduced self-esteem or to regain more sense of control over people's lives (Public Health England and UCL Institute of Health Equity, 2015). This strategy should be based around local primary care centres. They could be provided with additional resources to spend more time as the frontline assessors of

multimorbidity and consistent coordinators acting as a link between patients and the specialist health care services (World Health Organization, 2016).

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4.12 Appendix

Different definitions of multimorbidity and social determinants

Table A1. Basic multimorbidity, complex multimorbidity, MM3+ and material determinants

	Basic MM		**Complex MM**		**MM3+**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
Household wealth						
High	1		1		1	
Medium	1.13	1.10-1.19	1.20	1.09-1.31	1.18	1.1-1.28
Low	1.47	1.34-1.61	1.73	1.52-1.96	1.66	1.49-1.86
Subjective social status						
High	1		1		1	
Medium	1.04	0.98-1.10	1.11	1.00-1.20	1.06	0.98-1.14
Low	1.14	1.04-1.24	1.21	1.07-1.35	1.16	1.04-1.28
Occupation						
Manager/prof.	1		1		1	
Intermediate	0.93	0.85-1.01	0.92	0.81-1.03	0.93	0.84-1.04
Semi/routine	1.07	1.04-1.24	1.03	0.92-1.15	1.05	0.95-1.16
Education						
A-level+	1		1		1	
0-Level or equiv.	0.93	0.86-1.00	0.92	0.81-1.03	0.94	0.86-1.05
Less than 0-Level	1.02	0.97-1.07	1.04	0.92-1.16	1.01	0.95-1.09

Table A2. Basic multimorbidity, complex multimorbidity, MM3+ and psycho-social determinants

	Basic MM		Complex MM		MM3+	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Participation						
Very active	1		1		1	
Active	0.97	0.92-1.03	1.03	0.95-1.12	1.03	0.96-1.11
Not active	1.04	0.96-1.12	1.01	0.91-1.12	1.04	0.99-1.24
Sense of control						
High	1		1		1	
Some	1.21	1.16-1.27	1.28	1.20-1.37	1.28	1.21-1.35
Low	1.57	1.41-1.74	1.70	1.51-1.91	1.62	1.44-1.92
Supportive children						
Very/some	1		1		1	
A little/not at all	1.02	0.94-1.11	1.02	0.90-1.15	1.05	0.95-1.16
No children	0.96	0.86-1.07	0.98	0.86-1.11	0.98	0.87-1.09
Supportive friends						
Very/some	1		1		1	
A little/not at all	0.99	0.94-1.06	0.96	0.89-1.04	0.99	0.93-1.06
No friends	1.14	1.02-1.26	1.07	0.95-1.2	1.06	0.95-1.18
Supportive partner						
Very/some	1		1		1	
A little/not at all	0.93	0.81-1.07	0.98	0.81-1.18	0.91	0.78-1.07
No partner	1.15	1.06-1.26	1.03	0.94-1.14	1.11	1.02-1.21
Loneliness						
Yes	1.19	1.11-1.28	1.22	1.12-1.33	1.20	1.14-1.33

Table A3. Basic multimorbidity, complex multimorbidity, MM3+ and behavioural determinants

	Basic MM		Complex MM		MM3+	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Physical activity						
Vigorous	1		1		1	
Moderate	1.22	1.16-1.28	1.32	1.22-1.42	1.29	1.21-1.37
Mild	1.57	1.46-1.68	1.92	1.75-2.12	1.79	1.65-1.94
None	1.60	1.45-1.76	2.01	1.78-2.27	1.78	1.60-1.99
Alcohol consumption						
Don't drink	1		1		1	
Monthly or less	0.90	0.83-0.99	0.79	0.71-0.87	0.80	0.73-0.87
Weekly	0.82	0.75-0.91	0.68	0.61-0.77	0.73	0.65-0.81
Daily	0.81	0.73-0.88	0.65	0.58-0.74	0.69	0.62-0.77
Smoking						
Never	1		1		1	
Ex-smoker	1.27	1.17-1.37	1.29	1.17-1.42	1.31	1.20-1.44
Current	1.03	0.91-1.14	1.04	0.90-1.21	1.11	0.97-1.26

Chapter 5

Material, psychosocial and behavioural pathways to multimorbidity and functional limitation of old people

5.1 Introduction

Rates of multimorbidity - the co-occurrence of multiple diseases within a person – are increasing in the United Kingdom (Kingston et al. 2018) and globally (Garin et al., 2015). More than a quarter of primary care patients older than 18 years in England have multimorbidity (Cassell et al., 2018). As a result of ageing, multimorbidity tends to combine with a decline in physical functioning (Ryan et al. 2015, Jindai et al. 2016). This reduces quality of life (Bayliss et al., 2012) and leads to more primary care consultations, prescriptions and hospitalisations than in people who have no or a single chronic disease (Cassell et al., 2018).

The prevalence of multimorbidity in people older than 65 years in England is projected to increase from 54% in 2015 to 68% in 2035 (Kingston et al., 2018). An additional problem is a persisting inequality in the prevalence of multimorbidity in advanced countries (Tetzlaff et al. 2018; Mondor et al. 2018). People with poorer socio-economic background (Taylor, 2010; Agborsangaya 2012, Schaefer et al. 2012), low education (Johnson-Lawrence, Zajacova & Sneed 2017; Pathirana & Jackson 2018), women (Prados-Torres et al. 2015, Agur et al. 2016), people who smoke, drink alcohol and the physically inactive (Dhalwani et al., 2017) are at higher risk of having multimorbidity in older age.

In order to prevent the growth of prevalence and reduce health inequalities in multimorbidity, we need to better understand what triggers these risks for some and not for others and how they develop over individual lives. We also need to

consider multimorbidity in conjunction with functional limitations and examine if and to what extent their development differs over the life span. Researchers need to consider the role of childhood circumstances and extra-individual social determinants of multimorbidity to assess its causality and temporal trends (Vetrano et al., 2018). The number of studies that have explored longitudinal trends in multimorbidity and their relationship with extra-individual factors is small (Schäfer et al., 2012; Jackson et al., 2015; Pavela and Latham 2015; Dhalwani et al., 2017). Furthermore, the studies that do exist did not develop explicit models of the relationships between the proximate and distal factors affecting multimorbidity. This makes the risk of omitted variables more likely. Some relevant factors may have remained "under the radar", while the role of those observed could have been inflated or attenuated depending on the failure to control for confounders and the inclusion of mediating factors (Frohlich, Corin and Potvin 2001).

Our study builds on a series of contextual analyses of multimorbidity and multiple functional limitations of the ageing population in England. We started with an investigation into the changes in prevalence between 2002 and 2015 as well as modification by age, sex and household wealth (Singer et al., 2019a). We found that multimorbidity and functional limitations were becoming more common in general, more common among women than men and among individuals with less wealth than more wealth. In the next step, we expanded the analysis by exploring the role of material, psychosocial and behavioural determinants. We found that household wealth, sense of control over individual life, physical activity and loneliness were associated with the risk of having multimorbidity and functional limitation (Singer et al, 2019b). However, the analysis did not attempt to establish the causal direction of these associations.

Our paper builds on the existing knowledge and on our own findings by setting out the following research questions:

What are the effects of childhood circumstances (social class, self-rated health and adverse childhood experiences) on individual differences in old age multimorbidity and functional limitation?

What is the role of material, psycho-social and behavioural pathways in mediating effects of childhood circumstances on individual differences in old age multimorbidity and functional limitation?

In order to achieve these goals, this paper develops a theoretical framework for life course pathways to multimorbidity and functional limitation. We have empirically tested this using data from the English Longitudinal Study of Ageing 2002-2018, including data on participants' childhood circumstances collected in 2006/2007.

5.2 Lifecourse models of health

Chronic disease and multimorbidity are characterized by a time lag between exposure to negative experiences and diagnosis or manifestation of a chronic disease and later development of other diseases. More specifically, it is the gradual accumulation of mundane experiences, wearing down the body systems rather than rare exceptional events that is characteristic for the period leading to the onset of multimorbidity (Hertzman and Boyce 2010). The onset is socially patterned. For example, people living in socially deprived areas of Scotland acquired multimorbidity 10-15 years earlier than people from affluent areas (Barnett et al. 2012). These features make inequalities in multimorbidity an appropriate subject for life course studies.

Life course analyses explore simultaneously the biological and social contexts and development of individual health and disease (Bartley, Blane, and Davey Smith, 2005). The common premise behind all life course approaches is that the antecedent circumstances in an individual's life influence the health states and their rate of change across an individual's life course. Therefore they explicitly require temporal ordering of exposures and their mutual relationships (Kuh et al., 2003). A variety of theoretical life course models have been formalized (Ben-Shlomo and Kuh 2002). The *critical period model* assumes that an exposure only has an effect within a circumscribed time window, an observation elaborated earlier by Kuh and Wadsworth (1993). For example, growth retardation in utero can change several physiological processes for the rest of life, such as cardio-metabolic, immune or inflammatory systems (Haas and Oi 2018). The concept of a sensitive period assumes exposures can act across multiple time windows but some are more sensitive to a specific exposure (Ben-Shlomo and Kuh, 2002). For example, smoking during puberty may have a stronger risk on future breast cancer than post-pubertal cigarette consumption (Clarke and Joshu, 2017). Barker and colleagues put forward the developmental origins of health and disease model arguing that chronic diseases resulted from short term

developmental perturbations that had long term maladaptive effects (Barker, 1998).

The *accumulation of risk model* postulates that factors increasing disease risk or protection from disease accumulate over a life time (Ben-Shlomo and Kuh 2002). For instance, a child from a poor family is more likely to fail at school, leave school at an early age, take up unskilled work that is hazardous and badly paid and, when retired, spend the rest of their life in financial insecurity. Early life advantage or disadvantage sets individuals on diverging *pathways or chains of risk*, as one exposure leads to another. The process is not deterministic but has been expressed as a probabilistic cascade, capturing how risks build up over time (Ferraro, Schafer and Wilkinson 2016).

Rather than being mutually exclusive, both models are combined in research practice (Ben-Shlomo, Cooper and Kuh 2016). Critical (sensitive) period, accumulation and pathways are increasingly treated as mutually entangled trends. For instance, Hallqvist et al. (2004) compared three hypotheses: critical period, accumulation and the role of social mobility in their study of trajectories leading to myocardial infarction. The study found strong interdependence between the critical period, accumulation and social mobility patterns. Power and Hertzman (1997) suggested that it might be useful to start thinking in terms of the relationship between latency (early-life) and pathway (or path-dependency) effects.

Despite their interdependencies, it is important to distinguish between critical/sensitive period models and accumulation of risk models because they can inform the timing of possible preventive interventions to reduce health inequalities (Green and Popham, 2017). Life course models can guide the choices about whether action must take early in life or whether it could be more effective when risk factors may be present but before disease onset. This is the time when individuals may be more willing to engage in preventative actions.

5.2.1 Socio-economic inequalities

The Black Report (Black, 1980) put forward four possible explanations for socio-economic inequalities in health: artefact (no relationship between social class and health), selection (health determines social class position), materialist (multi-faceted social class affects health) and cultural/behavioural (socially patterned risky behaviours affect health). These explanations later turned into competing perspectives guiding subsequent research, especially divided between proponents of health selection versus social causation (Warren, 2009) and materialist versus psychosocial (Marmot & Wilkinson, 2001) or materialist versus behavioural approaches (Davey Smith, Blane & Bartley 1994). The arrival of life course theory allowed researchers to redefine these hypotheses into temporal pathways and to integrate them into a coherent framework (Macintyre, 1997; Moor, Spallek and Richter, 2016).

