

**Socioeconomic Inequalities in
Polypharmacy Amongst Older People**

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**Submission for the Degree in Doctor of
Philosophy**

Population Health Sciences Institute

January 2025

Abstract

The use of multiple medications, polypharmacy, is common amongst older people and is an increasing public health challenge. The prevalence of polypharmacy across different populations has been well characterised, but what is less clear is how polypharmacy varies according to socioeconomic position. This thesis aims to address this evidence gap by exploring if there are social inequalities in polypharmacy, amongst older people.

First a systematic review and meta-analysis were undertaken to synthesise international evidence on social inequalities and polypharmacy. The evidence showed people with low socioeconomic status had greater likelihood of being in receipt of polypharmacy. Education was the most commonly used socioeconomic measure, and individuals with lower levels of education had a 21% increased likelihood of polypharmacy.

Second, data from longitudinal cohort studies, the two Cognitive Function and Ageing Studies (CFAS), were used to explore how socioeconomic status (measured by years of education) was associated with polypharmacy and how relationships have changed over time. Data from CFAS I (from 1991-1993) and CFAS II (2008-2009) were used in the analyses. Baseline waves of both CFAS I and CFAS II were compared. The analysis highlighted the sustained high level of polypharmacy, and multivariable logistic regression showed the widening inequalities in polypharmacy over the 20-year time period. Results from this chapter therefore informed the final analyses, to understand how inequalities in polypharmacy change across different medication groups. These analyses demonstrated that inequalities persist across different medication groups, although for some such effects (such as medications belonging to the cardiovascular group) were more pronounced than others.

The work of this thesis has highlighted inequalities in polypharmacy that are widening over time. This has happened at a time when healthcare is more sophisticated and expenditure has risen, but arguably insufficient importance has been placed on prevention and public health. People working in policy and practice should consider how to address social inequalities in polypharmacy alongside current policy initiatives (*e.g.* the use of Structured Medication Reviews).

Impact Statement

The Covid-19 pandemic had a significant impact on both my PhD progress and subsequent plans for the project. Progress of my PhD was also impacted with the delayed General Pharmaceutical Council pre-registration exam and remote working - both of which posed considerable challenges. I was unable to travel to Newcastle to access face to face support from my supervisors as well as additional resources for my research - both vital for helping to address any challenges and maintaining progress. Working remotely was particularly challenging during the data analysis stages of the project given I had not previously worked with statistical software packages. In addition, a large proportion of statistical training courses that I required to advance my skills were postponed and later switched to hybrid - while this was useful, the hybrid format lacked the engagement and interaction of in person courses. Given such challenges, my data analysis of my PhD was pushed back in terms of timing to ensure I had appropriate knowledge and skills to handle the data and construct the strategy of my analyses.

Dedication

To My Parents,

To my father and mother, thank you for the encouragement, guidance, and unwavering love throughout my life. Thank you for supporting me and for instilling in me the belief from an early age that, nothing should hinder me from pursuing my dreams. The support and sacrifices that you have shown, I forever am truly grateful for. I am truly blessed to have such amazing parents; may Allah continue to keep you in the best of health. I hope to have made you both proud and will continue to do so.

Love Anum

Acknowledgments

I would like to thank the contributions and acknowledgments of the following individuals and organisations.

- I. First and foremost, I would sincerely like to thank my supervisors, Professor Adam Todd, Professor Barbara Hanratty and Professor Fiona Matthews. I have learnt so much from you all and truly appreciate of the time, guidance, and support throughout my PhD. It has been an absolute pleasure working with you and I truly feel I have been extremely fortunate in having such a great team of experts. Adam thank you for providing me the encouragement and opportunity to take on this PhD, you have guided me through the ups and downs, and with all the challenges that life has thrown at me over the last few years, I really would not have been able to overcome them without your support. It has been an absolute pleasure to come back to Newcastle, and work with you over the last few years and you have invested a lot of time and patience in nurturing me. I feel extremely excited to start the next chapter of my career and will always like you to know that you have been a true part of building so many integral foundations. Fiona, thank you for having a lot of patience with me whilst battling through the statistics, you have been beyond supportive and really shown me a great insight into epidemiology and statistics. It has been truly amazing to be under your supervision, and it was extremely sad to hear that you were leaving Newcastle. I am beyond grateful for you choosing to continue providing me your support despite leaving the institution. And if there is one thing I will never forget, do not use a pie chart! Barbara, thank you for being supportive particularly through all NIHR work and providing me multiple opportunities to present my research, I have learnt so much from you over these years. You have played a fundamental part in my Early Research Career and thank you for giving me the opportunity to take my research further.
- II. David Sinclair, my unofficial fourth supervisor and friend. Thank you for everything that you have done for me over these last few years. Your countless support and advice I will always be grateful for.
- III. Connor Richardson, I appreciate the guidance and support you have provided me through my Early Research Career.
- IV. Professor Andy Husband, thank you for being a great academic tutor, I did not ever think I would be back doing a PhD, and you play a huge driving factor in this! You always said the perseverance would be worth it!

- V. My annual report panel, Professor Katie Brittain and Dr Yu-Tzu Wu for the advice and feedback provided throughout annual progress meetings. Your guidance has been truly appreciated.
- VI. I would like to extend my heartfelt gratitude to the amazing administrative team, Anosua Mitra, Julie Pencott and Stephanie Roe. Your meticulous organisation of meetings really made all the difference! I truly appreciate of all you have done over the years.
- VII. National Institute for Health and Care Research (NIHR), for funding my PhD.
- VIII. My brother, my constant source of inspiration. Through all my challenges and triumphs, your wisdom and presence has always guided me. I am truly thankful for having you in my life, and for the encouragement and support that you have always provided.
- IX. To my sister, thank you for bringing joy, inspiration, and support throughout this journey. From the laughter we have shared to the thoughtful conversations that we have had; you have made this journey memorable.
- X. Last but not least, to my wonderful friends. You are the incredible individuals that have made this journey brighter and more meaningful. Your friendship has been a source of strength throughout this process, and I am deeply grateful. Each of you have played an invaluable role not only in my academic success but also shaping me into the person that I am today. Thank you for being such an integral part of this chapter of my life.

Conference Presentations, Publications and Awards

Conference Presentations

Iqbal A, Sinclair D, Richardson CD, Hanratty B, Matthews FE, Todd A – Are there socioeconomic inequalities in polypharmacy among older people? A systematic review and meta-analysis. Poster pitch at Prescribing and Research in Medicines Management (PRIMM) June 2022, Manchester. Abstract published in *Pharmacoepidemiology and Drug Safety Journal*, August 2022.

Iqbal A, Sinclair D, Richardson CD, Hanratty B, Matthews FE, Todd A – Are there socioeconomic inequalities in polypharmacy among older people? A systematic review and meta-analysis. Poster pitch at the European Society of Clinical Pharmacy October 2022, Prague. Abstract published in the *International Journal of Clinical Pharmacy*.

Iqbal A, Sinclair D, Richardson CD, Hanratty B, Matthews FE, Todd A – Understanding the impact of socioeconomic inequalities on polypharmacy in England. Poster pitch at the European Society of Clinical Pharmacy October 2023, Aberdeen. Abstract published in the *International Journal of Clinical Pharmacy* January 2024.

Iqbal A, Hanratty B, Matthews FE, Sinclair D, Richardson CD, Todd A – Inequalities in Polypharmacy in adults aged 65+ in England. Presentation at the Gerontological Society of America, Annual Scientific Meetings November 2023, Tampa. Abstract published in *Innovation in Ageing*.

Publications

Iqbal A, Richardson C, Iqbal Z, O'Keefe H, Hanratty B, Matthews FE, Todd A. Are there socioeconomic inequalities in polypharmacy among older people? A systematic review and meta-analysis. *BMC Geriatrics* 2023, 23(1), 149.

Iqbal A, Matthews F, Hanratty B, Todd A. How should a physician assess medication burden and polypharmacy? *Expert Opinion on Pharmacotherapy* 2022, 23(1), 1-4.

Awards

Harold and Majorie Moss Charitable Trust Fund September 2023 (£1350)

Pharmacy Research UK, Research Training Bursary April 2021 (£5000)

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
AGS	American Geriatric Society
BNF	British National Formulary
CFAS	Cognitive Function and Ageing Studies
CINAHL	Cumulated Index in Nursing and Allied Health Literature
COPD	Chronic Obstructive Pulmonary Disease
CREDO	Clopidogrel for Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ELSA	English Longitudinal Study of Ageing
GDP	Gross Domestic Product
GP	General Practitioner
GRADE	Grading Of Recommendation Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
IMD	Index Multiple Deprivation
LTC	Long Term Condition
MAI	Medication Appropriateness Index
MLTC	Multiple Long-Term Condition
MTBQ	Multimorbidity Treatment Burden Questionnaire
NHS	National Health Service
NICE	National Institute for Health And Care Excellence
NIHR	National Institute for Health and Care Research
OADR	Old Age Dependency Ratio
OTC	Over The Counter
PAF	Population Attributable Fraction
PCN	Primary Care Network
PMDRP	Pharmacist Management of Drug Related Problems
QOF	Quality Outcomes Framework
RRR	Relative Risk Ratio
SDH	Social Determinants of Health
SEP	Socioeconomic Positions
SES	Socioeconomic Status
SMR	Structured Medication Reviews
TBQ	Treatment Burden Questionnaire
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1. Introduction

Some of the work from this chapter has been published and can be found at Appendix A:¹ Iqbal A, Matthews F.E, Hanratty B, Todd A. How should a physician assess medication burden and polypharmacy? *Expert Opin Pharmacotherapy*. 2021; 23(1):1-4

1.1 Introduction

“One of the first merits of this bill is that it provides a universal health service..... It is available to the whole population, and not only is it available to the whole population freely, but it is intended, through the health service, to generalise the best health advice and treatment.”² Tuesday 30th April 1946 marked a pivotal point in British history whereby Aneurin Bevan introduced the National Health Service (NHS) to the people of Britain, which offered free universal coverage to all at the point of contact.³ The NHS strives by these principles with the overarching aim of offering a comprehensive service to all, irrespective of individual attributes such as race, gender, or religion. It also endeavoured to have a wider societal duty in ensuring equality through its services and providing particular focus on groups within society of which their life expectancies and health do not mimic the wider population.³

Fast forward 64 years where Professor Sir Michael Marmot was commissioned by the British government to chair an independent review process to understand and propose the most effective evidence-based strategies to reduce inequalities in England - Marmot Review (2010).^{3,4} Consequently, a published report entitled *Fair society, Healthy Lives* (2010), concluded: i) premature death is reflective of inequalities, ii) there is an evident social gradient in health and iii) the NHS could play a role in delivering the reports policy objectives. The report showcased that poorer people in society are not only prone to a shorter life but are also subject to greater disability. Ten years on from this report, health inequalities are more evident than before, with a growing health gap between wealthier and deprived areas.⁵ Evidence has also demonstrated inequalities in the provision and utilisation of healthcare services.⁵ While the NHS is highly valued and continues to play a pivotal part in promoting and maintaining healthy lives of the UK population, from the evidence of healthcare inequalities discussed, it is becoming increasingly apparent that its founding principles, of equitable distribution of services and access to healthcare, may not align with society of today. It is therefore important to understand how inequalities present within society are mirrored in healthcare services, particularly medication utilisation; this thesis therefore sets out to explore this issue further. Specifically, the thesis will focus on older people with polypharmacy (using five or more

medicine) and examine if there are inequalities in medication usage and, if so, have they these inequalities have changed over time.