Material pathways link lower social class position to health and mortality through the role of occupational status, income and financial wealth across the life course. Material inequality can affect health in two ways, either through the lack of resources of individuals and/or through the under-investment in services and community infrastructure (Kaplan et al., 1996; Lynch 2000) which may interact. Within this pathway, studies identified a range of determinants, such as working conditions (Benach, Muntaner, Solar et al. 2013), housing conditions (Krieger & Higgins 2002), neighbourhood deprivation (Pickett & Pearl, 2001; Barnett et al., 2012) and environmental pollution (Briggs, 2003).

Lack of education is a major determinant through which inequality is passed between generations (Bartley 2017; Cockerham 2007) as it reflects parental social class. Research has found that socially patterned literacy levels (i.e. number of books at home) translate to school achievement in childhood and adolescence which has implications for the risk of school drop-out and the total time spent in education (Due et al., 2011). A child from a family with multiple disadvantages is more likely to fail at school, leave it at an early age and take up unskilled work. There is a higher probability that when retired, the person

spends the rest of their life in financial insecurity and with disease accumulation (Bartley, 2017; Due et al., 2011).

The *psychosocial* pathway comprises a variety of psychosocial resources, such as leisure, social activities and networks, from the level of the family or household out to the wider community and society (Bartley, 2004). These pathways benefit health by providing social support, social influence and attachment, and access to resources and goods (Berkman and Glass, 2000). The perception of control over life is another determinant with effects on later health (Whitehead et al., 2016). One pathway associated with the lack of subjective control acts through passive response and induced depression. An alternative route is through chronic stress leading to higher risk of cardiovascular disease and lower endocrine and immune function (Bosma, 2006). Research has also reported a relationship between multimorbidity and social support. The risk of multimorbidity was reduced for people living as a couple, in a family, who had a large social network and a sense of control over their lives (Marengoni et al., 2011).

Behavioural pathways (or health behaviours) define how consumption and leisure activities affect health and are, to some extent, modifiable by individual decision-making (Bartley, Blane, and Smith Davey, 2005). Examples of health behaviours include physical activity, smoking, substance use, diet, risky sexual activities, health care seeking and adherence to prescribed medication (Short and Mollborn, 2015). Individuals with a higher number of risk factors are more likely to develop multiple health issues than those who engage in only one type of risky behaviour (Fortin et al. 2014, Dhalwani et al. 2017; Katikireddi, 2017). Several theories exist to explain behavioural inequalities. Bourdieu (1984) notes that members of the same class do not consciously choose to act in a risky way. Instead, they reproduce practices, formed within their social locations, which instil them with a corresponding world view and values. Factor, Kawachi and Williams (2011) proposed that engaging in risky behaviours forms part of practices of resistance by minority groups as long as healthy lifestyles are associated with the dominant groups and ideas.

Material, psycho-social and behavioural pathways are commonly described as the key life course mechanisms explaining socio-economic inequalities in health (Bartley, Blane, and Smith Davey, 2005; Van Lenthe et al., 2014). A review of studies using this classification of pathways (Moor, Spallek and Richter, 2016) found that most studies have focused on single pathways, which led to an over-estimation of their effects. In contrast, only four studies examined all three pathways simultaneously (Moor, Spallek and Richter, 2016). The review found that material conditions were the strongest mediator of the relationship between socio-economic status and self-reported health, which supports the materialist hypothesis from the Black Report. However, all studies were based on cross-sectional data which makes causal interpretation problematic.

5.2.2 Adverse experiences

Childhoods differ by more than just their socio-economic positions. Adverse childhood experiences (ACEs) include direct harm to children (physical, sexual, verbal abuse) and indirect experiences such as domestic violence, parental separation, substance absuse, mental illness and crime (Hughes et al. 2017). ACEs have been recognized as important determinants of adult health (Felitti, et al., 1998) for adult mental health, respiratory disease, cardio-vascular diseases, cancer, diabetes and risky health behaviours including self-harm (Felitti et al., 1998; Taylor et al. 2015).

The ways in which early adversity contributes to the risk of multimorbidity and functional limitation remains unclear. There is some evidence for the behavioural pathway where individuals with a history of ACEs adopt hazardous lifestyles (Sinnott et al., 2015). Other studies proposed that adversity in childhood creates a vulnerability to increased chronic stress later in life (Raposa et al., 2014) which translates into higher risks of mental and physical health problems (Font and Maguire-Jack, 2016). Therefore early adversity should be considered simultaneously with childhood social class in any life course model of multimorbidity. Distinguishing between the causal chains of social class and

those of adverse experiences will help better understand the explanatory mechanisms behind the development of adult multimorbidity.

5.2.3 Childhood health

Experiences of poverty, parental abuse, neglect or domestic violence can be intertwined with concurrent child health problems. Childhood health is another determinant that can influence later health development of individuals (Haas 2006; Haas and Oi, 2018; Pavela and Latham 2015). Early studies of this relationship used birthweight, child's height and weight as proxies for health or nutrition and showed an inverse relationship between the scores in childhood and later health outcomes (Bartley, Blane, and Smith Davey, 2005). The collection of more specific medical information in the British Birth cohorts facilitated a direct examination of health development from early years to young and middle age. For example, participants with chronic illnesses in childhood were at a higher risk of chronic disease, psycho-social problems and social isolation at age 23 years (Power, 1992). In the U.S., self-reported conditions in childhood were directly associated with cancer, lung disease, cardiovascular conditions, and arthritis/rheumatism in a nationally representative sample of Americans aged 55 to 65 years (Blackwell, Hayward and Crimmins, 2001). The associations were explained by direct biological effects (the critical period) but social pathways were also found to be relevant. Using a U.S. longitudinal study covering the period 1968-1996, Haas (2006) developed a mediation model showing that socio-economic deprivation increased risk of poor birth outcomes and childhood illness. Children with worse health later completed education at an earlier age, progressed to lower status occupation, leading to lower income and household wealth. The social pathway was associated with worse adult health (Haas, 2006).

5.2.4 Multimorbidity and functional limitation

Life course models of multimorbidity and functional limitation are rare. Those that exist (Pavela & Latham, 2015; Ferraro, Schafer and Wilkinson, 2016; Haas & Oi, 2018) conceptualized multimorbidity as a multi-causal phenomenon and used multiple domains of circumstances in childhood and adult life. Pavela and Latham (2015) used recalled information about childhood SES and health and adult multimorbidity observed over 18 years in the Health and Retirement Study in the U.S. After controlling for adult SES and adult health behaviours (obesity, smoking, visiting a doctor in the past 2 years, having health insurance), the study found no effect of childhood SES, but the effect of childhood health did persist. They characterized the model as the accumulation of risk where the socio-economic circumstances from early life followed a pathway model while the childhood health effects reflected a critical period model. The authors concluded that childhood health seemed to be an indicator for an increased risk of multimorbidity.

Haas and Oi (2018) used multimorbidity and functional limitations as alternative outcomes. They found that, despite variation across 13 European countries, the relationship between childhood illness with multimorbidity and functional limitations in later life persisted in the presence of adult socioeconomic circumstances and health behaviours. The effects of childhood social class were attenuated by socio-economic circumstances in adulthood. Unlike the two previous studies, which built models in a series of stepwise logistic regressions, Ferraro, Schafer and Wilkinson (2016) explicitly tested hypothesized pathways via a mediation model of multimorbidity. Using data from the National Survey of Midlife Development in the United States, childhood disadvantage was measured across three domains – SES, family composition and abuse with three types of pathways considered: SES (index composed of years of education, household income and financial strain), lifestyle risk (obesity, smoking, drinking) and psychological resources (family and friend support, family and friend strain, a scale of social integration and the level of personal control). Childhood social deprivation was indirectly related to

multiple health problems via smoking and lack of personal control. The physical and emotional abuse in childhood affected later health through smoking, lack of family support and personal control. The limited evidence indicates that social and psychological factors in childhood influence the risk of multimorbidity and functional limitation in late life but the effects are mediated via material, psychosocial and behavioural pathways. However, it is important to note that the impact of childhood health was not tested by Ferraro, Schafer and Wilkinson (2016).

5.3 Life course model of multimorbidity and functional limitation for ageing people in England

In order to answer our research questions, Figure 5.1 represents a framework that identifies pathways to multimorbidity and multiple functional limitation from childhood to adult and old age. Both direct and indirect effects of childhood circumstances on health in old age are included. We expect that the paths will follow the accumulation of risk model with mediation through independent material, psychosocial and behavioural indirect effects (pathways) which may or may not explain the total effect leaving little or no direct effect. We adopt a theoretically informed "life stage" approach (Stone, Netuveli and Blane, 2014). We assume that a series of social exposures during life will contribute to the total effect on multimorbidity in a cumulative rather than a simple additive effect, i.e. some periods in life have greater importance than others. For this reason, we chose four life stages where literature has documented specific effects on individual health process. Some of them (childhood, adolescence) can be related to the concept of *sensitive period* from lifecourse epidemiology (Ben-Shlomo and Kuh, 2002; Stone, Netuveli and Blane, 2014). We extend the idea of sensitivity from the biological to the social terrain by including the cohort aged between 50 and 64 years. In Britain, this is the period in life when individual and household wealth is at its peak and surpasses

the role of income (Crawford, Innes and O'Dea, 2016). A detailed analysis of the pathways of accumulation for this age cohort revealed that the accumulation is wider than economic, involving psychological and cultural mechanisms (McGovern and Nazroo, 2015). Individual differences in smoking, alcohol consumption, physical activity and BMI at age 59 years predicted greater differences in the probability of developing multimorbidity than at younger or older ages (Katikireddi et al., 2017). This adds to the relevance of the pre-retirement life stage for our model, as the focus is on pathways to inter-individual differences in old age health.

In order to capture a diversity of experiences that might differ between children, we use three domains of childhood circumstances: social class, adverse childhood experiences and self-rated health. We acknowledge their mutual inter-relationships by allowing them to correlate in the model (Hoffman, Kröger and Geyer, 2019). In line with the accumulation of risk theory and the findings summarized in Sections 5.2.1 to 5.2.4, we expect that the differences in the social class of children will set them on diverging material, psychosocial and behavioural pathways. Children in higher socio-economic positions will increase their likelihood of improving their material and psychosocial circumstances as well as health-related behaviours in pre-retirement. These differences will in turn increase their likelihood of lower multimorbidity and functional limitation. Similarly, we expect that those who avoided adverse experiences in childhood will be more likely to score better in the measures of adult social class, psychosocial support and health behaviours, which will translate to a lower degree of multimorbidity and functional limitation.

It is unlikely that the indirect effects of childhood circumstances on multimorbidity and functional limitation can exist without some mediation through the health status. Our model tests for this possibility by predicting direct effects of childhood exposures on the risk of multimorbidity in pre-retirement which then affects the risk of multimorbidity and functional limitation in the old age. These paths are illustrated as red arrows in Figure 5.1 to distinguish them from the other pathways. At the same time we assume

that multimorbidity at pre-retirement can act as confounder of the relationships between the pre-retirement mediating factors and the outcomes (illustrated by the red arrows leading from multimorbidity in pre-retirement to the mediators and to the outcome variables).

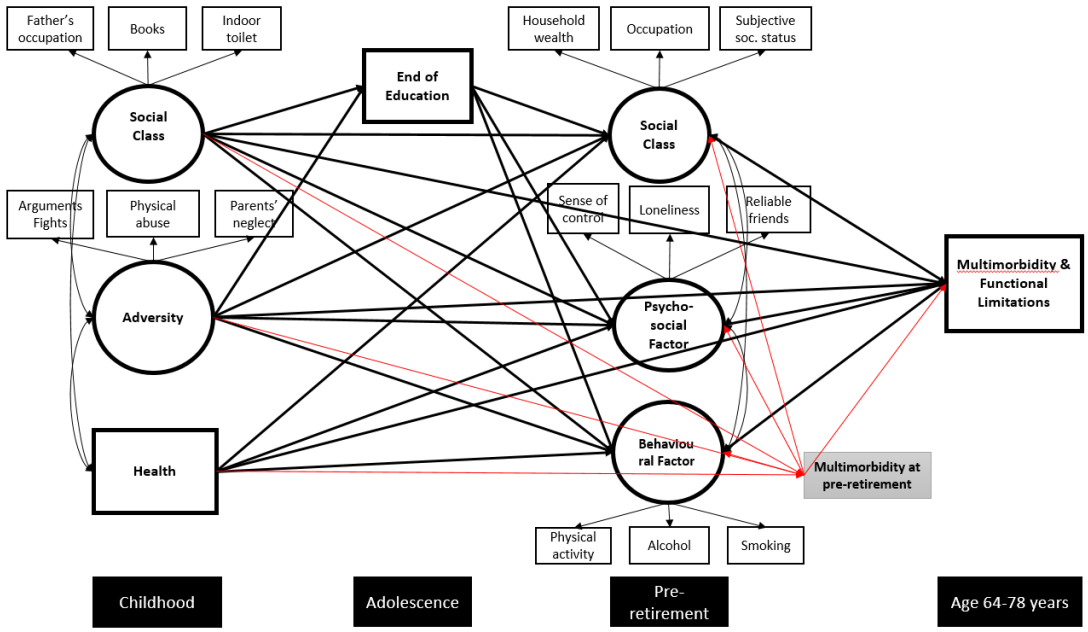

Figure 5. 1 Theoretical framework for lifecourse pathways to multimorbidity and functional limitation. The circles indicate latent variables whilst squares indicate measured variables.

Several more assumptions in our model of lifecourse multimorbidity include: (a) Moving from left to right assumes passage of time, (b) vertically aligned variables are contemporaneous and (c) relations among contemporaneous variables are correlational. The correlation reflects that the causal order is unknown. (d) directional relations express the passage of time. (e) there are no additional unmeasured confounders in the model (f) measurement error is minimal. These conditions, although unrealistic, determine the hypothetical path that can exist between two variables in our model (MacKinnon, Fairchild and Fritz, 2007).

5.4 Data

The English Longitudinal Study of Ageing (ELSA) is a representative study using a panel of individuals aged 50 years and older in England. ELSA is focused on understanding the physical, psychological, social and economic aspects of ageing. The first wave of ELSA was carried out in 2002 and over 12,000 core sample members and their partners were interviewed during this wave. Participants are interviewed every two years, with a total of eight waves of observations. Retrospective data on the participants' childhood were collected in the Life History interviews recorded at wave 3.

Following from our conceptual framework (Fig. 5.1) we merged the recalled data from the Life History interviews with data from wave 1 and wave 8 in order to achieve the maximum time lag between the measurement of the hypothesized mediators and their effects on the outcome. Only individuals who took part in Life History interviews, wave 1 and wave 8 were selected for analyses. The final selection included only those who were aged 50-64 years (n) at wave 1 and 157 cases were excluded from analysis due to missing values on all variables. The resulting sample size was 3,088 individuals. We took into account the longitudinal complex structure of the data by using three types of variables provided by ELSA. A stratification variable took into account the geographic stratification, a cluster variable addressed the non-independence of observations due to cluster sampling and the longitudinal weight at wave 8 to deal with the unequal probability of selection.

Table 5. 1 Variables selected for the analysis

Variable	Category	Number	Frequency
Wave 1			
Sex			
Male	1	1391	45.0
Female	2	1697	55.0
Occupation			

High	1	1178	39
Intermediate	2	709	23.5
Low	3	1130	37.5
Household wealth			
Top	1	835	27.6
Medium	2	1858	61.4
Low	3	333	11
Subj. social status			
Top	1	591	19.4
Medium	2	2215	72.8
Low	3	235	7.7
Sense of control			
Maximum	1	1245	40.8
Some	2	1691	55.4
Low	3	118	3.9
Loneliness			
No	1	2804	91.1
Yes	2	275	8.9
Physical activity			
Vigorous	1	1108	35.9
Moderate	2	1515	49.1
Mild	3	305	9.9
No	4	158	5.1
Alcohol consumption			
Don't drink	1	212	6.9
Monthly or less	2	806	26.1
Weekly	3	1145	37.1
Daily	4	925	30
Smoking			
Never	1	1171	37.9
Ex-smoker	2	1317	42.6
Current smoker	3	600	19.4
Recall at wave 3			
Main carers job			
Higher	1	819	26.7
Intermediate	2	1187	38.7
Lower or poor	3	986	32.1
Other	4	79	2.6
Number of books			
Many	1	548	18.5
Some	2	1710	57.6
Few or none	3	710	23.9
In-door toilet			
Yes	1	2046	68.5

No	2	941	31.5
Physical abuse			
No	1	2575	96.2
Yes	2	103	3.8
Parents' neglect			
No	1	2482	92.9
Yes	2	190	7.1
Arguments & Fights			
No	1	2071	78.4
Yes	2	571	21.6
Child's health			
Excellent	1	1133	36.9
Very good	2	1009	32.9
Good	3	578	18.8
Fair	4	258	8.4
Poor	5	89	2.9
Educational completion			
Age 17 years or older	1	1074	34.8
Age 14-16 years	2	2013	65.2
Wave 8			
Basic multimorbidity			
0 conditions	1	359	16.4
1	2	591	27
2	3	531	24.3
3	4	379	17.3
4	5	165	7.6
>5 conditions	6	160	7.3
Complex multimorbidity			
0 ICD chapters	1	360	16.5
1	2	654	29.9
2	3	611	28
3	4	377	17.3
>4 ICD chapters	5	183	8.4
MFL			
0 FLs	1	605	27.7
1	2	424	19.4
2	3	278	12.7
3	4	170	7.8
4	5	125	5.7
5 to 9	6	341	15.6
10 or more	7	242	11.1

5.5 Measures

Data on childhood and the age of educational completion originate from self-reported interviews collected in ELSA at wave 3 (2006-07). The variables Adversity, Social Class (in childhood and pre-retirement), Psychosocial Factor and the Behavioural Factor were measured as latent factors. Latent constructs represent processes which are not directly measurable and are only identifiable through chosen indicators.

Social Class in childhood

Social class is a key determinant of health (Bartley, 2017; Krieger, 2011). It is a marker of social stratification, leading to socio-economic inequality between individuals that transmits from generation to generation (Link and Phelan, 1995; Bartley 2017; Cockerham, 2007). The concept of social class is more appropriate for our aims than the concept of socio-economic status, which typically reflects direct indicators such as income, educational attainment and occupational classification. This reduces class position to single economic issues and complicates the explanation of the underlying mechanisms between social positions and health (Galobardes et al., 2006; Nazroo, 2017). Social class reflects both objective aspects of social stratification as well as its subjective dimension, i.e. cultural differences between people and their self-identification in the social hierarchy (Kraus, Piff and Keltner 2011). Wealth, education, and occupational status combined form the objective substance of social class (Kraus, Piff and Keltner, 2011; Oakes and Rossi, 2003). These objective domains of social class give rise to patterned distinctions in the material lives of individuals: living in different areas, belonging to different social clubs, attending different schools, enjoying different forms of leisure, wearing different clothes (Kraus, Piff and Keltner, 2011). To the extent that these stratified behaviours are observable and associated with individual wealth, occupation and education, they become signals to others of a person's social class.

In the absence of data on parental income and education in ELSA Life History interviews, Social Class was measured by three indicators. The number of books at home exemplifies inter-generational reproduction of social stratification and class identity (Krieger, 2011). The measure was found to independently affect quality of life at later life in Australia (Kendig et al., 2016) suggesting it is a useful measure within our framework. The presence of an indoor toilet at home articulated the aspect of material circumstances of households for children born between 1938 and 1952 in England. The third dimension of social class is represented by the father's or main carer's occupational status, a useful measure of health inequality with origins in the UK (Bartley, 2017).

Adversity

There is a limited evidence base about the relationship of ACEs with lower income (Font and Maguire-Jack, 2016; Nurius, Fleming and Brindle, 2019), educational attainment (Raposa et al., 2014), divorce or separation (Font and Maguire-Jack, 2016), risky health behaviours, lack of social support (Nurius, Fleming and Brindle, 2019) and multimorbidity (Sinnott et al., 2015). Physical, emotional or sexual abuse had both direct and indirect effects on negative health outcomes in adulthood while experiences of neglect were related only indirectly (Font and Maguire-Jack, 2016). The risk of subsequent chronic problems and negative health behaviours increases with the number of different types of ACEs reported per individual (Felitti 2002; Bellis et al., 2014).

The latent variable Adversity was constructed from three binary indicators. The variable Arguments & Fights was based on the survey question asking whether parents argued or fought very often when the respondent was younger than 16 years of age. The variable Physical Abuse reflects the question whether the respondent was physically abused by their parents when under the age of 16. The third indicator Parents' Neglect measured whether parents drunk excessively, took drugs or had mental health problems when the respondent

was younger than 16 years of age. The three variables were chosen to reflect aspects of both direct and indirect harm (Hughes et al. 2017).

Health

Self-rated health in childhood, inquired by the question whether the respondent thought their health in childhood was excellent, is coded in five categories: excellent, very good, good, fair or poor.

End of Education

The effect of education on adult health increases with increasing years of education. Additional time spent in education contributes to lower mortality and lower risks of chronic conditions (Cutler and Lleras-Muney, 2006). We categorized the variable into two categories, those who left education before the age of 16 and those who stayed in education after 17 years of age.

Social Class in pre-retirement

An individual's social class before and after retirement in England may have the largest effect through the material resources accumulated since childhood (Nazroo, 2017). These resources are related to previous income, employment and occupational status and combined they affect how individuals perceive their life achievements and social status (Bolam, Murphy and Gleeson, 2004; Nazroo, 2017). In our study social class in the pre-retirement period will be constructed from three indicators. The net household wealth is the sum of savings, investments, physical wealth and housing wealth (after financial debt and mortgage debt were subtracted). It is based on 22 distinct components of wealth and debt (Marmot et al., 2016) and divided into three categories (top, medium, low). The second measure is last occupation, re-categorized from the standard NS-SEC classification into three categories (managerial/professional,

intermediate, semi/routine). The subjective aspect of the social class is reflected in the measure of subjective social status (high, medium, low).

Psychosocial Factor

Psychosocial factors were found to be associated with childhood socio-economic status, health and adversity as well as with later multimorbidity (Pavela & Latham 2015, Sinnott et al. 2015, Ferraro, Schafer & Wilkinson 2016). The latent variable Psychosocial Factor was constructed from three indicators, sense of control, loneliness and reliable friends. The variable Sense of control was measured by the question whether the respondent felt that what happened to them was out of their control. Four options were coded to three categories (never, not often/sometimes, often). Having sense of control over life was found to be a protective factor for the risk of multimorbidity (Marengoni et al. 2011, Melis et al. 2014). The second variable Loneliness (whether respondent felt lonely last week) was binary. Loneliness was associated with multimorbidity in England but the direction of influence remained unclear (Stickley and Koyanagi, 2018). The third variable Reliable Friends had three categories (very/some, a little/not at all, no friends). Supportive friendships as part of social support networks belong to protective factors for multimorbidity (Marengoni et al. 2011).