This chapter sets out to describe the fundamental concepts that underpin this thesis. It will first introduce key terms central to the work such as the ageing population and multimorbidity, of which are two pivotal factors in driving polypharmacy. This will follow discussion around the epidemiology of polypharmacy, including the long-standing discourse centred around its definition. Finally, key concepts will be introduced and discussed, both in relation to the broad aspects of socioeconomic inequalities and through a more focused lens regarding its presence within healthcare, particularly including medicine utilisation. Understanding these terms is essential to provide sufficient background to this area of research and subsequently identifying key gaps within this field, thereby illustrating the context in where the work of this thesis contributes. The chapter will conclude by providing an overarching structure for my thesis.

Chapter aim:

To provide an overview of my thesis and research area.

Objectives:

- I. Describe and provide context to the significance of an ageing population in relation to medication usage.
- II. Describe the significance of polypharmacy in relation to the challenges associated with its measurement and wider challenges in an ageing population.
- III. Understand and provide context to health inequalities in healthcare.
- IV. Describe the rationale of this research and thereby present the research question, its purpose and significance.
- V. Provide an overview of the structure of this thesis.

1.2 Ageing population

Globally there is a noticeable demographic shift characterised by a growing ageing population.⁶ According to the *United Nations' World Population Prospect Report* (2022), individuals aged 65 and above are expected to increase from 10% (2022) to 16% by 2050, whereby there will be more than twice the number of individuals aged 65 years and above, than the number of children under the age 5.⁷ Lower-income countries typically display higher fertility rates, than high-income countries.⁸ The reasons for this are complex, but potential factors to explain these observed lower fertility rates could include the high economic burden associated with children, or that women are delaying having children to pursue professional careers.⁸ In the United

Kingdom (UK) the population is projected to exceed 74 million by 2039,⁹ primarily driven by birth rates outgrowing mortality, and immigration outnumbering emigration.

This growing ageing population has led to a rise in the old age dependency ratio (OADR), which reflects the number of individuals over 65 years old per, 1,000 people aged 16 to 64 years old. In the UK, the OADR is predicted to increase from 10% (1922) to 50% by 2111,¹⁰ as reflected in Figure 1.1. This has raised concerns particularly regarding the policy and economic implications, as a high OADR can often lead to a decrease in employment rates,^{10,11} and subsequently affecting Gross Domestic Product (GDP) – a measure of a country's economic performance and growth. There are further concerns in the potential increase in expenditures on pensions, healthcare, and government debts.^{10,12} Table 1.1 shows data obtained from the Office of National Statistics which illustrates the changing age distribution, with the proportion of children from 0 to 15 years declining from 24.5 (1976) to 18.9% in 2016. Such trends are projected to continue but accompanied by an increase in the population aged 65 years and older.

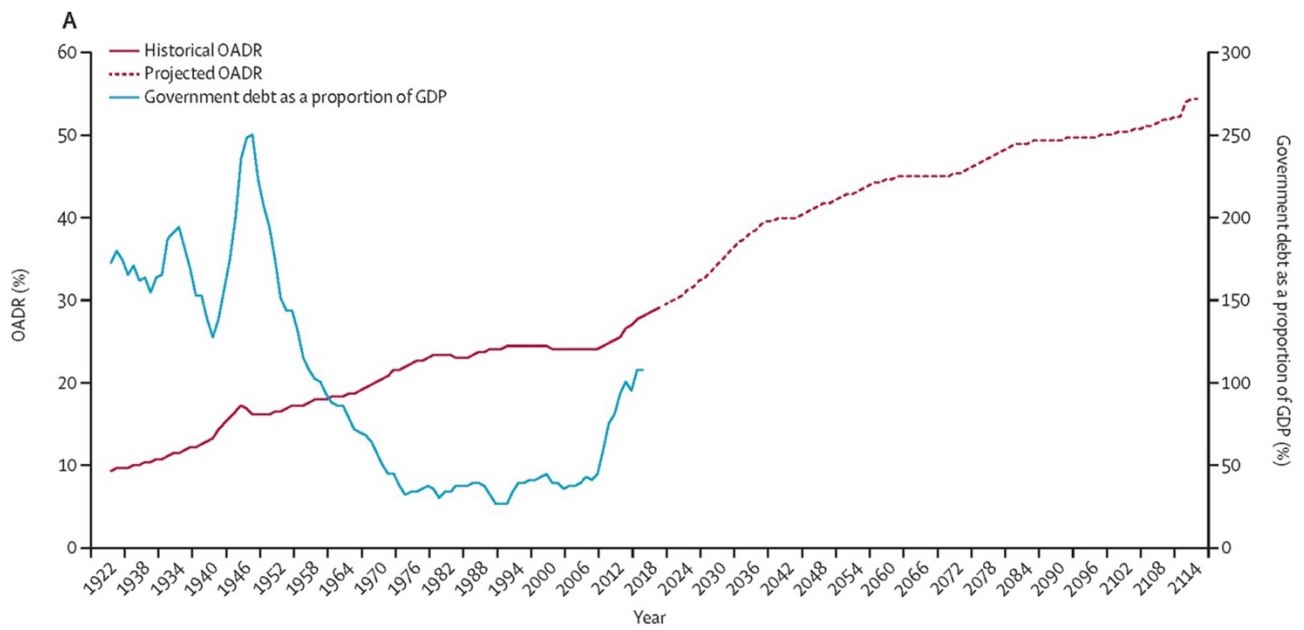


Figure 1. 1: Graph showing the past and predicted UK OADR trend.

Source: Human mortality database and office of national statistics, adapted from Scott.¹⁰

Table 1. 1: Age distribution of the UK population, 1976 to 2046 (projected).
Source: Office for National Statistics⁹

	0 to 15 years (%)	16 to 64 years (%)	Aged 65 and over (%)	UK population
1976	24.5	61.2	14.2	56,216,121
1986	20.5	64.1	15.4	56,683,835
1996	20.7	63.5	15.9	58,164,374
2006	19.2	64.9	15.9	60,827,067
2016	18.9	63.1	18.0	65,648,054
2026	18.8	60.7	20.5	69,843,515
2036	18.0	58.2	23.9	73,360,907
2046	17.7	57.7	24.7	76,342,235

Source: Office for National Statistics

Notes:

1. Population estimates data are used for 1996 to 2016, while 2014-based population projections are used for 2026 and 2036.

There are many factors that have contributed to the upward trajectory of an ageing population. Firstly, the global decline in mortality has led to an overall rise in life expectancies globally, projected to reach 77.2 years by 2050.⁷ A significant contribution to this is the improvement of sanitation and living conditions, facilitating more people having access to clean drinking water and thereby reducing the likelihood of disease transmission.^{13,14} Second, advancements in healthcare and better access to medical services plays a pivotal role in improving life expectancy.¹⁵⁻¹⁷ For instance, advancements in managing diseases that were once associated with high mortality, such as HIV,¹⁸ along with the availability of preventative measures such as vaccines have positively improved life expectancies.¹⁹ Individuals are also adopting healthier behaviours, for example improvement in smoking cessation rates,²⁰ inevitably leading to better health outcomes.²¹ Finally, public health interventions serve as significant drivers, with government policies aimed at improving population health, disease prevention, and healthcare infrastructures.²² There is also a growing presence of charities, particularly in low-income countries, which have and continue to contribute to better health outcomes.²¹

Although there has been an increase in life expectancy, this growth is not equal, with there being considerable differences amongst countries. The United Nations has highlighted that life expectancy of the low-income countries remained 7 years behind the global average.⁷ This highlights the pronounced health inequalities in between countries, resulting in considerable burden on governments worldwide to try and address this gap.

Despite an overall increase in life expectancy, this has not been met with a proportional increase in healthy life expectancy,²³ *i.e.* the number of years spent in healthy life. This is often assessed through measures such as i) disability free life²⁴ (activity limitations/dependencies) or ii) healthy life expectancy, subjective to self-reported health.²⁵ Disability free life is referred to as the time an individual will be free of life limiting illness and or disability, that would affect their ability to perform daily activities and is based upon self-assessment.²⁶ Whereas healthy life expectancy is a measure of the number of years an individual is said to live in good health, considering broader aspects such as physical and mental ability.²⁶ A King's Fund report²⁷ described a reduction in healthy life expectancy in England over a ten-year period, with an average decline of 0.8 years in males and 1.2 years in females. Similarly, disability free life expectancy, were two decades shorter than life expectancy. Overall, people are living more years in poor health, an urgent priority for governments to address.²⁸ The ageing population is vulnerable and places many challenges particularly for healthcare services, with their increased frailty, multimorbidity, cognitive impairment and dependency.

1.3 Multimorbidity

As previously discussed, despite the increase in life expectancy, healthy life expectancy is not increasing at the same rate, and more people are developing long term conditions and disabilities.^{23,29} In 2015, approximately 15 million people, in England, were living with a long term condition (LTC) – defined as a condition that cannot be cured, but is controlled by medication/and or other therapies/treatments.²⁹ Data indicated that 58% of individuals with an LTC, were over the age of 60, with 25% having two or more LTCs.²⁹ Evidence has suggested LTCs are continuing to rise and are linked to poorer health outcomes and severe healthcare burden, through their associated high healthcare costs to manage.³⁰ For example, in England individuals with LTCs accounted for 50% of GP appointments and 70% of total healthcare spending.²⁹

Multimorbidity, defined as the presence of two or more LTCs,^{31,32} has been associated with negative health outcomes, such as shorter life expectancy, poorer quality of life, longer hospital stays, and key issues around patient safety,^{32–34} as shown in Figure 1.2. People with multimorbidity commonly encounter different healthcare professionals across primary and secondary care, which can lead to fragmented care. This issue is often compounded by a lack of clinical guidance associated with multimorbidity and people with multimorbidity are often assessed based on their individual disease states rather than collectively as a whole.³⁴

The prevalence of multimorbidity is increasing rapidly,³² and it is considered a growing public health challenge.^{32,35,36} The presence of multimorbidity can vary internationally,³⁷ nevertheless, on a global basis, it is becoming the norm rather than an exception.³² Such a rise in prevalence has allowed for a new categorisation - complex multimorbidity - defined as the presence of three or more conditions.³⁸ Complex multimorbidity can exacerbate challenges with frailty, functional decline, and lower healthy life expectancy.³² In England, there has been a notable rise in multimorbidity over the years. For example, a study using data from the English Longitudinal Study of Ageing, revealed an 11% increase in multimorbidity between 2002-2013.³⁹ Whereas complex multimorbidity doubled between the years 2004-2019. Although age has shown to be a strong contributing factor to multimorbidity, many younger people are also at risk of having multimorbidity.^{32,40} For example, a study carried out in the UK highlighted 40% of individuals developed multimorbidity between the ages of 16 and 39⁴¹ and is continually rising.⁴²

Fragmentation and poor coordination of care • Results from seeing multiple health professionals in primary and secondary care.	Polypharmacy • Attendant risk of adverse drug events, potentially inappropriate prescribing, and problems with drug concordance.	Treatment burden • Results from the necessity of learning about and adhering to management plans and lifestyle changes suggested for different conditions and engaging with multiple healthcare professionals.	Mental health difficulties • Anxiety and depression are more common in patients with multimorbidity and can impact on patients' ability to manage other long term conditions. Patients living in deprived areas are particularly vulnerable to multimorbidity that includes mental health conditions. Those with cognitive impairment are also particularly vulnerable and may have added difficulties in managing their conditions.	Functional difficulties • Functional difficulties increase with increasing number of conditions and in people aged more than 75 years.	Reduced quality of life • Associated with the number of chronic medical conditions.	Increased healthcare utilisation • Includes an increased risk of emergency admission to hospital.
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Figure 1. 2: Common problems encountered by individuals with multimorbidity.
Adapted and modified from Wallace et al⁴³