Behavioural Factor

Physical activity, tobacco smoking, alcohol consumption, diet and BMI were found to independently predict the risk of multimorbidity in Quebec (Fortin et al. 2014), England (Dhalwani et al. 2016, 2017) and Scotland (Katikireddi 2017). Our latent Behavioural Factor was constructed from three indicators: Physical Activity (vigorous, moderate, mild, none), Alcohol (never, monthly or less, weekly, daily) and Smoking (never, ex-smoker, current smoker).

Basic multimorbidity

We follow the most common definition of multimorbidity as "the co-occurrence of two or more diseases within a person" (Van den Akker et al., 1998). This variable was created by summing up the number of morbidities reported by the ELSA participant, separately for each wave of measurement. The minimum number is zero and maximum 5 or more morbidities (Table 5.2).

Complex multimorbidity

Complex multimorbidity was defined as "the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without an index chronic condition" (Harrison et al., 2014, p. 8). We chose it as an alternative measure of multimorbidity as it reflects disease accumulation across disparate body systems. Compared to basic multimorbidity, complex multimorbidity leads to more complex care (Piette and Kerr, 2006) with higher health care utilization. We constructed this measure by selecting only individuals with three or more body systems affected by at least one disease per system. Body systems were classified according to the Chapters of the International Classification of Diseases 10th Revision (ICD-10) (Table 5.2). We grouped the variable to range between zero chapters and maximum of four or more.

Multiple functional limitations

The measure of multiple functional limitations was constructed by combining the variables for mobility, Activities of Daily Living (ADL) and on health symptoms (Table 5.2). ADL refers to the abilities necessary for basic functioning and for living in a community (Chatterji, Byles & Cutler et al., *2015).* The total number of functional limitations per individual was summed up.

Table 5. 2 Health data used to measure basic multimorbidity, complex multimorbidity and multiple functional limitations

	Morbidities	Body systems		Functional limitations
1	High blood pressure	1. **Eye disorders**		**General mobility**
2	Angina	1.1. Glaucoma	1	Walking 100 yards
3	Congested heart failure	1.2. Macular degeneration	2	Sitting for 2 hrs
4	Heart murmur	1.4. Cataracts	3	Getting up from chair
5	Abnormal heart rhythm	2. **Circulatory disorders**	4	Climbing several flights of stairs
6	Heart attack	2.1. High blood pressure	5	Climbing one flight of stairs
7	Diabetes	2.2. Angina	6	Stooping, kneeling or crouching
8	Stroke	2.3. Heart attack	7	Reaching arms above shoulders

9	Lung disease	2.4. Congestive heart failure	8	Pulling or pushing a chair
10	Asthma	2.5. Heart murmur	9	Lifting/carrying weights over 10 pounds
11	Arthritis	2.6. Abnormal heart rhythm	10	Picking up a 5p coin
12	Osteoporosis	2.7. Stroke		**Activities of daily living**
13	Cancer	3. **Endocrine, nutritional and metabolic**	11	Dressing, including putting on shoes and socks
14	Parkinson's disease	3.1 Diabetic eye disease	12	Walking across a room
15	Dementia	3.2. Diabetes	13	Bathing or showering
16	Alzheimer's disease	4. **Musculoskeletal and connective system**	14	Eating, such as cutting up your food
17	Hallucinations	4.1. Osteoporosis	15	Getting in or out of bed
18	Anxiety	4.2. Arthritis	16	Using the toilet, including getting up or down
19	Depression	5. **Respiratory**	17	Using a map to figure out how to get around
20	Emotional problems	5.1. Lung disease	18	Preparing a hot meal
21	Mood swings	5.2. Asthma	19	Shopping for groceries
22	Glaucoma	6. **Neoplasms**	20	Making telephone calls
23	Diabetic eye disease	6.1. Cancers	21	Taking medications
24	Macular degeneration	7. **Nervous disorders**	22	Doing work around the house or garden
25	Cataracts	7.1. Parkinson's disease	23	Managing money (paying bills, track of expenses)
		7.2. Alzheimer's disease		**Symptoms**
		7.3. Hallucinations	24	Difficulty walking 0.25 mile
		8. **Mental and behavioural**	25	Pain in general
		8.1. Anxiety	26	Problems with eyesight
		8.2. Depression	27	Problems with hearing
		8.3. Emotional problems	28	Balance on level surface
		8.4. Mood swings	29	Dizzy walking on level surface

5.6 Methods and analyses

Using Structural Equation Modelling (SEM) we integrated our conceptual framework of lifecourse multimorbidity and functional limitation with the latent factors and other variables (Figure 5.1) outlined in Section 3. SEM is an extension and combination of multivariate regression analysis, path analysis and factor analysis. SEM is commonly used to test hypotheses about simultaneous relationships among variables as well as path effects across time, which makes it appropriate for the needs of our study (Geiser 2013; Schumacker & Lomax 2016). Another advantage of SEM is its use of latent factors (constructs) that allows us to take measurement error into account for both independent

and dependent variables. Parameter estimation, especially the regression coefficients for dependent variables, and the association between variables are less biased (Warren 2009; Schumacker & Lomax 2016).

We conducted bivariate analysis of the associations between the variables chosen from our literature review. Weakly correlated variables were eliminated and those making theoretical sense were further tested in a confirmatory factor analysis (Appendix, Table A2). We assessed which of the potential explanatory variables shared sufficient variance so that they could be explained by a shared, directly unobservable commonality, a latent factor_(Appendix, Table A2). We then specified the paths between measures of childhood circumstances, mediating latent factors (adult Social Class, the Psychosocial Factor and the Behavioural Factor), the confounder (adult multimorbidity) and the outcomes (basic/complex multimorbidity and functional limitation).

We used Stata version 13 for data cleaning and to prepare the data in panel format. For model estimation we used the Weighted Least Square Means and Variance adjusted estimator (WLSMV) in Mplus 7.4. WLSMV has been shown superior to the alternative Maximum Likelihood estimator, as its standard errors are more accurate when data are non-normally distributed and the sample size is large (Li 2015). As we could not assume a normal distribution of the path effects, their statistical significance was inferred by the bootrapping method rather than the t-test (Taylor, MacKinnon & Tein 2008). The bias-corrected bootstrap confidence intervals were calculated for standard errors of the path effects by resampling 10 000 times from the raw data with replacement.

5.7 Results

Table A4 in the Appendix presents the results from three SEMs for our theoretical framework (Figures 5.2.- 5.3), including an assessment of overall model fit. We proceed by presenting the results in relationship to our two research questions.

We did not find evidence of direct effects of childhood circumstances - social class, adverse experiences and health – on basic multimorbidity, complex multimorbidity and functional limitation for people aged 65 to 74 years. We found evidence of indirect effects of the three domains of childhood circumstances on the three health outcomes. The indirect effects were mediated via material, psychosocial and behavioural pathways and via multimorbidity in pre-retirement.

The total indirect (pathway) effect of social class was 0.255 (CIs: 0.080-0.408) for basic multimorbidity, 0.265 (CIs: 0.125-0.265) for complex multimorbidity and 0.320 (CIs: 0.229 to 0.708) for multiple functional limitations. This means that 26% of the variation in basic multimorbidity, 27% of the variation in complex multimorbidity and over 32% in functional limitation can be explained by changes in the pathways. The pathways of childhood social class varied depending on the outcome. Basic and complex multimorbidity were influenced via all three pathways – material, psychosocial and behavioural – but multiple functional limitations only via the material and behavioural pathways. The paths in Figures 5.2-5.3 can be interpreted in the following way. Individuals with lower social class in childhood are more likely to have lower social class as adults which predicts a higher risk of having one of the three health outcomes in old age. For instance, two participants who differed by one unit in their reported childhood social class are estimated to differ, due to their difference on adult social class, by 9 % in the risk of basic multimorbidity, by 8 % in the risk of complex multimorbidity and by 6.8% in the risk of multiple functional limitation at old age. The effect was significant with 95% BC bootstrap confidence intervals 0.034 to 0.169 in the first model, 0.031 to 0.161 in the second model and 0.005 to 0.312 for functional limitations (Appendix, Table A4). Some of the effect of social class was mediated via the role of education. A shorter school attendance predicted worse material circumstances and more unhealthy behaviours later in life, increasing the risk of multimorbidities and functional limitation (Figures 5.2-5.3).

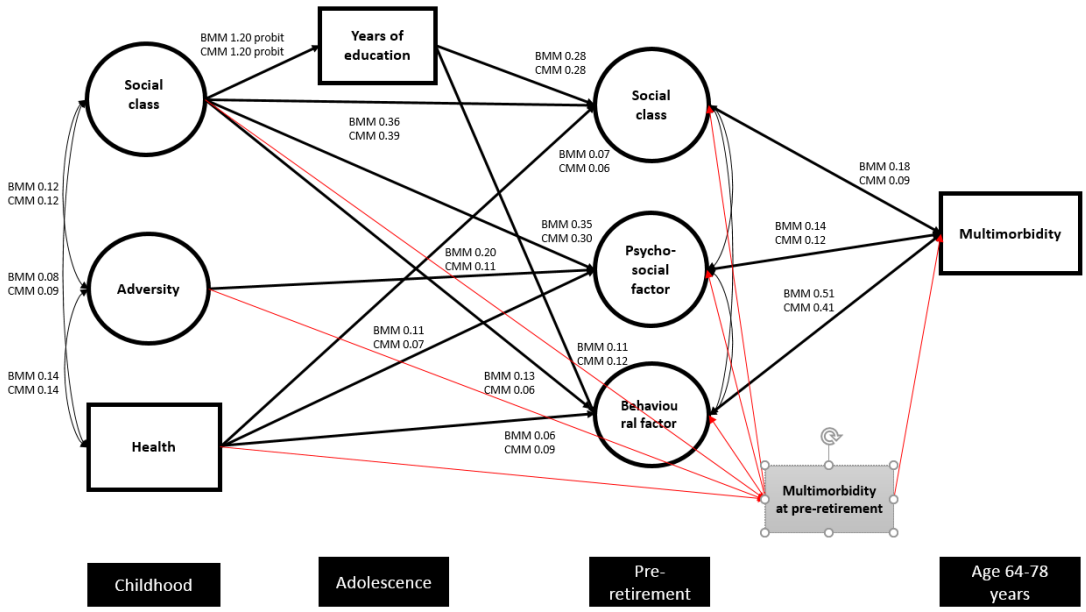

Figure 5. 2 Lifecourse pathways of basic and complex multimorbidity (correlation values for mediators shown in the Appendix, Table A3).

Note: BMM refers to OLS regression coefficients for basic multimorbidity, CMM is for complex multimorbidity. The paths to and from adult multimorbidity is highlighted in red.

Adversity in childhood influenced three health outcomes through the psychosocial pathway. The pathway effect of the adverse experiences was 0.239 (CIs: 0.084 to 0.461) for basic multimorbidity, 0.169 (CIs: 0.045 to 0.331) for complex multimorbidity and 0.245 (CIs: 0.016 to 0.363) for multiple functional limitations. This means that 24% of the variation in basic multimorbidity, 17% of the variation in complex multimorbidity and almost a quarter of the variation in functional limitation can be explained by changes in the psychosocial pathway from childhood adversity. Due to the Psychosocial Factor, two participants who differed by one unit in their reported ACEs are estimated to differ by 6.6 % in the risk of basic multimorbidity, by 5.7% in the risk of complex multimorbidity and by 11.3% in functional limitations. The 95% BC bootstrap confidence intervals 0.020 to 0.158, 0.020 to 0.115 and 0.029 to 0.742 indicate that we can be 95% confident that the effects exclude the null effect (Appendix, Table A4). Outside the psychosocial pathway, early adversity exerted some influence via multimorbidity in pre-retirement (Figures 5.2 and 5.3).