Multimorbidity can be influenced by factors such as gender,⁴⁴ ethnicity,^{41,45} and socioeconomic background.^{40,42,44} Living in an area of high social deprivation has also been identified as an important factor in the prevalence of multimorbidity.⁴⁶ For example, a study conducted in Scotland investigated data across 314 medical practices, and demonstrated that the onset of multimorbidity occurred 10-15 years earlier in individuals living in deprived neighbourhoods in comparison to more affluent neighbourhoods.⁴⁷ In addition, living in areas of higher deprivation has been shown to be associated with higher prevalence of conditions such as depression, anxiety, coronary heart disease and diabetes for people with multimorbidity.⁴⁸

Despite the continual rise⁴⁹ of multimorbidity, there is a lack of research focusing on interventions in terms of managing it, with healthcare professionals continually expressing the need for better guidance.⁵⁰ A large proportion of clinical guidance is often disease specific, and the inconsistency of acknowledging individuals with multiple health conditions.⁵¹ International consensus however suggests patient centred care is important in the management of multimorbidity,^{52,53} defined by NHS England as focussing care on the needs of individuals, supporting people to develop the knowledge....to more effectively manage and make informed decisions about their own health.⁵³ The National Institute for Health and Care Excellence (NICE) identifies patient centred care as being central to good quality health services⁵⁴ and is thus firmly imbedded in the NHS Long Term Plan.⁵⁵ Essentially patient centred care ensures that the patient is listened to, informed, respected and involved in their care⁵⁶ – important factors given the physical and mental challenges such individuals face. However, Salisbury *et al*⁵⁷ carried out a cluster-randomised trial in 6 GP practices across the UK, with the aim to implement a new approach in managing patients with multimorbidity. This would encompass the 3D approach, (reflective of a patient centred care model encompassing a variety of international guidelines). Such model essentially aims to replace traditional disease centred reviews of an individual condition with a 6 monthly comprehensive multidisciplinary review. Each review would consist of 2 appointments – with a nurse and a named responsible physician in the practice. It would also encompass a medication review by a pharmacist, of which may not be based in the practice. The patients were asked to think about the health problems that *bother* them the most. The nurse has a key role in assessing the patient needs and identifying most important challenges for the patient. The pharmacist optimises treatment, and the physician reflects on all the aforementioned recommendations and customises a treatment plan for the patient. The results of the trial demonstrated no improvement in quality of life, in comparison to standardised care – isolating diseases and providing isolated care. It did however

show significant improvements in measuring patient centred care, of which can be argued as an important attributor to the triple aims of healthcare – improving patient experience of care, improving the health of a population and reducing per capita cost of care.^{57,58}

The Academy of Medical Sciences have suggested that further work is required to better understand the growing challenges of multimorbidity.³² This includes the clusters of conditions that are most prevalent and problematic for an individual and how best to improve the organisation of healthcare systems to manage risks associated for patients.³² A systematic review further investigated clustering of multimorbidity,⁵⁹ and identified three groups: cardiovascular and metabolic disease, musculoskeletal disorders, and mental health related illnesses. Hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) were reported as three of the most prevalent conditions, and overall results demonstrated that certain LTCs could potentiate multimorbidity.^{59,60}

Multimorbidity has shown to be a prominent factor interlinked with polypharmacy, whereby an increase in LTCs can result in an increase in medication usage, however, this may not always be the case.⁶¹ This is an ongoing challenge for prescribers: the need to balance the risks and benefits of medications whilst ensuring that patients receive evidence-based care.^{62,63} Therefore, when trying to understand outcomes, and implications of either polypharmacy or multimorbidity, the prevalence of both should be considered. Literature has suggested in particular more research around the additive and independent effects of polypharmacy and multimorbidity on health outcomes is required.⁶¹

1.4 Epidemiology of polypharmacy

1.4.1 Introduction

The term polypharmacy originated from ancient Greek, “polous” meaning many, and “pharmakeia” referring to “the use of drugs.”⁶⁴ This term has become a ubiquitous aspect of clinical practice and is widely recognised among healthcare practitioners. With an increase in life expectancy⁶ and prevalence of LTCs,³² a notable consequence of this is an increase in medication usage and, subsequently, the rise of polypharmacy.⁴³ Polypharmacy has emerged as a growing public health concern, especially within the ageing population.⁶⁵ Older people with polypharmacy are often at risk of frailty,^{66,67} hospitalisation,^{68,69} drug-drug interactions,^{43,70} and other key issues affecting patient safety.⁷¹

1.4.2 Prevalence

The pervasiveness of this problem is worldwide, with many researchers commenting on the rise of polypharmacy over the years.^{43,64,72,73} The challenges associated with polypharmacy are expected to increase in the future given the global rising ageing population.⁶ A recent study carried out in the North East of England, examined prevalence of polypharmacy amongst individuals 85 years and over. The study highlighted almost half of the participants were taking between 5 to 9 medications (49.6%, n = 419, with a median of 6).⁷⁴ Similar studies have demonstrated a high prevalence of polypharmacy, particularly in an ageing population.⁷⁵ For example, a study in Denmark demonstrated 51% of individuals ≥ 75 years had polypharmacy, compared with only 12% of the entire population.⁷⁶ In Japan⁷⁷ through a large cross-sectional study, 64% of individuals were reported to have polypharmacy. In Europe, using data from the Survey of Health Ageing and Retirement in Europe (SHARE) Study, Midao *et al* examined prevalence of polypharmacy across 17 European countries (and Israel) and showed prevalence of polypharmacy ranged from 26.3% in Switzerland to 39.9% in Czech Republic.⁷³ Switzerland, Croatia and Slovenia presented with the lowest prevalence of polypharmacy, with Portugal, Israel and Czech Republic presenting with the highest. Findings further demonstrated lower prevalence was associated with engagement in physical activities, having no difficulties in taking medication and less than two diseases. Further socioeconomic factors such as lower income also demonstrated a higher prevalence of polypharmacy, of which ranged from 26.3% in Switzerland to 39.9% in Czech Republic. Highlighting the wide range of prevalence across the continent.

Observations through longitudinal analysis has also shown a rise in prevalence of polypharmacy over time. For example, data from a Scottish population demonstrated that between 1995 and 2010 polypharmacy increased from 11.4% to 20.8% and, individuals with ≥ 10 medication tripled to 5.8%.⁴³ Looking further afield, similar trends are shown globally. For example, a study across Australia showed that the number of older people experiencing polypharmacy increased by 52% from 2006 to 2017,⁷⁸ however a modest increase in prevalence of only 9%. Studies suggest that there have been steeper increases in polypharmacy in other healthcare systems; for example, in the United States (US) where – 24% of older people had polypharmacy in 1992 compared to 39% in 2012.⁷⁹ This is further supported through analysis of prescription data in the US between 1999-2006 (Figure 1.3) highlighting the rise of polypharmacy, from 6.3% to 10.7%. This graph has also demonstrated an increase in general medication usage over time. Similar trends of increased medication utilisation have been observed across other countries including Sweden,⁸⁰ Ireland⁸¹ and Netherlands.⁸²

Some studies have focused on polypharmacy across specific patient groups or within a certain class of medication. For example, patients with diabetes, which is increasingly considered as a significant issue, indicates that almost two-thirds of individuals have polypharmacy.^{83,84} Furthermore, individuals with heart failure or cardiovascular disease⁸⁵ have also demonstrated a high prevalence of polypharmacy.⁸⁶ However, it is unclear whether the findings are attributed to increased multimorbidity; for example, patients with diabetes are often prone to an increased likelihood of multiple long term conditions (MLTCs) such as renal, respiratory, and cardiovascular disease.⁸³ While the intricate relationship between polypharmacy and multimorbidity will be explored further in this thesis, studies investigating prevalence of specific medication groups reveals cardiovascular medications are the most common.⁴³ Similar observations have been demonstrated in a British cohort study, with medication usage increasing by 13.4%, with a corresponding increase in cardiovascular polypharmacy.⁷⁵ In addition, findings from a Danish study also highlighted the widespread use of cardiovascular medications.⁷⁶ Further discussion around the prevalence of polypharmacy associated with specific medication groups will be addressed in Chapter 5 of this thesis.

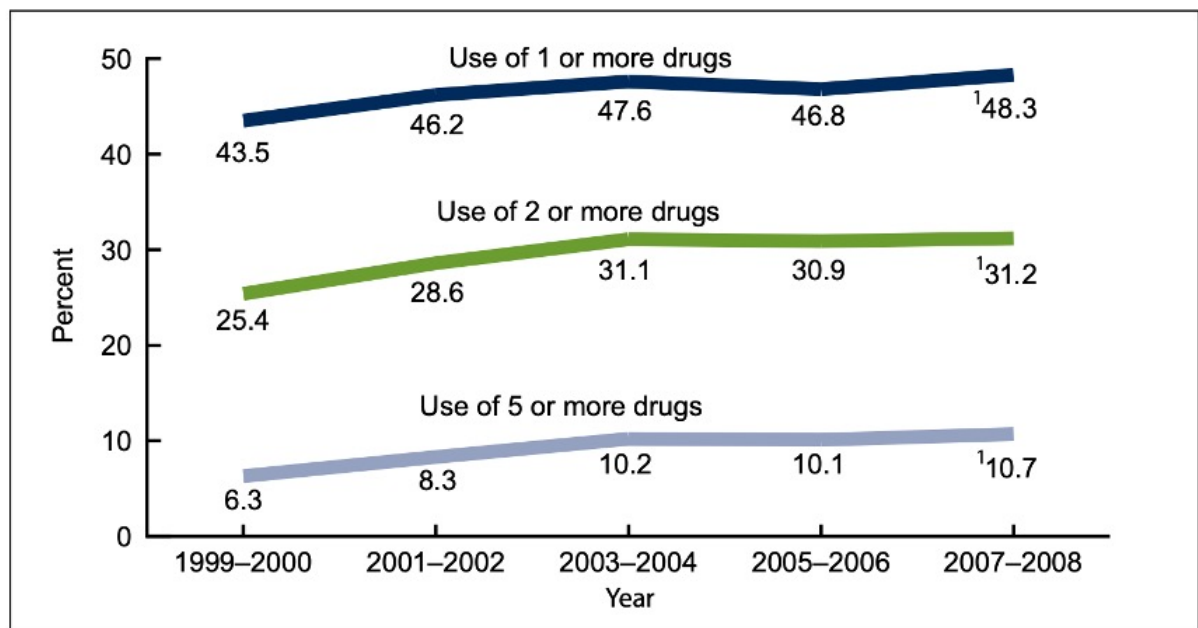


Figure 1. 3: Trends in the percentage of individuals using a prescription drug: United States 1999-2008.

Source: CDC/NCHS National Health and Nutrition Examination Survey, adapted from Qiuping et al. ⁸⁷

1.4.3 Definition and classification

Polypharmacy is used to describe a complex healthcare scenario whereby an individual uses multiple medications. Whilst there is no universal way to define polypharmacy, the use of five or more medications concurrently is the most accepted definition within clinical practice.⁸⁸ The work of Masnoon *et al*⁸⁹ aimed to understand and synthesise existing literature around polypharmacy definitions and identified a total of 138 definitions. Definitions were categorised as the following: based solely on numerical threshold, numerical values incorporating a duration of therapy or a specific healthcare setting, descriptive definitions, or a definition reflective on appropriateness. A numerical threshold included an arbitrary value, which ranged from 2-11 medications, with ≥ 5 being the most common. Fifty-one of the included studies referred to polypharmacy by this definition.⁸⁹ While it may be useful to have a threshold or so called *cut off* in order to identify patients with polypharmacy, an arbitrary value offers limited practicality especially in clinical practice.⁸⁹ A numerical cut off does not factor in the complexities of real-life challenges,⁹⁰ and while it may help suggest potential patients at risk or help prioritise medication reviews, the usefulness of this definition in approaching medication safety risks can be limited.⁹¹ This limitation arises as a specific value or threshold is unable to completely reflect prescribing quality or drug-related problems.^{92,93} Furthermore, setting an arbitrary value for polypharmacy will require review over time, particularly with growing multimorbidity and increasing life expectancy; raising the threshold to 10 or more medicines has been suggested.⁸⁸

Masnoon *et al*, further demonstrated that, some of the studies not only incorporated a “cut off” but also incorporated categorical classification. For example: “minor,” referring to <4 medications,⁹⁴ “moderate,” indicating 4-5 medication,⁹⁵ “major” representing 5-11 medications,^{94,96} “hyper” being ≥ 10 ,⁹⁷ and “excessive” suggesting ≥ 10 – ≥ 21 .^{98,99} Studies have also combined these terms; for example, “super hyperpolypharmacy,”¹⁰⁰ referring to an individual heart failure using ≥ 15 medications. Conversely individuals with <5 medications have been referred to as having “non-polypharmacy”¹⁰¹ or “oligopharmacy”.¹⁰² Similar to an arbitrary cut off, there is limited consensus amongst these categories; for example, 10 medications can be referred to as “major” in one study and “excessive” in another.⁸⁹

Another definition discussed by Masnoon *et al*, is the consideration of using a duration of therapy, for example ≥ 5 medications used in the same month, or within a particular setting such as the hospital.⁸⁹ The authors of this review discussed the limited clarity that this provides in relation to appropriateness of prescribing, particularly the consideration the potential for a

medication causing harm. In this instance it would be important to acknowledge the long-term exposure to inappropriate medication.¹⁰³

In view of this complexity, some definitions of polypharmacy have explored the possibility of adding in a descriptive element, which may include assessing medication appropriateness.⁸⁹ Assessing medication appropriateness allows for the individual patient needs to be considered, as well as the rationale behind prescribing. Nevertheless the arbitrary measurement of polypharmacy is still a useful starting point in identifying people with multiple medications; however, the significance lays with assessing the medication indication, efficacy, and interactions, which overall help to indicate prescribing appropriateness.^{89,90,104} This is further supported by findings from a Kings Fund report,¹⁰⁵ which indicated that rather than being solely guided by a numerical threshold, the assessment of medication should focus on appropriateness of treatment.^{105,106}

1.4.4 Appropriate or inappropriate polypharmacy

Appropriate polypharmacy involves identifying if the treatment choices have been reflective of best evidence-based practice, and the medication is optimised according to patient needs.⁷¹ A Scottish primary care study¹⁰⁷ highlighted that while unplanned hospitalisation was strongly associated with the number of medications that an individual was using, this effect was reduced with individuals with multiple conditions. Results showcased that, individuals with one condition, were more likely to have an unplanned hospital admission with an increase in medication usage. Whereas individuals with multiple conditions (six or more), the effect of taking more medications on unplanned admissions were less pronounced. In essence, this study highlights that the potentially undesirable and negative outcomes that are often associated with polypharmacy are not so problematic once the individual patient requirements have been assessed and addressed. Appropriate polypharmacy can often be considered where the benefits of treatment outweigh the potential risks.

Problematic, or *inappropriate* polypharmacy, presents a situation whereby the harms of medication outweigh the benefits, or where medication is prescribed inappropriately.¹⁰⁵ This may result in increased potential drug interactions, adverse drug reactions, poor adherence and reduced quality of life.^{104,105} Examples of problematic prescribing may include: ^{105,108}

- i. a hazardous drug combination due to drug interactions;
- ii. a high pill burden resulting in a burdensome medicine regimen causing reduced adherence;

- iii. medicines used to manage prescribing cascades; and
- iv. medications prescribed when there is questionable evidence of benefit.

Both problematic or inappropriate polypharmacy are often used interchangeably; however, Guthrie *et al*⁴³ suggested that there can be differences between them, with polypharmacy being “potentially problematic rather than always inappropriate.” In essence, not all serious interactions manifest to patient harm, and sometimes such risks are worth it if the benefits are potentially more rewarding.⁴³

1.4.5 Assessing medication appropriateness

In some contexts, an increase in medication prescribing represents appropriate and necessary practice, as multiple medications are often required to manage certain conditions.⁹¹ For example, in the initial treatment of acute ischemic stroke, dual antiplatelet therapy¹⁰⁹ (a combination of two antiplatelet drugs) is initiated 72 hours after the stroke. In this instance, the use of these medications is important to reduce the risk of a recurrent episode.¹¹⁰ Similarly, in the treatment of heart failure patients are often currently prescribed a beta blocker and an angiotensin converting enzyme (ACE) inhibitor, which has been shown to reduce mortality.¹⁰⁹ However, it is only possible to evaluate medication appropriateness by looking at individual patient circumstances and contexts.¹¹¹ It has previously been highlighted that older people have increasing levels of inappropriate polypharmacy, which can result in poorer patient outcomes.^{112,113} Factors such as an increase in medication usage,^{113,114} specific drug classes,¹¹³ health status^{113,115} and demographic variables such as gender^{113,115} have been shown to be important factors when considering inappropriate polypharmacy.

Healthcare professionals, therefore, have an important role to play when prescribing, as well as reviewing, medication in older people.¹⁰⁸ Whilst there is no agreed consensus on the best approach to evaluate medication appropriateness, there are several assessment tools that can be used.¹¹⁶ Current practices involve the implementation of explicit (criterion based) and implicit (judgement based) tools, which are used to identify medications that present a higher risk in certain patient groups. Kaufmann *et al* identified a total of 46 tools available - all of which have major differences in their structure and content.¹¹⁶ A summary of these tools is provided below.

Explicit tools are developed from literature, expert opinions, and consensus techniques.^{116,117} They are often orientated around specific diseases or medications, with rigid criteria and, therefore, little clinical judgment is required to use the tool.^{118,119} Furthermore, such tools often

do not consider disease burden or MLTCs and therefore lack the personalisation to individual patient needs or understanding the complexities of medication regimens. As such these tools may be limited in their usefulness in assessing patient level medication appropriateness. Explicit tools also require regular updates to remain valid, and with medication guidelines and different treatment available across different countries, such tools need to be adapted to meet specific country requirements to ensure applicability.¹¹⁶ However, these tools are useful in the application to large datasets, given that the required information to complete them is often available.¹¹⁹

Examples of explicit tools include the STOPP-START criteria¹²⁰ and the AGS Beers Criteria.¹²¹ The Beers criteria, endorsed by the American Geriatric Society (AGS), was first developed in 1991.¹²² The criteria also provided information on dose adjustments as well as addressing concurrent medications that could potentially result in drug-drug interactions. The AGS Beers Criteria has had a total of seven revisions: 1997, 2003, 2012, 2015, 2019 and 2023.¹²³ At first the AGS Beers Criteria was developed with the aim of improving the quality of care in geriatric services across nursing home.^{118,124} Subsequent revisions included additional groups of people such as community dwelling older adults.¹²⁴ Later updates further incorporate newer scientific evidence.¹²⁴ The most recent update, in 2023, provided explicit medications that should be avoided in the older people, with the exception of those receiving end of life or hospice care.¹²³ All revisions involve an expert panel that consist of a variety of clinicians with extensive experience and knowledge in the care of older people. With the latest update, a rigorous evidence review and synthesis were implemented, reflective of suggestions of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool used to grade quality of evidence.¹²⁵ The criteria were further made available for public comment; the AGS circulated the criteria to over 40 organisations, which further highlights the rigour applied to this update.¹²³

Another explicit tool that is widely used is the STOPP-START criteria, first published in 2008.^{123,126} This tool was originally developed and revised by experts across Ireland and the UK from medical backgrounds with experience in geriatric pharmacotherapy.¹²⁶ The STOPP-START criteria provides a list of medications that should be avoided in older people and, conversely, when it is appropriate to commence treatment (*e.g.* stopping an ACE inhibitor in hyperkalaemia; starting an ACE inhibitor in congestive heart failure).¹²⁰ Similarly to the AGS Beers Criteria, this tool has had several updates, 2015 and 2023^{127,128} – with the most recent revisions extending to consensus from experts across Europe and a more extensive list reflective

of changes to clinical practice; for example, the introduction of new medicines.¹²⁸ Both the AGS Beers Criteria and the STOPP-START criteria can provide a good foundation for clinicians when assessing medication appropriateness; however, studies^{129–131} have shown there is variability between tools and that the identification of potentially inappropriate medication will be dependent on the chosen tool.

To assess challenges that polypharmacy may have on an individual, it is important to consider the use of the implicit tools. Such tools are patient-specific, judgment based, and often consider the entire medication regimen of an individual.¹¹⁸ Unlike explicit tools, they require experience and knowledge of the user to be implemented.¹¹⁶ However, while it being advantageous of requiring clinicians to evaluate the appropriateness of treatment through a patient centred approach and the use of their professional judgment,¹¹⁶ such tools are often time consuming and have low reliability and reproducibility.¹¹⁷ Therefore the use of implicit tools can often be limited, particularly with the practical constraints faced in busy clinical practice. To further improve medication assessment, it has been suggested to combine both explicit and implicit tools, which is the subject of further study.¹¹⁸ An example of an implicit tool is the Medication Appropriate Index (MAI).¹³² This tool consists of 10 questions with three rating choices ranging from: being appropriate, being marginally appropriate, and being inappropriate.^{132,133} Guidance includes general instructions on how to answer the questions with appendices for further support. A narrative review carried out by Hanlon *et al*, suggested that while it may be useful that the MAI conceptualises the patient in the review, the actual usefulness and applicability in addressing suboptimal prescribing (*i.e.* polypharmacy or underuse of medications) is not as good when compared to other tools (*e.g.* Liptons tool¹³⁴ or the Pharmacists Management of Drug Related Problems (PMDRP) tool¹³⁵).¹¹⁶ Furthermore, the authors of this review also commented that as these tools are heavily based on clinical assessment and what may be seen as inappropriate for clinicians, the tools may not necessary capture what a patient perceives is important.^{132,136}

Overall, both categories of tools have their strengths and weaknesses, and no single tool covers all aspects of inappropriate prescribing.¹¹⁶ Instead, as suggested by Kaufman *et al*,¹¹⁶ such tools should not be used to substitute clinical judgment but instead, be useful indicators for drawing potential inappropriate prescribing to the attention of healthcare professionals.

1.4.6 Contributing factors to prevalence of polypharmacy

There are many direct and indirect factors contributing to the prevalence of polypharmacy, these are outlined and discussed below:

1.4.6.1 Shared decision making and patient expectations

The concept of shared decision making has actively encouraged prescribers to support patients in collaboratively working with clinicians to reach decisions regarding their treatment. This process involves clinicians providing evidence-based information about various treatment options, documenting and incorporating patient preferences, with the aim to ensure patients get “the care they need and no less, the care they want, and no more.”¹³⁷ However, the literature has demonstrated that, in reality, patients’ requests have the potential to influence prescribers decision making.^{138–140} Therefore this requires careful management, in order to ensure that prescribers are not giving patients what they necessarily request (*e.g.* antibiotic treatment). It is important for clinicians to manage patient expectations throughout a consultation, especially when patients have increased expectations for their health.¹⁴¹ This can also result in patients wanting rapid symptom relief and, therefore, in some cases unnecessary medication being prescribed, leading to inappropriate polypharmacy. The desire to *please patients* or the perceived expectations that a clinician may assume a patient has, has been shown to be a challenge in modern healthcare practices.^{142,143} Inevitably, these challenges have the potential to result in increased medication usage and ultimately polypharmacy.