Childhood health influenced multimorbidities in old age via all three pathways, irrespective of the outcome. The sum of the pathway effects of childhood health was 0.161 (CIs: 0.117 to 0.225) for basic multimorbidity, 0.132 (CIs: 0.096 to 0.187) for complex multimorbidity and 0.146 (CIs: 0.078 to 0.667) for multiple functional limitations. This means that the variation in the pathways from childhood health can explain 16% of the variation in basic multimorbidity, 13% of variation in complex multimorbidity and almost 15% of variation in functional limitation. Childhood health directly influenced adult social class and childhood social class influenced multimorbidity at pre-retirement age (Figure 5.2). This indicates a cross-lagged type of effect (Warren 2009, Hoffman, Kröger and Geyer 2019).

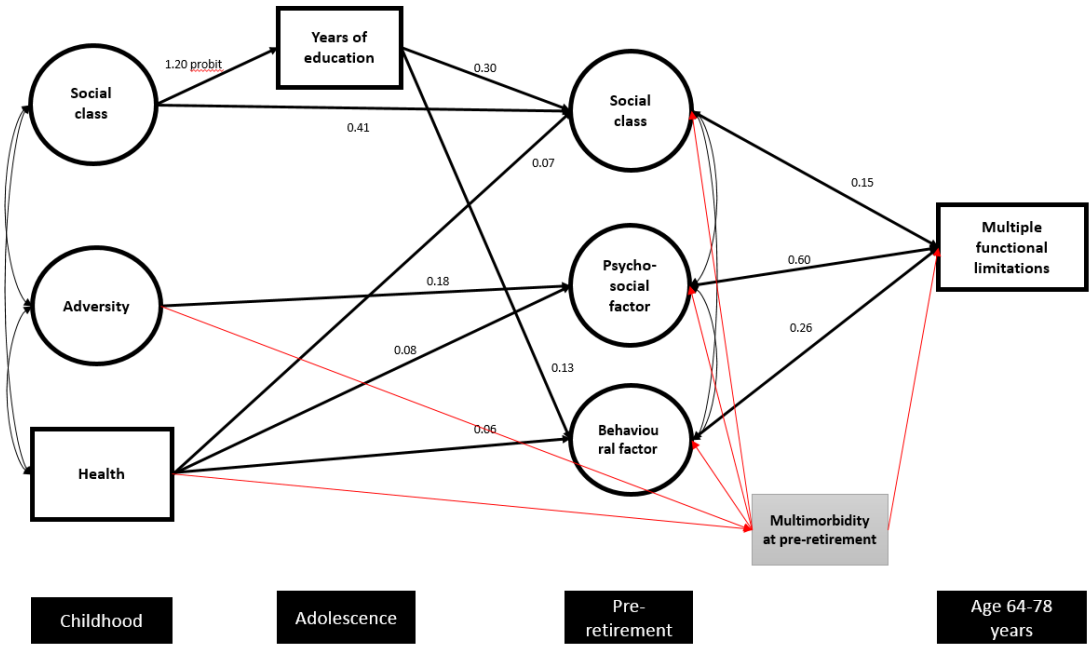

Figure 5. 3 Lifecourse pathways of multiple functional limitations.

Our framework enables us to compare and assess the difference in the magnitude of the effects measured at two life stages. Following the approach by Green and Popham (2017) we found that the effects of the adult SES,

Psychosocial Factor and Behavioural Factor at pre-retirement age on old age multimorbidity and functional limitation were larger than the total effects of childhood social class, adverse experiences and child's health. The only exception is complex multimorbidity where childhood adversity had a stronger effect than adult Psychosocial factor (0.239 versus 0.150), suggesting a possible early sensitive period.

5.8 Discussion

5.8.1 Key results

Assessed simultaneously, childhood social class, adverse childhood experiences and childhood health did influence basic/complex multimorbidity and multiple functional limitations in old age. Childhood social class and childhood health affected basic and complex multimorbidity through material, psychosocial and behavioural pathways. Childhood social class influenced functional limitations only via the material pathway. Adversity affected both types of multimorbidity and functional limitation through the psychosocial pathway. The three domains of the childhood circumstances had no direct effect on basic/complex multimorbidity and functional limitation. The years of completed education were an intervening mechanism influencing material and behavioural pathways from childhood social class to all three outcomes. The effects of adult social class, Psychosocial Factor and Behavioural Factor on old age multimorbidity and functional limitation were larger than the effects of childhood social class, adverse experiences and child's health. Interestingly, childhood adversity had a stronger effect than the Psychosocial Factor for people with complex multimorbidity.

5.8.2 Interpretation

Our study presents a life course model exploring pathways for understanding the risk of multimorbidity and functional limitation from childhood to old age.

People in England, who grew up in worse circumstances in childhood than their better-off peers, had a greater risk of multimorbidity and functional limitation when aged 64-78. Childhood circumstances influenced multimorbidity and functional limitation at old age indirectly via the completed years of education in combination with material, psychosocial and behavioural pathways. These pathways acted as magnifiers of early inequalities, in the way that they expanded the unequal impacts of the pre-existing differences between individuals in socio-economic position, psychological connections and health. The pathway effects measured at age 50-64 years were larger than the total effects of childhood social class, adverse experiences and child's health. Pre-retirement appears to be an important period for adults in England. However, in people suffering from complex multimorbidity the total effect of the adverse experiences of abuse and family dysfunction in childhood surpassed the effect of adult psychosocial circumstances, which suggests an early-life sensitive period for this outcome.

The combined effect of childhood social class was pervasive. Those who were born between 1938 and 1952 and grew up in homes with fewer financial, material and cultural resources were estimated to be set on a probabilistic trajectory leading through lower accumulated wealth, lower occupational and subjective status (either directly or through the contributing effect of education) to worse health at the age 64-78. Independently from home adversity (presence of abuse, violence or chaos from parents), their family social class predicted also the access to psychosocial resources in adulthood such as social networks, reliable friendship or the sense of control over their lives. The cascade of disadvantage in childhood continued to shape their multimorbidity status in old age. Children from these families were more likely to engage in risky health behaviours – less physically active, more smoking and alcohol consumption which in turn translated into higher degrees of multimorbidity. Children born to more affluent conditions were likely to progress in the opposite direction, along all three pathways. Compared to Ferraro, Schaffer and Wilkinson's (2016) mediation model of multimorbidity, which found evidence of smoking and lack

of personal control as pathways to multimorbidity, we identified a broader range of mediating mechanisms.

As with social class, negative experiences such as physical abuse, domestic violence and substance abuse in a child's home had the potential to set individuals on diverging paths in later life. Adversity predicted a higher burden of multimorbidity via psychosocial attributes such as lack of control in life, social isolation and lack of support from reliable friendships. The results are consistent with Ferraro, Schaffer and Wilkinson (2016) who found mediating effects through smoking, lack of family support and lack of personal control. These associations can be explained with the help of the stress proliferation theory, which states that early adversity increases the likelihood of subsequent stress exposures, which undermines self-esteem and makes problematic the building and maintainance of supportive relationships (Pearlin, 2010). The cascade further increases the chances of disease accumulation (O'Rand and Hamil-Luker, 2005).

Chains of risks between adversity and harmful health behaviours have been well documented (Felitti 2002; Hughes et al. 2017), but in our sample physical activity, alcohol consumption and smoking were influenced by ACEs only indirectly, via adult multimorbidity (Figures 5.2 and 5.3). A significant pathway between ACEs and adult social class was also mediated via adult multimorbidity. Strong clustering of adversity and further diseases might be underestimated in the literature as it is less visible than material pathways (Nurius et al., 2017). A recent study reported that the risk of developing chronic diseases for people who experienced multiple ACEs was higher at a young age (18-34 years) than at old age. (Sonu, Post and Feinglass, 2019). Our path model shows that the chain of risks does not stop with adult multimorbidity but affects other determinants of health.

Childhood health directly influenced adult social class and childhood social class influenced health measured as multimorbidity at pre-retirement for both basic and complex multimorbidity (Figure 5.2). This suggests a simultaneous presence of both social causation and health selection in our sample. A similar

co-occurrence of both types of effects was reported by Hoffman, Kröger and Geyer (2019) but only for the period between childhood and the age 30-50 years. The relationship between both pathways at later age reflected only social causation. Bi-directional relationships highlight the need to assess both variables jointly rather than choose a single hypothetical direction (causation *or* selection) a priori.

Life course models of health implicitly rest on the theory that social factors interact with human biology (Diez Roux 2007; Blane et al. 2013). This interaction is part of our lives from the foetal period until death. Therefore an explanation seeking to explain causal mechanisms must consider the role of biology. Material, psychosocial and behavioural pathways would never be able to influence risks of multimorbidity and functional limitation in a patterned stable way, if there were no socio-biological interacting mechanisms. One such mechanism is stress (Pearlin, 2010). In general, poor people experience higher doses of stress due to their living conditions and daily problems with just getting by (Krieger 2011; Bartley, 2017). According to the stress proliferation theory, exposure to one stressor (an event or a process) leads to exposure to other secondary, stressors (Pearlin, 2010). These stresses interact with psychosocial risks such as lack of social support, insecure employment and job strain, all of which are associated with health difficulties. Stress during the life course becomes embodied by changing the body's immune and neuroendocrine responses which leads to higher cumulative physiological burden and the onset of disease accumulation (Krieger, 2011). Another biological pathway associated with multimorbidity and functional limitation is chronic inflammation (Friedman et al., 2019). Levels of inflammatory proteins rise in a linear fashion with the number of chronic conditions in individuals with multimorbidity (Fabbri et al., 2015). A life course study of six European populations identified a robust inverse relationship between SES and level of inflammation (Berger et al., 2019). The pathway may be explained by a pro-inflammatory environment in childhood, such as infections, risky health behaviours, and continued pro-inflammatory factors in later life (Berger et al., 2019).

5.9 Strengths and limitations

This paper developed and tested a life course model of pathways leading to old age multimorbidity and functional limitation. We approached childhood circumstances from a broader angle than the usual focus on either the material conditions or extreme experiences of children. Our framework integrated multi-causality with accumulation, the two key features essential for explaining development of multimorbidity over time. It was based on a complex mediation analysis with both parallel and serial mediators where the SEM framework with latent factors is an excellent tool to handle multiple regression relationships and measurement error. Bias-corrected bootstrapping is a more powerful approach to statistical inference than the normal theory testing (Hayes, 2013). Our bootstrap confidence intervals follow the irregularity of the sampling distribution and the inferences are more accurate than when using the normal theory based approach.

Compared with the three other life course studies of multimorbidty and functional limitation (Pavela and Latham, 2015; Ferraro, Schaffer and Wilkinson, 2016; Haas and Oi, 2018) that were identified, our study improved the methodology and study design in several aspects. We developed a model with clear temporal lags between observations. We intervened against the possibility of a spurious effect by adding a variable for multimorbidity measured simultaneously with potential mediators. SEM with latent factors enabled us to make stronger statistical inference about the standard errors in our model while the other studies relied on observed variables only. From a conceptual perspective, our study considered a range of material, behavioural and psychosocial resources and risks, an approach also taken by Pavela and Latham (2015) and Ferraro, Schafer and Wilkinson (2016).