1.4.6.2 Self-care management

The ease of purchasing over the counter (OTC) medications and increased accessibility to health-related information, has contributed to individuals taking an active role in managing their own health. Whilst there are many advantages to having access to medication, such as the ability to treat minor illnesses and therefore freeing up both patient and clinician time, it may introduce avoidable interactions and adverse effects.^{144,145} Often patients purchase items without the expertise of a healthcare professional, such as a pharmacist, and thus inappropriate medication usage can be common in this context. The accessibility of medication, while convenient also has drawbacks. Individuals are often shown to seek quick symptom relief by trying multiple medications and, in some instances, taking new medications to address side effects of existing medication. This inevitably results in individuals accumulating more medication over time, with an increase likelihood of developing inappropriate polypharmacy.

1.4.6.3 Medication reviews

In the UK prior to 2013, general practices were incentivised to provide medication reviews, under the Quality and Outcomes Framework (QOF),¹⁴⁶ particularly every 15 months for patients on repeat medications. Such reviews are important in ensuring medicine optimisation and safe prescribing.¹⁴⁷ Under the improved and revised setting, structured medication reviews (SMR)¹⁴⁸ were introduced with the aim to allow clinicians to target specific population groups, such as those that may be house bound, prone to severe frailty or with complex or problematic polypharmacy. Therefore, SMRs aimed to reduce patient harm, improve quality of care and reduce medicine waste.¹⁴⁸ Past evidence has shown that pharmacist-led reviews have reduced drug-related problems in the older population, further highlighting the importance of reviews in clinical practice to reduce inappropriate polypharmacy.¹⁴⁹ Work carried out in care homes, an area where multiple medication usage is extremely common, showcased that medication reviews were an important component in reducing polypharmacy,¹⁵⁰ highlighting their importance if carried out correctly. However, studies have shown that SMRs are not a priority for some primary care networks (PCNs) and implementation of such reviews has been varied.^{151–153}

1.4.7 Challenges of polypharmacy

1.4.7.1 Treatment burden

The use of multiple medication has shown to affect the quality of life of an individual, particularly in relation to how burdensome a treatment can be. Treatment burden, broadly defined as the “workload” associated with healthcare and the impact on patient well-being, can cover many different aspects of care including administering medication, financial challenges, and the additional pressures placed upon family members.¹ It has been suggested that having polypharmacy is one specific aspect of treatment burden.

Whilst there is no formal definition of treatment burden, some researchers have suggested that the “workload” generated with treatment regimens (*e.g.* people taking a proactive role in understanding their condition, having an awareness of when to administer their medication, or understanding adverse effects associated with multiple medications) all contribute to the concept of treatment burden.¹⁵⁴ Other factors have been identified in contributing to treatment burden and include managing medical appointments, enlisting support from families and friends, financial challenges and limitations placed on daily activities.¹⁵⁴ Meanwhile, it has been suggested that treatment burden is often subjective and may change according to context. For

example, whilst patients may be accommodating towards the use of multiple oral medications, challenges can arise – in terms of treatment burden – when the medications are self-administered through other routes.¹⁵⁵ In addition, treatment burden may not only be problematic for the patient, but also amongst those involved within their care, with many studies showing family carers have experienced deteriorating health, lack of support, self-neglect and, in some countries where healthcare systems are privatised, financial burden associated with treatment.¹⁵⁵

There are many tools available for clinicians to use in order to evaluate appropriate treatment and assess the impact it has on patient lives. For example, a widely available instrument in this regard is the Treatment Burden Questionnaire (TBQ) – a tool originally composed of 13 items on a Likert scale ranging from zero (not a problem) to 10 (a big problem).¹⁵⁶ The TBQ considers the direct burden associated with taking medication, such as the size of tablets, route of administration and frequency. It further assesses burden associated with broader aspects of healthcare such as laboratory testing, planning for medical appointments, and self-monitoring (*e.g.* taking blood pressure). Another tool used for assessing treatment burden is the Multimorbidity Treatment Burden Questionnaire (MTBQ), which focuses specifically on people with multimorbidity.¹⁵⁷ Similarly to the TBQ, focuses on potential burdensome factors related to using multiple medications (*e.g.* patients remembering to take their medication, collecting their prescriptions and attending appointments with healthcare professionals). Although such tools may be useful in helping to determine the treatment burden associated with a specific disease, it is important that they are not used in isolation to determine treatment decisions. Tran *et al* have shown a negative correlation between treatment satisfaction and treatment burden,¹⁵⁶ which furthers strengthens the argument that such tools should be used as a starting point to facilitate treatment discussions between a clinician and their patient.

Although there are a range of tools available that can be used to assess polypharmacy, inappropriate prescribing or treatment burden, there is not one specific instrument that assesses all three aspects. When considering treatment burden, tools measure a range of factors; however, they cannot cover all possible elements that contribute to burden, as this is subjective to each patient. Whilst polypharmacy may contribute to an aspect of burden, the role that tools, such as the STOPP-START criteria, the AGS Beers Criteria, and the Medication Appropriateness Index, have are useful in assessing medication appropriateness. However, just because a prescribed medication is clinically appropriate does not necessarily mean that it is

free of burden; similarly, a medication that is considered clinically inappropriate might not necessarily be burdensome.

1.5 Health inequalities

1.5.1 Introduction

Health inequalities have been defined as “avoidable, unfair and systematic differences in health between different groups of people.”¹⁵⁸ Health inequalities are prominent in the UK¹⁵⁹ and worldwide,^{160–162} and associated with variation in access to healthcare services and the overall uptake of medical treatments.^{158,163} Such inequalities can stem from socioeconomic and environmental factors, particularly affecting those at the bottom of the social gradient.¹⁶⁰ Evidence has shown that these individuals face shorter life expectancies and have a poorer quality of life due to a higher incidence of multimorbidity, particularly emerging at a younger age compared to those from more affluent neighbourhoods.^{160,164–166} These inequalities may manifest across many levels such as ethnicity, race, gender, and socioeconomic, all of which require a multifaceted approach to address.¹⁵⁸

1.5.2 Health inequalities in a UK context

Health inequalities remain a significant challenge in the UK, despite the provision of the NHS, that aims to provide free, universal healthcare to all at the point of need. The Marmot Review (2010)⁴ highlighted the so-called health gradient, with those that are more socioeconomically deprived more likely to develop long-term health conditions. The health gap in the UK is such that people living in the most deprived areas (Blackpool, North West England, 2020-22) and the least deprived areas (Hart, South East England, 2020-22) have a gap in life expectancy of 10.3 years for males and 7.1 years for females.²⁷ Such inequalities have been reported to have widened in recent years.²⁷ Similar statistics have been reported for healthy life expectancy, whereby it is estimated to be 7 years shorter for males and 6 years shorter for females living in North East England compared to those living in South East England. The north-south divide is well characterised, whereby individuals residing in the north of England have lower life expectancies and find it more difficult to access healthcare services, than their southern counterparts.^{158,167} Evidence has shown that such inequalities have widened over time, which has been further exacerbated post-Covid-19.¹⁵⁹ There are examples of other health divides, which can be observed around the world, with “all countries [having] a north.”¹⁶⁴ In addition, the inverse care law, originally proposed by Hart in 1971,¹⁶⁸ suggests that inequalities exist for access to healthcare, with those most in need of medical care are the least likely to access it.

This demonstrates fundamental challenges in the provision of healthcare; by demonstrating those needing medical care the most are likely to face multiple barriers in obtaining it, irrespective of the NHS principles of healthcare to be comprehensive, universal, and free for all at the point of contact. The inverse care law still persists today with GP practices in the most deprived neighbourhoods often underfunded, under-doctored, and performing less well on quality indicators.^{169,170}

Addressing health inequalities in the UK has been a concern for decades. In 1980, the Labour government commissioned Sir Douglas Black to investigate variations in health outcomes across social classes to consider implications for policy. As a result, the Black Report highlighted unequal distribution of ill-health and death, with a widening health gap between those of high and low social classes. The report suggested four possible theories i) artefact ii) natural/social selection iii) materialist/structural iv) cultural/behavioural, concluding that structural theory provided the best explanation for the observed inequalities.¹⁷¹ This theory suggests that differences in socioeconomic circumstances among social groups causes differences in health outcomes.¹⁷¹ The report provided 37 recommendations, particularly prioritising giving children a better start to life and other social policy measures to help tackle health inequalities.^{164,172} However, some have argued¹⁷² that despite the government commissioning the report there was a lack of engagement with the report outcomes. This was shown through limited accessibility of the report findings, and very few copies of the report being printed. The then Secretary of State for Social Services disregard most recommendations provided by Black.¹⁶⁴ Following on from this The Health Divide Report (1987)^{173,174} was commissioned and led by Margaret Whitehead, independent from the government. The report revisited issues from the Black Report and concluded gaps in health outcomes persisted, with a direct link with social class.^{173–175} The report stimulated widespread debate, however disregarded by the government much like the Black Report.

We then saw the commissioning of the report into an independent inquiry into inequalities in health (chaired by Sir Donald Acheson, 1988, Chief Medical Officer), which set out to inform the development of the government's public health strategy, particularly in contributing to the upcoming white paper, *Our Healthier Nation*.¹⁷⁶ The Acheson inquiry recommended all policies having an impact on health, direct or indirect, should be evaluated. High priority should be given to the health of families with children and further steps should be taken to reduce income inequalities and improve living standards for poor households.^{164,177} The report's findings were very similar to that of the Black Report, however, it has been suggested that the fundamental

difference between both reports was the far more favourable political climate that the latter report was released more broadly thereby having greater political impact.¹⁶⁴

Fast forward two decades in 2008, the WHO published a report *closing the gap in a generation*, resulting in the British government pushing to review health inequalities in England. This led to the commissioning of the *Marmot Review 2010: Fair Society, Healthy Lives*. This report provided six policy objectives (reflecting much of what had been addressed in previous reports) ranging from: giving children the best start to life, creating fair employment, and strengthening the role of ill health prevention. Subsequently since a follow-on report – *Health Equity in England: The Marmot Review 10 years on* showcased that child poverty has increased, deprived areas are showing shorter life expectancy and a rise in homelessness and housing crisis, inevitability highlighting limited success. Addressing inequalities remains a priority for the British government, and at the forefront of policy initiatives, as shown through the NHS long-term plans.⁵⁵

1.5.3 Terminology and theories

Despite health inequalities being at the forefront of public health discussion, there is still much standing discourse around the definition of this term, with words such as inequity, inequality and disparities being used interchangeably. As mentioned above, health inequality is a generic term that often refers to the differences in health of an individual or group/demographics.^{178,179} For example, the prevalence of a disease amongst two groups of individuals within a population.¹⁷⁹ Health disparities and health equity are often intertwined, with health disparities being the metric used to measure progress toward achieving health equity. Therefore, a reduction in disparity is suggestive of greater health equity.¹⁸⁰ Whereas health inequity is often more focused and refers to a specific type of health inequality that is resulting to an unjust difference in health.^{178,179} Such unjust and avoidable systematic differences between groups stem from social and structural factors. In essence distinguishing between inequalities and inequity involves normative judgment based on 1) theories of justice 2) theories of society 3) reasoning regarding origins of health inequalities.¹⁷⁹

In the context of disparities among social groups, particularly when examining factors such as an individual's social class or race, it can be argued that such discrepancies are unjust, due to the unequal distribution of the underpinning social determinants of health such as education and healthcare.¹⁸¹ However, on the contrary, some have suggested that these inequalities have in fact arisen from an individual's decision and therefore making them accountable,

emphasising the duty of self-care.¹⁷⁹ For example, an individual may choose to consume food of little or no nutritional value, overall contributing to poorer health outcomes. As such some people suggest that personal accountability is an important factor, given individuals are not coerced into making poor decisions and thus moral responsibility in such matters is of significance.¹⁸² However, individuals that advocate social determinism¹⁷⁹ may argue that this is a result of affordability, and systematic inequalities can lead to individuals from certain communities finding it more difficult to make healthy choices. Despite differing opinion, it is important to remember that “equity is not the absence of all disparities; it is the absence of systematic disparities between social groups.”^{183,184}

There are numerous perspectives on the theories of justice, which concern the fairness in distribution of resources within society. For instance, one theory is that of prioritarianism or the priority view.¹⁸⁵ This fundamentally places a significant emphasis on seeking to increase human well-being, fairly distributing across people, but tilting in favor of the worse off.^{186,187} More emphasis is placed on people who are worse off in society in order to reduce inequalities. However, egalitarians advocate that everyone should have equal and fair access to healthcare services regardless of factors such as income, race and gender¹⁸⁸ – for example universal free public schooling. Egalitarians suggest all should have the same opportunities to lead healthy lives, irrespective of their backgrounds. Utilitarians take a more modest stance on this matter, suggesting that while it is important to focus on achieving equity, achieving the greatest good for the greatest number of people takes priority.^{185,189} Therefore, the greatest improvement in a health outcome for a given population would take precedence. Lastly, another viewpoint, one that is in between egalitarianism and prioritarianism, is sufficiency, which highlights the significance of a sufficient level of resources needed to meet basic needs.¹⁹⁰ Therefore, like utilitarianism this viewpoint does not strive for complete equity, but more so ensures that essential healthcare services and basic living is provided, and no one falls below such a threshold.

1.5.4 Socioeconomic inequalities

Socioeconomic status (SES) refers to an individual or groups position in society by combining economic, social and education status.¹⁹¹ It is often used to demonstrate health outcomes and is thereby an indicator for health inequalities. While there are numerous markers to measure SES (*e.g.* income, education, wealth, and occupation) there is no best choice of a single indicator, and therefore the exact approach is often influenced by the research question, population studied and the measures that may be available.^{192,193} In this context, it is important to remember that

there is *no one size fits all approach* and each indicator in turn captures different aspects of SES. Some have categorised SES indicators as i) compositional ii) contextual iii) composite, as discussed below. Whilst the terms socioeconomic position, social class and social stratification are often used interchangeably with SES,¹⁹³ some have suggested socioeconomic position differs from that of a socioeconomic status, with SEP a broader concept encapsulating current and life-course circumstances, discussed further below.

1.5.4.1 Compositional SES measures

Compositional indicators assess SES at the individual level, focussing on behavioural characteristics. This may include occupation, education and income.¹⁹⁴ For instance, occupation can be used to measure health outcomes, by placing an individual within a *societal structure* reflective of their occupation. This is essentially referred to as *occupational prestige*, and indicates how members of the communities collectively evaluate the social standing of a job.¹⁹⁵ Occupations have also been linked to specific health conditions, for example stress-related illnesses, or respiratory conditions such as asthma or COPD, resulting in poorer health outcomes. However, there are limitations to using occupation as a measure; for example, it is limited to people who are employed or who are employable,¹⁹³ therefore, individuals who are retired, students, or too young to work would be excluded from this assessment. In addition, there is no accountment for racial and or gender differences in benefits from the same employment.¹⁹⁴ Some have suggested that education and income can directly influence occupation and therefore would be a more suitable markers for SES.¹⁹⁴

Using education as a compositional SES measure has shown to be a common way to assess health inequalities.¹⁹⁶ The number of years of education for an individual can be presented in multiple ways, such as a categorical value (highest level of education obtained) or a continuous value, through showing the years of education completed or the highest level of credentials earned (*e.g.* a bachelor's degree).¹⁹⁴ Unlike some of the other markers of SES, education captures the transition of an individual over the years and has been shown to reflect income and occupation.¹⁹⁴ For example, those with more years of education often have better work and economic conditions and engage in better health-promoting behaviours.^{197,198} This marker in particular is easy to categorise and obtain from an individual, with often higher response rates.¹⁹⁴ However, there are limitations such as the changes in education opportunities for some women and minority groups that have occurred over the years.^{193,194} Such changes can also vary across generations – for example older generations may be portrayed as being less educated as the threshold of education levels may have changed over time.¹⁹³ In view of this, some studies

have acknowledged the so called *cohort effect* and rather than categorising education as *low medium* or *high* they have adjusted specifically to the birth cohort.¹⁹³ Others have carried out age stratified analysis¹⁹⁹ which has allowed for health inequalities to be investigated in respect to a specific age group. Similarly, such differences will also be shown if an individual has obtained their education in a different country, where both quality of education and the number of years taken to obtain a qualification may be different. For example, high school in the US encompasses a different age or number of years than high school in the UK. Furthermore, a simple count of the number of years of education fails to provide an insight into the quality of education received and thus how such education affects health through the ability of critical thinking and knowledge.¹⁹³ Nevertheless, if using education as a sole marker to gauge social status, then the quality is often of little significance.

Using income for a measure of SES is particularly useful in capturing the resources available to an individual or a household. Similarly to education, income has shown to indirectly improve health outcomes, whereby a higher income has provided for the means for better access to healthcare services, nutritious food, and an overall improved quality of living.¹⁹⁴ Unlike education, income is most susceptible to short term fluctuations; for example, changes in employment that can lead to a fluctuation in wages. Income can be measured as an absolute income (exact money an individual earns) or categorisation within a predetermined income bracket.¹⁹⁴ Many studies, however, report income based at a household level opposed to an individual level, which may be advantageous for example if a woman is not the primary earner, however, this approach also results in limitations with regards to accuracy.¹⁹³ In some cases this has been acknowledged through adjusting for the size of a household and the associated cost of living.^{200,201} While income can be an effective measure for SES, it is often perceived as a personal matter, leading to higher rates of non-response, compared to other SES markers.¹⁹⁴ Furthermore, similar to education, income levels can vary from countries and age groups and thereby may not be reflective of an individual's SES position.

1.5.4.2 Contextual SES measures

While compositional SES measures offer a useful indicator of an individual's position within society, contextual SES measures can help to provide a more comprehensive understanding of a person's environment²⁰² and thereby the broader social and economic context within which an individual lives. This is particularly useful in understanding the structural inequalities and thereby guiding policy interventions to address such inequalities. Contextual SES measures often use neighbourhood or geographic area measures, which may include a postal code (known

as Zip Code in countries such as the US) which are useful in reflecting the demographics in a particular neighbourhood. More broader measures may include combining the demographics of neighbourhood or regions, typically obtained from sources such as the Office of National Statistics. Often such data is collected every decade and should therefore be considered regarding its representativeness. In addition, a large disadvantage to using such measures is that they may not always be reflective of an individual's level of experiences, and thus drawing conclusions solely based on contextual measures paves the way for ecological fallacy, a concept further discussed in Chapter 2 of this thesis.

1.5.4.3 Composite SES measures

Composite SES measures are determined through combining multiple indicators of SES; for example, education, income and home ownership. These measures can either be grouped as i) material and social deprivation measures ii) measures of social standing or prestige.¹⁹⁴ For example, the Townsend Index, the Index of Multiple Deprivation (IMD) and the Carstairs Index would be categorised as material and social deprivation measures. All three indices are often used to demonstrate deprivation in neighbourhoods or regions to help inform policies to address health inequalities. The Townsend Index incorporates factors such as unemployment, lack of car ownership, homeownership and overcrowded housing.²⁰³ IMD, however, combines indicators such as: income, employment, education, health, crime, barriers to housing and living environment and therefore encompasses more broader indicators than the Townsend Index.²⁰⁴ Similarly to the Townsend Index, the Carstairs Index (developed and primarily used in Scotland) considers factors such as social class, overcrowded houses, male unemployment and lack of car ownership.²⁰⁵

1.5.4.4 Life course theory

Overall, SES is a complex and dynamic concept that can impact health outcomes over an individual's lifetime. Commonly used indicators and measures can often overlook the long-term effect of social disadvantage and essentially such socioeconomic factors can accumulate over time and have negative health impacts on an individual. Pollitt *et al*²⁰⁶ has demonstrated the significance of SES across the life course and how exposure and experiences from childhood to adulthood can shape health outcomes. It is therefore important to consider the cumulative impact of various life events and circumstances when thinking about health inequalities. The work of Pollitt²⁰⁶ particularly focused on health trajectories through applying and understanding various conceptual methods in understanding SES in cardiovascular disease development.

Overall, the work demonstrated that a holistic approach in understanding and addressing health inequalities should be considered.

1.5.5 The determinants of health

Understanding the importance of addressing health inequalities through a holistic approach and that health outcomes can be shaped by an individual's life experiences (life course theory), it is also important to consider the wider social and economic factors that can influence health. The social determinants of health (SDH) are referred to as the non-medical factors that can influence health outcomes;²⁰⁷ they are important in demonstrating that health outcomes are not solely determined by medical care or individual choices. The social determinants demonstrate that factors such as income, employment, social support systems and housing can all contribute to health outcomes. There are several proposed models that have been developed to help visualise the complexity of these determinants. Most notably the Dahlgren-Whitehead *rainbow model* (Figure 1.4) showcases the relationship between different factors that are present within society. At the core of the model, there are biological and genetic factors, such as age and gender, which are limited in their ability to be modified. The inner layer comprises of factors that are often impacted by behavioural and lifestyle choices, for example diet, exercise, smoking and other health related behaviours. Individual choices play an important role in determining health outcomes and can be influenced by general knowledge, beliefs, and attitudes. These choices can therefore promote or deteriorate health outcomes. Surrounding the inner layer of the model are social and community networks; for example, family relationships, peer influences and social support networks. Evidence has often shown such support systems may be reduced for individuals from marginalised communities.²⁰⁸ In essence, better social support provides has the potential to improve health outcomes whereas a lack of support can result in isolation and poorer health outcomes. The middle layer of the model focuses on living and working conditions, such as unemployment, education, and access to healthcare services. The outer layer of the model focuses on broader socioeconomic, cultural and environmental factors that have the ability to shape the overall way in which people live; for example, economic policies (taxation). While there are distinct layers to the model, each layer has the ability to influence health outcomes. For example, socioeconomic policies can have an influence on living and working conditions which, in turn, can impact access to nutritious food. Another example can be reflective of cultural norms and values of which can impact social and community networks and the level of support an individual may have available to them.