As a retrospective study, our information on the circumstances in early life was dependent on participants' subjective recall. This introduces a potential bias but

studies have shown that the difference relates to the magnitude of associations, not changes to direction of effects (Niedzwiedz et al., 2012). Reliability of recall in ELSA was tested in comparison with prospective data from the 1958 Birth Cohort by selecting participants of similar age and the same time point (Jivraj et al., 2017). The results were the most similar for parental occupation, but in general, statistical significance and direction of effects were similar but not the magnitude of regression coefficients. A general limitation common to all life course studies is the potential bias from selective survival (Liu, Jones and Glymour, 2010; Niedzwiedz et al., 2012). Childhood experience of poverty and illnesses may lead to premature mortality, thus the cohort aged 64-78 might have been pre-selected into those who had a more advantageous early life. This potentially underestimates the disparities between individuals due to childhood circumstances.

5.10 Conclusion

In conclusion, we have shown that the conceptualization of lifecourse pathways into the material, psychosocial and behavioural, dating back to the Black Report (Black, 1980), is useful and can explain how social exposures shape the risks of health problems into old age. Unlike the usual focus on pathways of socio-economic status, we identified three types of pathways across three domains of early life disadvantage simultaneously. Depending on the domain and the health outcome, these pathways explained between 13 percent (the pathways from health to complex multimorbidity) and 32% (the pathways from social class to functional limitation) of the variation in outcomes. The remaining variance can be attributed to the effect of multimorbidity in pre-retirement which we took into account plus other unexplained factors.

Rather than the individual strength of any particular relationship, it is the range of childhood factors and their relationships with a number of social determinants of health that is the most striking. Our findings show that a

variety of pathways is operating between early life and adult health and a lifecourse approach to multimorbidity is vital (Kuh and Wadsworth, 1993).

Our study provides a convincing argument for life course models to integrate dimensions of social class, psychosocial adversity and health. We tested empirically our hypothesis that multi-dimensional childhood circumstances shape later-life multimorbidity through a diversity of social, psycho-social and socio-biological pathways. The approach to childhood circumstances developed in this paper will be beneficial for those researchers who are interested in exploring early life effects on other multi-factorial and cumulative outcomes (processes) than multimorbidity and functional decline, such as disability, frailty or allostatic load.

5.11 References

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5.12 Appendix

Table A.1 Polychoric correlation with variables selected for the analysis

	Arguments & Fights	Parents' neglect	Physical abuse	No. of books	Father's/Carer's occupation	In-door toilet	Occupational level	Household wealth	Subjective social status	Sense of control	Loneliness
Arguments & Fights											
Parents' neglect	0.606										
Physical abuse	0.571	0.480									
No. of books	-0.085	-0.149	0.008								
Father's/Carer's occupation	-0.020	-0.040	-0.049	0.355							
In-door toilet	-0.053	0.024	-0.046	-0.329	-0.241						
Occupational level	-0.010	-0.033	0.034	0.326	0.269	-0.213					
Household wealth	-0.026	-0.051	-0.093	0.294	0.274	-0.214	0.464				
Subjective social status	-0.042	-0.043	-0.061	0.259	0.208	-0.126	0.390	0.478			
Sense of control	-0.125	-0.085	-0.151	-0.008	-0.031	0.038	0.052	0.133	0.216		
Loneliness	-0.130	-0.112	-0.089	0.152	0.114	-0.115	0.205	0.300	0.282	0.286	
End of education	0.075	0.040	0.031	0.496	0.376	0.256	0.546	0.410	0.400	0.173	0.140
Baseline Model fit index											
Chi-square (df)	9166.932 (55)***										

Table A.2 Measures of latent constructs with significance and model fit

Observed variable	Latent construct (LC)	B	SE	R-Square
Father's/Carer's occupation	Childhood SC	0.560***	0.025	0.313***
In-door toilet	Childhood SC	0.319***	0.037	0.102***
Number of books	Childhood SC	0.629***	0.027	0.395***
Arguments & Fights	Adversity	0.752***	0.043	0.566***
Parents' neglect	Adversity	0.766***	0.048	0.586***
Physical abuse	Adversity	0.721***	0.044	0.520***
Occupational level	Social Class	0.610***	0.022	0.372***
Household wealth	Social Class	0.731***	0.019	0.535***
Subjective social status	Social Class	0.683***	0.020	0.466***
Loneliness	Psycho-social factor	0.677***	0.050	0.458***
Sense of control	Psycho-social factor	0.360***	0.034	0.194***
Reliable friends	Psycho-social factor	0.377***	0.040	0.142***
Physical activity	Behavioural factor	0.426***	0.038	0.181***
Smoking	Behavioural factor	0.328***	0.032	0.107***
Fit indices				
Model Chi-square (df)	394.913*** (91)			
RMSEA (90% CI)	0.033 (0.030 - 0.036)			
CFI	0.959			
TLI	0.924			

Table A.3 Correlation between the latent factors

	Childhood SC	Adversity	Adult SC	PS Factor	BH Factor
Childhood SC	1				
Adversity	0.165***	1			
Adult SC	0.660***	0.108***	1		
P-S Factor	0.280***	0.345***	0.631***	1	
BH Factor	0.449***	0.135***	0.806***	0.660***	1

Table A.4 Pathway effects from childhood circumstances to basic/complex multimorbidity and functional limitation

Childhood circumstances	**Basic multimorbidity**				**Complex multimorbidity**				**Multiple functional limitations**			
Social Class	Coefficient	SE	Lower 2.5% C.I.	Upper 2.5% C.I.	Coefficient	SE	Lower 2.5% C.I.	Upper 2.5% C.I.	Coefficient	SE	Lower 2.5% C.I.	Upper 2.5% C.I.
Total indirect effect	**0.255**	**0.111**	**0.08**	**0.408**	**0.265**	**0.097**	**0.125**	**0.265**	**0.320**	**0.101**	**0.229**	**0.708**
Material pathways												
via adult SC	**0.090**	**0.038**	**0.034**	**0.169**	**0.079**	**0.034**	**0.031**	**0.161**	**0.068**	**0.680**	**0.005**	**0.312**
via Edu and adult SC	**0.080**	**0.030**	**0.035**	**0.137**	**0.069**	**0.025**	**0.032**	**0.130**	**0.058**	**0.463**	**0.007**	**0.322**
Psychosocial pathways												
via PS Factor	**0.049**	**0.036**	**0.006**	**0.131**	**0.046**	**0.033**	**0.011**	**0.137**	0.097	0.371	-0.165	0.276
via Edu and PS Factor	0.021	0.021	-0.007	0.084	0.019	0.019	-0.007	0.065	-0.048	0.320	-0.578	0.043
Behavioural pathways												
via BH Factor	**0.077**	**0.052**	**0.012**	**0.199**	**0.064**	**0.044**	**0.010**	**0.168**	0.116	0.584	-0.066	0.379
via Edu and BH Factor	**0.103**	**0.046**	**0.041**	**0.198**	**0.079**	**0.036**	**0.032**	**0.169**	**0.194**	**0.407**	**0.065**	**0.381**
Adjusting for MM at wave 1												
via MM	**0.038**	**0.020**	**0.004**	**0.085**	**0.027**	**0.014**	**0.007**	**0.061**	-0.059	0.065	-0.836	0.004
Adversity												
Total indirect effect	**0.239**	**0.093**	**0.084**	**0.461**	**0.169**	**0.071**	**0.045**	**0.331**	**0.245**	**0.603**	0.016	0.363
Material pathways												
via adult SC	-0.004	0.016	-0.023	0.046	-0.005	0.003	-0.037	0.018	-0.005	0.073	-0.036	0.007
via Edu	0.019	0.020	-0.001	0.036	0.009	0.012	-0.006	0.044				
via Edu and adult SC	-0.011	0.009	-0.016	0.000	-0.010	0.008	-0.032	0.000	-0.005	0.054	-0.049	0.000
Psychosocial pathways												

via PS Factor	**0.066**	**0.033**	**0.020**	**0.158**	**0.057**	**0.026**	**0.020**	**0.115**	**0.113**	**0.603**	**0.029**	**0.742**
via Edu and PS factor	0.003	0.004	0.000	0.021	0.003	0.004	0.000	0.002	0.004	0.039	-0.003	0.112
Behavioural pathways												
via BH Factor	0.017	0.045	-0.062	0.101	0.006	0.034	-0.043	0.065	0.007	0.058	-0.063	0.137
via Edu and BH Factor	-0.014	0.014	-0.054	0.002					**-0.017**	**0.038**	**-0.066**	**-0.001**
Adjusting for MM at wave 1												
via MM	**0.113**	**0.038**	**0.046**	**0.203**	**0.078**	**0.029**	**0.028**	**0.130**	**0.072**	**0.041**	**0.020**	**0.323**
via MM and SC	**0.010**	**0.004**	**0.003**	**0.021**	**0.008**	**0.004**	**0.002**	**0.017**	**0.028**	**0.033**	**0.012**	**0.225**
via MM and PS Factor	**0.015**	**0.009**	**0.004**	**0.038**	**0.014**	**0.007**	**0.004**	**0.033**	**0.036**	**0.118**	**0.011**	**0.145**
via MM and BH Factor	**0.033**	**0.015**	**0.012**	**0.068**	**0.025**	**0.012**	**0.008**	**0.053**	**0.041**	**0.041**	**0.012**	**0.090**
Health												
Total indirect effect	**0.161**	**0.028**	**0.117**	**0.225**	**0.132**	**0.023**	**0.096**	**0.187**	**0.146**	**0.194**	**0.078**	**0.667**
Material pathways												
via adult SC	**0.014**	**0.007**	**0.004**	**0.032**	**0.013**	**0.006**	**0.004**	**0.029**	**0.012**	**0.017**	**0.001**	**0.048**
via Edu	0.007	0.006	0.000	0.025	0.003	0.004	-0.001	0.018				
via Edu and adult SC	0.004	0.003	0.000	0.012	0.003	0.002	0.000	0.010	0.002	0.006	-0.001	0.020
Psychosocial pathways												
via PS Factor	**0.016**	**0.009**	**0.003**	**0.036**	**0.015**	**0.008**	**0.004**	**0.029**	**0.052**	**0.174**	**0.015**	**0.353**
via Edu and PS Factor	-0.001	0.001	-0.005	0.000	-0.001	0.001	-0.005	0.000	-0.002	0.007	-0.049	0.001
Behavioural pathways												
via BH Factor	**0.035**	**0.017**	**0.012**	**0.076**	**0.028**	**0.014**	**0.009**	**0.072**	**0.075**	**0.037**	**0.023**	**0.135**
via Edu and BH Factor	0.005	0.004	0.000	0.002	0.004	0.003	0.000	0.011	**0.007**	**0.010**	**-0.003**	**0.025**
Adjusting for MM at wave 1												
via MM	**0.061**	**0.012**	**0.040**	**0.086**	**0.044**	**0.009**	**0.028**	**0.064**	**0.050**	**0.077**	**0.006**	**0.082**
Fit indices												

Model Chi-square (df)	376.823*** (96)	374.205*** (96)	784.456*** (101)
RMSEA (90% CI)	0.031 (0.028 - 0.034)	0.031 (0.027 - 0.034)	0.046 (0.043-0.049)
CFI/TLI	0.961/0.930	0.961/0.930	0.898/0.831

Mediation effects were tested for statistical significance. This involved testing the significance of the paths between each childhood exposure and each adult latent factor and the paths from the mediating factors to the outcomes (MacKinnon, Fairchild and Fritz 2007). We could not assume a normal distribution of the path effects and their statistical significance was inferred by the bootrapping method rather than the t-test (Taylor, MacKinnon & Tein, 2008). The bias-corrected bootstrap confidence intervals were calculated for standard errors of the path effects.