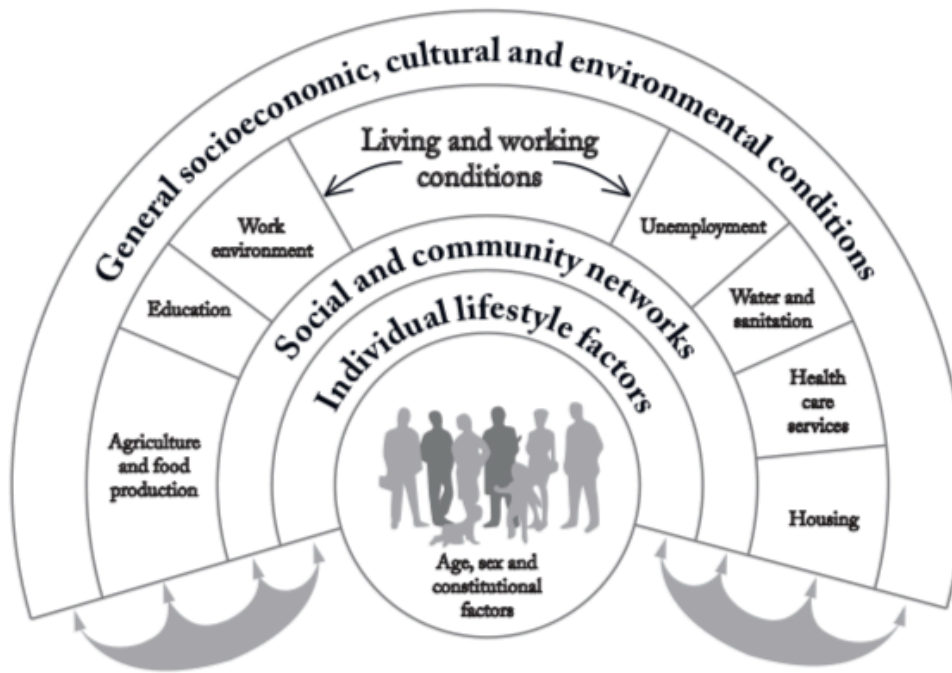


Figure 1. 4: The Determinants of Health Model. Taken from Dahlgren and Whitehead.²⁰⁸

While the Dahlgren-Whitehead *rainbow model* is a useful in providing a conceptual understanding of the social determinants of health there are other frameworks that are used to measure progress across the social determinants. For example, The Progress Plus Framework considers the key determinants of health through recognising key social, environmental, and economic factors (*i.e.* education, gender equality, social capital and occupation).²⁰⁹ By considering these broader factors, the framework provides a useful holistic platform to guide interventions to promote health equity and equality, thus helping policymakers to understand and monitor effect of interventions to reduce health inequalities.

1.5.6 Inequalities in polypharmacy

The concurrent use of multiple medications (polypharmacy) is an area of healthcare that has generated some debate.^{91,210} While there have been suggestions as to what factors may contribute to the prevalence of polypharmacy (*e.g.* the interplay between multimorbidity and polypharmacy, a concept further developed in chapter 5 of this thesis), there is still significant scope to address research relating to inequalities in polypharmacy. It has been suggested that individuals from socioeconomic disadvantaged backgrounds use more medications. This could be attributed to a combination of factors, including an increased prevalence multimorbidity, lower health literacy and reduced access to healthcare services.^{211–213}

As previously discussed in this chapter, Hart's proposal of the Inverse Care Law (1971) suggests that inequalities exist within access to healthcare, with those most in need of medical care the least able to access it.¹⁶⁸ Since then, the Marmot Review (2010) further developed this concept and highlighted the so-called health gradient, with those that are socioeconomically deprived suffering from more long-term health conditions.⁴ The Dahlgren-Whitehead model has been a useful pointer in allowing people to understand how some of these factors can play an important role in medication usage. For example, studies have highlighted factors, such as income^{214–218} and employment,^{219–221} as possible contributors to the prevalence of polypharmacy. Further studies have also illustrated that sociodemographic factor, such as gender and race, can also contribute to inequalities in healthcare,^{222,223} while not a direct relationship to medication usage it inevitably presents challenges with medication access and utilisation. Some studies, however, suggest after adjustment have been made for co-morbidities, any relationships observed between polypharmacy and SES lose their significance. For example, Silva *et al.*,²¹⁸ discussed how gender, age, education, income, and access to private health insurance affected prevalence of polypharmacy. The authors of this study used a large longitudinal dataset in Brazil (ELSA Brazil) and included participants from 35-75 years. Middle aged individuals were included as from both a public health and clinical perspective it has been shown to be a marker for multimorbidity, medication use quality and potential adverse reactions.²¹⁸ The study identified that lower education levels were associated with higher levels of polypharmacy, but a negative relationship was observed between income and polypharmacy. Nevertheless, after the analysis adjusted for co-morbidities, the significance of the association was lost. While some researchers suggest more educated members of society have greater access to healthcare services and take a more active role in their health,²²⁴ thus potentially displaying higher use of preventative medication, other argue that more educated people have increased awareness of the risk associated with medications and thus display lower levels of polypharmacy.¹⁹⁶ These contrasting views highlight the importance of understanding the potential role that socioeconomic factors may play in polypharmacy.

1.6 Aim and scope

The overarching aim of this thesis is to examine if there are socioeconomic inequalities in polypharmacy, amongst older people.

The research objectives are as follows:

- Systematically review and appraise the literature identifying and exploring the associations between SES and polypharmacy, amongst older people.
- Determine the association between SES and polypharmacy within a population in England.
- Explore the association between SES and polypharmacy in England over time.
- Understand the wider public health implications of the findings.
- Identify any changes and patterns observed between SES and polypharmacy across different medication groups.
- Provide policy and practice suggestions in relation to the findings of this thesis.

Hypotheses

- Lower SES (measured by the number of years of education) is associated with a higher likelihood of polypharmacy after adjusting for confounding variables such as age, sex and multimorbidity.
- The association between SES and polypharmacy has increased over time.
- The association between SES and polypharmacy varies across medication groups particularly with certain groups such as cardiovascular, with such conditions being more prevalent among individuals with lower SES.

1.7 Thesis structure

This chapter has introduced fundamental concepts that underpin the work of this thesis and demonstrates the current research around inequalities and polypharmacy. The remainder of this thesis is structured in four chapters, a brief synopsis of each chapter is included below.

Chapter 2: Describes the rationale to carry out a systematic review and meta-analysis of the literature, investigating the associations between SES and polypharmacy. This chapter introduces the current literature and discusses the outcomes of the review, including outlining the gaps for further research.

Chapter 3: Discussion of all available relevant datasets, with the justification provided for using the Cognitive Function and Ageing Studies (CFAS) datasets. The chapter also details the key information about CFAS, including the scope of data.

Chapter 4: Determines if polypharmacy has changed over time both in prevalence and in relevance to the relationship with SES. Methods are discussed along with analysis and discussion of results.

Chapter 5: Explored how different the observed polypharmacy across the chosen dataset is. It also reflects on the results from Chapter 4, in regard to polypharmacy and SES, to understand if such results are reflective across specific medication categories.

Chapter 6: Summarises the thesis, through drawing together the main findings, discussing the strengths and limitations of this work and future research directions.

1.8 Conclusions

This chapter has provided a background into key aspects to this area of research. It has discussed some of the challenges that are face as an ageing population, the interplay between multimorbidity and polypharmacy and inequalities in healthcare. The literature search used to frame this chapter showed there is a gap in understanding in terms of how polypharmacy is associated with polypharmacy in older people. While some primary studies have reported this, there is no clear systematic summary that seeks to synthesise information, appraise the quality of the evidence, and address this important question. To address this evidence gap, Chapter 2 will systematically examine the current literature to examine if polypharmacy is associated with SES.

Chapter 2. Are There Socioeconomic Inequalities In Polypharmacy Among Older People? A Systematic Review And Meta-Analysis

The work from this chapter has been published and can be found at: Iqbal A, Richardson C, Iqbal, Z, O’Keefe H, Hanratty B, Matthews F.E, Todd A. Are there socioeconomic inequalities in polypharmacy among older people? A systematic review and meta-analysis. *BMC Geriatr* 2023; **23**:149

2.1 Introduction

Chapter one introduced key concepts that are fundamental to this thesis, such as polypharmacy, social inequalities and the challenges surrounding prescribing for an ageing population. It concluded with discussion around inequalities in access to healthcare particularly within the UK and whether similar inequalities are evident in polypharmacy. At the time of conducting this work no single article had synthesised an analysis of the current literature on this specific topic, therefore it was essential to gather relevant information in this topic area and to understand if further research is needed.

Chapter aim:

Systematically review and meta-analyse the current literature to investigate the association between socioeconomic status and the prevalence of polypharmacy, in older people.

Objectives:

- I. Synthesis of existing evidence on the association between socioeconomic status and polypharmacy. This will be achieved through reviewing current literature, globally and using different measures of SES.
- II. Quantify the association of SES and polypharmacy through performing a meta-analysis combining the data reporting on a variety of SES measures and the likelihood of being in receipt of polypharmacy.

The work undertaken in this chapter has been published (Iqbal *et al* 2023,¹⁹⁶ Appendix B). The information presented in this chapter reflects this work with additional detail where necessary in order to provide coherence of this thesis.

2.2 Background

In some contexts, the trend to increase prescribing of medication and the resulting polypharmacy is appropriate and necessary; multiple medications are often required to manage LTCs. As such, with rising multimorbidity and increasing life expectancy, polypharmacy may be clinically appropriate and thus reflective of treatment needs.^{225,226} While previous studies have shown that certain patient-based factors, such as age, are associated with increased levels of polypharmacy, the role of socioeconomic factors such as education, income, and occupation, is less clear. The literature has suggested that such socioeconomic factors could play an important role in polypharmacy, with studies highlighting measures such as income^{218,225–228} and employment^{220,221,229} as possible contributors to the prevalence of polypharmacy. For example, a Swedish study²³⁰ investigated the relationship between polypharmacy, SES and inappropriate medication usage. The results showed that lower levels of education were associated with increased levels of polypharmacy and potential drug-drug interactions. Nevertheless, that work focused on a Swedish population and primarily on the inequalities observed with the use of psychotropic medications.

Whilst there is significant academic interest on this topic, there is no single review and meta-analysis which draws together the current literature around polypharmacy, how prevalence may differ according to SES and other measures of socioeconomic position. This systematic review and meta-analysis aimed to investigate the association between socioeconomic status and the prevalence of polypharmacy, in older people. A meta-analysis approach was used to aggregate data across studies, and provide an overall effect of this association, thereby contributing to inform future research surrounding health inequalities in older people.

2.3 Methods

2.3.1 Rationale for review

In order to address the aim of this work, and subsequently focus the analysis for my thesis, it was important to first identify current literature within this topic area. Therefore, the initial step

would be to carry out a review and I took the decision to carry out a systematic review, justification for my thought process is as follows.

An initial scoping of the literature was carried out to understand the existing research on this topic and to narrow down the focus of my review question. While scoping of the literature provided a valuable overview of the topic area, I wanted my review to provide a more in-depth insight into addressing the research question at hand (understanding the extent of SES on being in receipt of polypharmacy) and to provide recommendations for clinical practice/policy. In order to achieve this a critical step would be to understand the quality of evidence and thereby, the addition of quality appraisal is a distinctive characteristic of a systematic review, opposed to a scoping review. Therefore, in order to ensure comprehensive identification and synthesis of the literature, using a structured methodology, a systematic review was adopted.²³¹

2.3.2 Protocol

This review was registered with accordance to The International Prospective Register of Systematic Reviews PROSPERO (CRD42021285455) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Appendix C.

2.3.3 Search strategy and study selection

A literature search was conducted across four databases: MEDLINE (Ovid), Web of Science, Embase (Ovid) and CINAHL, from inception to July 2021, with no limitations on publication year or geographical location. An initial preliminary search was carried out to identify the current literature within this topic area. All papers identified from this preliminary search underwent review and analysis to help determine the most suitable databases for this topic, help direct the development of an inclusion and exclusion criteria and refine the research question. While the selected databases captured many of the initial papers that were identified, they were also chosen for their scope and popularity in healthcare research.