The chi-square fit index tests whether the sample variance-covariance matrix and the model generated variance-covariance matrix are similar. Statistical significance implies that this difference might be due to the sampling variation while a statistically non-significant chi-square value indicates that the theoretical model significantly reproduces the actual data structure. However, the usefulness of this test has been discussed due to its sensitivity to sample size. With increasing sample size (above 200), the chi-square test tends to show a significant probability value which may lead to an exclusion of a well-specified model (Schumacker and Lomax 2016). The chi-square value generated by our analysis was statistically significant. Given the mentioned sample size sensitivity and our aims being to assess the role of pathways and not to search for the best fitting parsimonious model, we do not see this as a reason for rejecting our model. In addition, the complementary fit indices the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI) and the Tucker-Lewis Index (TLI) showed acceptable levels of fit.

Chapter 6

Conclusion

6.1 Introduction

This final chapter seeks to summarise the major results and the contribution of the thesis to the current state of research in multimorbidity. The chapter presents key research gaps identified in the literature review. It recapitulates the research aims and the research strategy chosen to achieve them. The chapter summarizes the key research findings and discusses their contribution to the current knowledge, methodology and policy. Next, the limitations of the research are established, with suggestions about how the thesis could be improved. The chapter concludes with a series of ideas for possible extensions of the research that could build upon the achievements of this thesis.

6.2 Research purpose and strategy

This thesis positions itself among the interdisciplinary efforts to understand the 'social drivers' of the increase in prevalence and inequalities in multimorbidity and functional limitation of ageing people. The purpose of this study is to intervene in the emerging discussions of the relationship between ageing, multimorbidity and functional decline, the role of the social determinants and the influence of early life circumstances on old age multimorbidity and functional limitation. With this purpose in mind, the literature review identified several gaps in the current state of knowledge. The first limitation is methodological. Studies based on general populations with self-reported information on health tend to define multimorbidity as two or more diseases.

This measure does not capture the multimorbidity of disparate body systems which is an important marker of ageing (Fabbri et al., 2015). Second, little is known about socio-economic inequalities in the prevalence of multimorbidity and functional limitation in general populations and their effect on ageing. A few studies that highlighted health inequalities and earlier onset of multimorbidity in deprived areas used primary care records (Barnett et al., 2012; McLean et al., 2014). Third, while ageing on its own cannot explain the rising trends in multimorbidity, the theory of social determinants of health has not become part of multimorbidity research yet. Contextual characteristics are instead being used due to data availability and in isolation from each other (Northwood et al., 2017, Pathirana and Jackson, 2018). Fourth, the role of childhood and pathway mechanisms in shaping multimorbidity at old age remains unknown. Elucidating the preceding factors would benefit attempts to prevent and reduce the burden of multimorbidity in society.

In order to address these gaps, the thesis formulated the following aims:

1. Explore the prevalence of multimorbidity and functional limitation and its variation by key socio-demographic characteristics.

2. Examine the association of key social determinants of health with the risk of developing multimorbidity and functional limitation.

3. Explain how childhood circumstances shape the risk of multimorbidity and functional limitation in old age.

The research strategy to approach these aims set out with an *exploratory* study of the trends in the prevalence of multimorbidity and functional limitation. Stratification analyses and marginal logistic regression were employed to examine the distribution of multimorbidity and functional limitation between age groups, men and women and according to household wealth. The investigation further applied the theory of the social determinants of health in order to consider a broader range of contextual characteristics. It used a population-averaged regression method that took into account temporal correlation between individual health states during the period 2002-2015. The

thesis concluded with an *explanatory* study of the chains of risks in multimorbidity and functional limitation from childhood to the old age. A complex Structural Equation Model was employed to test theoretical hypotheses. Latent factors were modelled to operationalize multiple dimensions of the key explanatory constructs.

6.3 Research aims and findings

Research aim no.1

To explore the prevalence of multimorbidity and functional limitation and its variation by key socio-demographic characteristics.

This aim was motivated by the emerging evidence of multimorbidity becoming more common and more socially stratified (Reilly et al., 2015; van Oostrom et al., 2016; Tetzlaff et al., 2018; Canizares et al., 2018). The study explored trends in prevalence and distribution of prevalence by age, sex and socio-economic status at a population level. The study argued that the measure of basic multimorbidity had limited ability to identify multimorbid individuals with higher care needs. It used a comparative measure of complex multimorbidity that defines a situation when three or more body systems are affected by chronic diseases (Harrison et al., 2014). The repeated cross-sectional analysis covered the period between 2002-03 and 2014-15, using a total of seven time points. Health inequalities in multimorbidity and functional limitation and interaction effects between age and wealth were verified in marginal effects logistic regression analysis.

Finding 1:

Multimorbidity and functional limitation are becoming more common in England. The prevalence of basic multimorbidity grew from 41.6% in 2002/2003 to 46.6% in 2014/2015. The prevalence of complex multimorbidity increased

from 12.2% in 2002/2003 to 21.1% in 2014/2015. The prevalence of 10+ functional limitations rose from 9.6% in 2002/2003 to 14.3% in 2014/2015.

Finding 2:

Multimorbidity and functional limitation were more common among females than males and among people with less wealth than more wealth. Complex multimorbidity and 10+ functional limitations reflected larger inequalities than basic multimorbidity. The disparities between the most and the least affluent groups were the largest for multiple functional limitations (5.9-fold in 2014/15), followed by complex multimorbidity (2.8-fold in 2014/15) and basic multimorbidity (1.9-fold) in 2014/15.

Finding 3:

The levels of complex multimorbidity among people from poorer social backgrounds in their early 50s were comparable to the levels among people 20 years older in the most affluent strata. For multiple functional limitations the difference was even greater, at 30 years. The study observed social polarization among multimorbid ageing population in England, with complex multimorbidity and multiple functional limitations increasing faster and reflecting stronger inequality than basic multimorbidity.

Research aim no. 2:

To examine the association of key social determinants of health with multimorbidity and functional limitation.

Building on the theories of social determinants of health and health inequalities, the analysis included a range of social determinants. The extension addressed the lack of contextual data in studies of multimorbidity which typically focus on a few risk factors (Northwood et al. 2017). The study

introduced material determinants (household wealth, occupational level and subjective social status), psycho-social determinants (sense of control over individual life, loneliness, supportive children, supportive friends, supportive partner and participation in community organisations) and behavioural determinants (level of physical activity, consumption of alcohol and smoking). The analysis explored the association of the social determinants with the likelihood of multimorbidity, complex multimorbidity and having ten or more functional limitations. The study used a population-averaged regression model, based on the Generalized Estimating Equations with autoregressive correlation structure. The model took into the account the within-individual correlation of outcomes over the period 2002-2015.

Finding 1:

Increasing odds of multimorbidity, complex multimorbidity and having ten or more functional limitations is associated with less household wealth, sense of control over one's life, physical activity and more loneliness.

Finding 2:

Larger health inequalities were observed when health was measured as complex multimorbidity and multiple functional limitations than basic multimorbidity. Compared to the population group with the highest wealth, those with the lowest wealth had 47% higher odds of basic multimorbidity (95% C.I. 1.34-1.61), 73% higher odds of complex multimorbidity (95% C.I. 1.52-1.96) and 90% higher odds of having 10 or more functional limitations (95% C.I. 1.59-2.26).

Finding 3:

A dose-response relationship between alcohol consumption, smoking and multimorbidity could not be found, but rather evidence of people in ill health actively moderating their health behaviour.

The study concluded that neither the common behavioural nor materialist models of multimorbidity and functional limitation at older age can, on their own, explain the observed health inequalities. Material, psychosocial and behavioural determinants simultaneously influence the risk of multimorbidity and functional limitation.

Research aim no. 3:

To explain how childhood circumstances shape the risk of multimorbidity and functional limitation in old age.

To achieve this aim, the strategy pursued two objectives. First, to establish if the effects of childhood circumstances on multimorbidity and functional limitation in old age were direct or indirect. Second, the study assessed the role of material, psycho-social and behavioural pathways in mediating the effects of childhood circumstances on old age multimorbidity and functional limitation. The methodology involved Factor Analysis in the initial stage of the analysis, which enabled to accurately measure the latent constructs. Next, a Structural Equation Model was used to formally test the hypothesized path effects between variables. A complex mediation analysis enabled simultaneously assessment of childhood's social class, psycho-social and health circumstances and their relative contributions to the late life inequalities in multimorbidity and functional limitation.

Finding 1:

Assessed simultaneously, childhood social class, adversity and health influenced basic multimorbidity, complex multimorbidity and functional limitation in old age through material, psychosocial and behavioural pathways.

Childhood social class influenced functional limitations only via the material pathway and behavioural pathways. Adversity affected both types of multimorbidity and functional limitation only through the psychosocial pathway. Childhood health influenced multimorbidities and function in old age via all three pathways, irrespective of the outcome.

Finding 2.

The material, psychosocial and behavioural pathways acted as magnifiers of inequalities from the early life period. The diverging pathways expanded the unequal impacts of the pre-existing differences between individuals in socio-economic position, psychological adversity and general health. Education was an intervening mechanism influencing material and behavioural pathways from childhood social class to all three outcomes.

Finding 3.

The effects of adult social class, the Psychosocial Factor and the Behavioural Factor on old age multimorbidity and functional limitation were larger than the effects of childhood social class, adverse experiences and child's health. Pre-retirement appears to be an important period for adults in England.

6.4 Contribution to the current knowledge and methodology

This thesis responds to the trend of increasing prevalence and health inequality in multimorbidity. The thesis addresses the gaps in the current state of research

in multimorbidity and functional limitation and makes a nnumber of novel contributions to the state of knowledge in this research field. These are expanded on below.

6.4.1 Higher inequality in complex multimorbidity and 10+ functional limitations

The first limitation in the current understanding of multimorbidity of the elderly is the lack of consideration for the effects of the biological process of ageing. These effects are manifested in chronic problems appearing across several body systems (Fabbri et al., 2015). Population-based studies at present prefer to measure multimorbidity as the count of single diseases and disregard the role of the body systems. The solution suggested by this study is to add two distinct measures to the common measure of multimorbidity based on the count of single diseases. Complex multimorbidity, proposed by Harrison et al. (2014), defines a situation when three or more body systems in an individual are affected by chronic diseases. Compared to basic multimorbidity, complex multimorbidity, as the more discriminating definition, leads to selecting populations with discordant chronic conditions (Piette and Kerr, 2006). The benefit of using this measure lies in "zooming in" on groups with higher health care need and more targeted resource planning and care management (Fortin et al., 2012; Harrison et al., 2014; 2016). This thesis also proposed the measure of having ten or more functional limitations as this might reflect the increase in limitations arising from multiple body systems as part of the ageing process (Jindai et al., 2016; Calderón-Larrañaga et al., 2019).

The comparison of the estimates of basic multimorbidity, complex multimorbidity and 10+ functional limitations in Chapter 3 is consistent with the literature that established the "zooming in" effect (Harrison et al., 2014; 2016). The two latter measures as employed in the thesis have selective effects on the larger multimorbid population measured by the count of two or more diseases. Further stratification by age groups in Chapter 3 shows that all three

health outcomes are more prevalent in older than younger age groups. However, the difference in prevalence between the youngest and the oldest is higher for complex multimorbidity and functional limitation than for basic multimorbidity. This indicates a relationship between simultaneous damage in several body systems and age. Expressing this link through the measure of complex multimorbidity and multiple functional limitations is a novel observation as the authors are not aware of it having been published yet.

6.4.2 Poorer people have complex multimorbidity 20 years earlier and functional limitations 30 years earlier then wealthier people.

An additional advantage of using complex multimorbidity and the cut-off 10+ functional limitations is that both measures capture health inequalities better than the basic multimorbidity. This is demonstrated by higher prevalence estimates in Chapter 3 and higher odds ratios in Chapter 4. The health inequalities become more obvious when set against the age of onset. The youngest group aged 50-54 years in the poorest quintile has a prevalence of complex multimorbidity identical to people 20 years older in the most affluent category and a level of functional limitations comparable to those 30 years older in the top wealth group. This implies that the current literature might under-report the actual scale of the inequalities when multimorbidity is defined as two or more diseases or when the cut-off for the number of limitations is too low. The earlier onset of multimorbidity was observed previously (Barnett et al., 2012) but this thesis is the first study to point out that the way multimorbidity is measured impacts on the scale of identified inequality.

The challenge of addressing the problem of health inequalities is a matter of life and death for some. The gap in healthy life expectancy (years lived in good health) between the most and least deprived areas of England was around 19 years for both males and females from 2014 to 2016. The extra costs to the NHS of health inequalities were estimated at £4.8 billion a year, caused by the greater use of hospitals by people in deprived areas alone (Public Health England, 2019).

6.4.3 Differences in the risk of multimorbidity and functional limitation cannot be explained only by lifestyle choices or material circumstances.

Studies pay insufficient attention to contextual factors of multimorbidity and functional limitation (Bayliss et al., 2014). Researchers use socio-demographic, socio-economic, psychological or behavioural characteristics in isolation from each other (Northwood et al., 2017, Pathirana and Jackson, 2018). As the current and predicted rise in the prevalence of multiple health problems cannot be explained by the forces of ageing only, understanding the societal influences becomes imperative. This thesis advances theory and methodology through its holistic approach to multimorbidity and functional limitation. It enriches existing literature by showing that material, psychosocial and behavioural determinants acting simultaneously can explain a share of the health inequalities across three different measures of multimorbidity.

The approach this thesis took is still rare. A systematic review by Moor, Spallek & Richter (2017) found only eleven studies which jointly examined the contributions of material, psycho-social and behavioural determinants to health inequalities. These studies were cross-sectional and used self-reported health as the outcome. None examined multimorbidity or functional limitation (Moor, Spallek & Richter, 2017). Identifying three simultaneously acting groups of determinants challenges the dominant approach stressing ageing in combination with lifestyle factors as the major explanatory factors and seeking behavioural strategies in prevention (Bartley, 2017; Northwood et al., 2017).

6.4.4 Multiple circumstances in childhood initiate diverging pathways in the risk of adult multimorbidity and functional limitation.

This thesis advances the methodology of multimorbidity studies through the application of complex Structural Equation Model with latent factors. Instead of a single measure of the situation in childhood, three domains are used in the

same holistic model. Three latent pathways that consist of the material, psychosocial and behavioural factors are hypothesized and tested.

The thesis brings several novel contributions to multimorbidity in the life course perspective. Firstly, this study found that the effects of the individual differences in social class, adverse experiences and health reported for childhood are magnified through the effects of the material, psychosocial and behavioural pathways. Secondly, the pre-retirement period (age 50 to 64 years) appears to be an important period for adults in England as its impact on multimorbidity and functional limitation in old age is larger than the influence of childhood circumstances. Thirdly, this does not apply for the psychosocial pathway to complex multimorbidity. The effect of adverse childhood experiences is stronger than the effect of adult psychosocial circumstances. The role of early life seems to be more important for people with complex multimorbidity than for people with basic multimorbidity and multiple functional limitations. Finally, Chapter 5 took a holistic, multi-causal approach to the conceptual framework. Structural Equation Modelling with latent factors facilitated operationalizing key variables into multiple domains and treating them in the same model. The literature review found only one study of multimorbidity with comparable complexity but it lacked latent factors (Ferraro, Schafer & Wilkinson, 2016). This thesis also included a broader range of mediating mechanisms than Ferraro, Schafer & Wilkinson (2016).

6.5 Limitations

6.5.1 Relationship between multimorbidity and functional limitation was not assessed.

Studies found that multimorbidity predicts functional limitations (Sibbritt, Byles and Regan, 2007; Ryan et al., 2015; Jindai et al., 2016). A linear association was suggested where increasing number of morbidities lead to increasing number of functional limitations or higher score in a validated measure of

function, SF-36. The relationship might be more complex than the one described. The one-directional view has been challenged recently and instead of causality a "multimorbidity-functional impairment circle" has been proposed (Calderón-Larrañaga et al., 2019, p.3). The rationale behind this conception is that functional decline and physical limitations during ageing related to multimorbidity affect a person's disease and treatment burden and their capacity to respond may further facilitate multimorbidity (Calderón-Larrañaga et al., 2019). In this framework, the life course psychosocial, lifestyle and biological factors act as determinants of the interaction between multimorbidity and physical functioning.

The life course model in the final analytical chapter indicated mixed evidence on the potential relationship between multimorbidity and functional limitation. On the one hand, the same explanatory mechanisms lead to increased risk in both types of multimorbidity and multiple functional limitations. This might be interpreted as questioning the assumption of an underlying causal pathway leading from multimorbidity to functional limitation. On the other hand, Figure 5.3 in Chapter 5 shows an independent chain of risk from health in childhood through multimorbidity in pre-retirement to multiple functional limitations after the age of 64 years. This suggests the presence of a causal effect. This thesis does not contribute to the current discussion on the relationship between multimorbidity and functional limitation. Such an understanding would help the society to identify ageing people with multimorbidity who are vulnerable to a range of adverse outcomes.

6.5.2 Specific patterns of multimorbidity were not assessed

Some combinations of multimorbid conditions have larger combined effects on specific health outcomes and use of health care than multimorbidity involving other conditions. For example, the common combination of diabetes with hypertension was found as causing less demand and the combinations of heart failure with COPD and heart failure with chronic kidney disease as causing

more demand on health care in England (Kadam et al., 2013). This implies that summing up the number of chronic diseases contains inherent limitations, especially if the research focus lies in the consequences of multimorbidity for health care and quality of life (Ng et al., 2018). This thesis uses the complementary measure of complex multimorbidity but this does not fully address the problem. The thesis does not consider specific patterns or clusters of multimorbidity and their relationship to the broad range of social determinants and life course pathways. A cluster of combined physical and psychiatric morbidities was found more common in deprived areas and among women (Barnett et al., 2012, McLean et al., 2014). More evidence of similar cluster-specific morbidities would be beneficial for a better targeting of public health interventions.

6.6 Ideas for future development

There are at least two research directions for future development of the subject of this study.

6.6.1 Elucidating the "multimorbidity-functional limitation circle" through modelling growth trajectories

Evaluating the progress in life course epidemiology over the last 20 years, Ben-Shlomo and Kuh (2016) emphasized the shift in research focus from outcomes fixed in time to temporal trajectories in the outcomes. Understanding the early development of multimorbidity and functional decline presents a chance for policy makers and health care professionals to delay the onset and decline of chronic outcomes. Taking the trajectory approach also enables the identification of high-risk population groups (Burton-Jeangros et al., 2015; Ben-Shlomo and Kuh, 2016).

Modelling change in intra-personal outcome could be creatively employed to explore one of the limitations of this thesis – the unclear relationship between multimorbidity and functional limitation. The 'multimorbidity-functional impairment circle' (Calderón-Larrañaga et al., 2019, p.3) could be disentangled by modelling a growth curve model with the number of functional limitations as an outcome, with basic and complex multimorbidity as time-varying predictors. The framework could combine the structure of the parallel pathways from Chapter 5 acting as predictors of the rate of change between multimorbidity and functional limitation. The study could examine if the diverse social determinants affect the relationship between the outcomes and the rate of change differently.

An alternative might be latent class analysis where individuals are classified into distinct groups based on individual response patterns so that those within a group are more similar than individuals between groups. Latent class growth analysis was used to summarize heterogeneity in the accumulation of multimorbidity over time in primary care in older adults. Five distinct longitudinal trajectories of chronic multimorbidity were modelled (Strauss et al. 2014, Jackson et al. 2015). They suggest that describing an entire population using a single growth trajectory is oversimplifying the complex growth patterns that describe continuity and change between different population groups. Latent class growth modelling seems to be better at capturing information about interindividual differences in intraindividual change while taking into account the unobserved heterogeneity (different groups) in a larger population (Burton and Jeangros, 2017).

6.6.2 Including biomarkers of allostatic load

Accumulating knowledge in life course research shows that health trajectories are a result of interactions between social and biological processes (Krieger, 2011; Burton-Jeangros et al., 2015). Incorporating socio-biological mesures into studies of multimorbidity opens up an exciting area for exploration.

The concept of allostatic load enables empirical measuring of the socio-biological interaction. Allostatic load is often explained as the "wear and tear" of the body that results from repeated attempts to maintain its integrity in response to prolonged periods of stress (Beckie, 2012). Such exposures have physiological effects that compound over time and trigger chronic disease. Allostatic load can be measured through various biomarkers, such as the increased production of stress hormones which disrupt the neuroendocrine, immune and metabolic systems (Delpierre et al., 2016). A cross-sectional association between allostatic load and multimorbidity has been observed by Tomasdottir et al. (2015) and explained from a systems biology point of view by Juster et al. (2016). As the two concepts are related, they likely share the same pathways. Nine biomarker scores of allostatic load were associated with material (income, home ownership) and behavioural (smoking) pathways during a 20 years period in a Scottish cohort study (Robertson et al., 2015).

The specific disease profile of the ELSA population, used in this thesis, suggests that the biomarkers of the allostatic load might be relevant for this sample. The most prevalent diseases that contributed to multimorbidity of the 64-78 age cohort in wave 8 were arthritis, respiratory diseases, diabetes, depression, coronary heart disease and cancer. Stress pathways with the related allostatic load have been found significantly associated with some of these chronic diseases (Beckie, 2012; Delpierre et al., 2016). A future study should explore if allostatic load represents an important biological mechanism underlying the three social pathways that were the focus of this thesis.

6.7 Summary

This thesis identified previously unmeasured polarization in the general population with multimorbidity and functional limitation aged 50 or more years in England. The polarization relates to an increase in two processes – in the complexity of multimorbidity and in social inequality. After establishing robust

inequalities in multimorbid population by differences in the amount of household wealth in Chapter 3, the focus of the thesis then narrowed down to explore if the polarization is related to factors other than the amount of household wealth. Chapter 4 introduced theory of social determinants of health and health inequalities in order to include a range of material, psychosocial and behavioural determinants into the analysis. These determinants were associated with the three outcomes. Whether people had minimum, medium or maximum of household wealth, sense of control over personal life, physical activity and loneliness was associated in a linear way with the risk of having basic multimorbidity, complex multimorbidity and functional limitation. The causal direction of these associations remained nevertheless unclear. Chapter 5 further developed the causal understanding of social determination of multimorbidity and functional limitation. A mediation model was postulated to test the relative contributions of childhood and adult life circumstances to late life multimorbidity and functional limitation. Multimorbidity and functional limitation of old people in England was explained by a life course model that included material, psychosocial and behavioural pathways.

6.8 References

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