A primary objective of this review was to search a wide range of literature while ensuring feasibility, within a reasonable time frame. This approach aimed to provide a well-informed overview of the topic area for healthcare professionals and stakeholders to make informed policy decisions. Therefore, the search criteria were kept broad, and a large part of the selection processes to inform the screening took place after the initial searches were conducted, for example restricting the year of publication as discussed in Section 2.3.4.

The search strategy was developed around three primary terms: *polypharmacy*, *socioeconomic status* and *ageing*. As discussed in Chapter 1, at the time of this work, there were no consensus for defining many of the key terms of this work. For example, SES encompasses various factors ranging from an individual's education to their income. Similarly, defining polypharmacy is subject to considerable debate particularly around providing thresholds and setting an arbitrary value. Therefore, the terms were deliberately kept broad to ensure a thorough search capturing a comprehensive range of articles on this topic. The complete search strategy can be found in Appendix D. All preliminary articles were screened, and the key terms included in them contributed to the development of the search strategy. The search was reviewed by the whole review team, of which included an information specialist, Hannah O'Keefe, to ensure robustness. The search strategy was subject to many iterations until all preliminary articles that had been identified were included, and the search yielded an appropriate number of articles feasible for screening within an appropriate time frame.

In line with Cochrane guidance,²³² both searching of reference lists and forward citation of included studies was conducted, resulting in an additional 23 articles (Figure 2.1). This additional step helped identify articles that may have been overlooked through conventional database searches, while also facilitating the identification of newer publications through forward citations. Overall, a broader scope of literature was identified, ensuring robustness and adherence with best practises as advocated by Cochrane.²³² Some authors suggest that searching grey literature can reduce publication bias and offer a more comprehensive overview of the literature.^{233–235} Others are of the opinion that grey literature requires rigorous methods to assess integrity because of its varying quality and lack of peer review.²³⁴ Furthermore, grey literature has been shown to generate few relevant studies²³⁶ and therefore, I took the decision against carrying out a search of grey literature. Given the extensive range of studies generated by my search and the considerable time that may be required to explore grey literature, it was unlikely to yield a significant number of valuable studies that would meet the required detail and criteria for inclusion, and beyond the scope of a PhD study.

2.3.4 Eligibility criteria

To be eligible for inclusion, articles were required to be accessible as full texts, published in English from 1990 onwards. The date restriction on the inclusion was due to many factors. Firstly, prescribing practices have evolved over the years, particularly in the early 1990s, with the integration of patient-centred care,²³⁷ evidence-based medicine^{238,239} and the emphasis on holistic based treatments, also known as social prescribing.²⁴⁰ These approaches combine both

current medical practices and patient preferences as a fundamental part of healthcare delivery. In the context of medication management, involving patients in treatment decisions and managing their expectations allows healthcare professionals to effectively personalise medication regimens. Similarly, adhering to guidelines and recommendations enables healthcare professionals to prescribe medications based on scientific evidence and a balanced assessment of potential benefits versus risks. Both are key drivers in potentially reducing the prescribing of unnecessary medicines, with a focus on tailored treatment approaches to address specific patient needs. Furthermore, this time marked the introduction of now significant medications such as statins (lovastatin 1987) and the more widely prescribed simvastatin (1988). Initial concerns about the effectiveness of these drugs were addressed in studies like the Scandinavian Simvastatin Survival Study (4S),²⁴¹ resulting in their widespread implementation in clinical practice during the mid 1990s. Overall, the 1990s marked a pivotal time period in key changes across prescribing practices. To ensure some degree of selectivity for this review, articles published before 1990 were not eligible for inclusion.

The following PECOS (Population, Exposure, Comparison, Outcome, Setting) was developed to help conceptualise the inclusion criteria for this systematic review, a summary can be found in Table 2.1.

Population:

As discussed in Chapter 1 of this thesis, on an international perspective, 65 years has been used as a common threshold to distinguish the old from the young, with it being a benchmark age for retirement and being in receipt of key healthcare initiatives such as Medicare in the US.²⁴² However, some are of the opinion that in actual fact no set numerical definition should be applied when referring to older people. This is due to factors such as; genetics, an individual's social circumstances, and overall health of which have the potential to contribute to someone's ageing profile and, in turn, what may constitute to older age.²⁴² However, a numerical cut off was used for multiple reasons. Firstly, it is important to have consistency to allow for reproducibility of the review and clear inclusion criterion minimise ambiguity. Secondly, studies identified during the preliminary search encompassed a range of countries and time periods, with wide variation in how older people were defined. Therefore, for precision and consistency, clarity in defining the population was necessary. Thirdly, a clear definition of the age criteria helps reduce the risk of selection bias. Without a numerical threshold there is a greater potential for inconsistency in study selection, and thereby introducing bias into the review processes. Therefore, in line with recent research,²⁴³ and to ensure inclusion of the key

literature that had been identified in the initial preliminary search, I took the decision to define older people as individuals aged 55 years and over. For the studies to be eligible for inclusion, the following criteria had to be met:

- i) Study participants were required to be over 55 years.
- ii) Studies reporting age groups in a stratified manner required at least $\geq 50\%$ of the total study population belonging to a category that explicitly included individuals 55 years and above.
- iii) In instances where age was categorised, if the data specified an age of 55 years and older for a particular socioeconomic measure, only this specific age group would be extracted.

Exposure:

This review set out to investigate the association between SES and polypharmacy and low SES was identified as the exposure. As discussed in Chapter 1, SES factors can be measured at area level, which relates to characteristics of the geographical area/neighbourhoods where an individual may reside, or at individual level, relating directly to the socioeconomic characteristics of an individual. Studies reporting both area-level or individuals level SES factors were included. Firstly, I wanted to evaluate if a specific measure of SES was most used across the literature, this would help direct the analysis in subsequent chapters. Secondly, assessing SES at area level will provide me with an insight into the broader socioeconomic contexts in which an individual lives, and how social circumstances can overall influence health outcomes. Contrary for a more nuanced and preferable approach it was also important to understand and assess from an individual context, and also not liable to ecological fallacy. Therefore, I did not prioritise individual or area level measures and both were included. This was further supported by the studies identified in the preliminary search, with key literature including both individual and areal level measures for analysis.

Comparison:

Comparison was carried out with those of a higher SES, therefore the SES category that was explored within each article should provide information of individuals from higher SES.

Outcome:

Polypharmacy was the outcome measure and therefore articles should highlight those in receipt of polypharmacy according to a given socioeconomic measure, for example: education, income, wealth, employment, occupation, social class, and socioeconomic status. Polypharmacy was defined as the use of (≥ 5 medications, as explained within Chapter 1 of this thesis, the most

adopted definition for clinical practice). Studies will need to be consistent with how no polypharmacy is defined and therefore should be those taking zero medications. Studies were included if they aligned to this definition and reported polypharmacy in line with a given socioeconomic measure. All studies were included irrespective of multimorbidity, geographical location, and definition of what constitutes a medication.

Setting:

This review investigated the association of SES and polypharmacy therefore, all care settings were considered, all countries, irrespective of healthcare systems – private or public. All observational study types including cohort and cross sectional were included.

Table 2. 1: PECOS summary used in this systematic review.

Population	Defined as older people, aged ≥ 55 years. Studies required at least 50% of participants to be over ≥ 55 years.
Exposure	Lower socioeconomic status (at area or individual level measures).
Comparison	Higher socioeconomic status (at area or individual level measures).
Outcome	Receipt of polypharmacy.
Setting	All settings were considered, irrespective of country, private or public healthcare systems.

2.3.5 Screening and study selection

All articles that were identified by the search were imported into EndNote and duplicates were removed. This was carried in a multiple step process. Firstly, the duplication tool on EndNote was used to allow for the scan of any duplicates across the databases. Then through various filters applied i.e. screening by authors alone, title and so forth, any additional duplicates were removed. This process was then replicated on Rayyan QCRI, which also facilitated the screening of titles and abstracts. All titles and abstracts were screened by one reviewer (AI). Two reviewers (CR, ZI) independently reviewed a random sample of 25%, of all articles, any discrepancies were then discussed and, if necessary, resolved by a third author (AT) who had consensus. The full texts were reviewed by (AI) and independently checked by the review team (CR, ZI); any discrepancies were resolved through discussion with a third author (AT) who had consensus. Appendix E shows a visual representation of the decisions involved in selecting a study for inclusion.

Cohens Kappa scores were calculated, to measure inter-rater reliability between agreement of included studies within the review team. Scores are determined through calculating observed and hypothetical probabilities of chance agreement, results obtained correlate to the degree of agreement. Agreement between reviewers was almost perfect, with a Kappa score of 0.85.²⁴⁴

2.3.6 Data extraction

Data were extracted by one author (AI) using a prepopulated form, the following information was extracted: study, year, country, study data, participant characteristics, socioeconomic measure and utilisation of SES, including the given socioeconomic measure, calculated odds ratio and quality appraisal score, deduced from the JBI toolkit. All information extracted was checked by the review team (CR, ZI) and any discrepancies discussed with another author (AT) who had consensus. Where required information was inconsistent or missing, the authors of the study were contacted by email. A follow up email was sent out to authors if no response was provided within 2 weeks. If, after a total of 6 weeks, there was no response then within the extraction table it was documented that data were not reported, or the paper was excluded as sufficient outcome data could not be extracted. In the event of multiple articles reporting similar or overlapping studies (*e.g.* using the same data source, over the same time period), these were recorded within the extraction form, and noted, with the latest published article progressing for inclusion in the systematic review. This was a valid rationale as later papers had the most up to date results. For all included studies where an odds ratio (OR) could be calculated (through the presence of unadjusted data reporting polypharmacy and a given SES measure) this was carried out and reported within the data extraction table. Subsequently such studies were included in the meta-analysis. In instances where this could not be calculated, the study was excluded from the meta-analysis and the calculated OR from the study was reported in the data extraction table and made transparent. If more than one model was reported then an unadjusted OR was extracted, whereby this was not possible than the OR from the most comprehensive model was referenced.

2.3.7 Quality appraisal

Critical appraisal of all included studies is an essential quality assurance process for a systematic review. This is to ensure included studies have minimised the possibility of bias, specifically to the design, conduct and analysis of the study.²⁴⁵ Although there are numerous tools available to help with this assessment, it is important to carefully select a tool that will ensure a robust process, especially considering the absence of a universally recognised “gold standard critical appraisal tool.”²⁴⁶

Tools such as AMSTAR and the Cochrane Risk of Bias Tool (ROB 2) were excluded as they were unsuitable for the included studies of this review. This is because the AMSTAR tool is used to assess the methodological quality of systematic reviews. Since my review does not include reviews of reviews it was inappropriate to use. Similarly, ROB 2 was excluded because it is tailored in assessing randomised control trials, a methodology of which none of the included studies used. However, other tools such as CASP and the Joanna Briggs Institute (JBI) were considered appropriate, but the JBI was primarily chosen for its simplicity. Both JBI and CASP provide various templates tailored to different study types, allowing for a more customised approach to assessing quality, and both tools consist of similar questions. However, the JBI provided a simpler interface, utilising tick box answers (yes, no, not clear or not applicable), which was more efficient than CASP which requires detailed reasoning and comments. Using the JBI tool, specific for each study type for example cross sectional study type (Appendix F), would enable an effective but equally as thorough appraisal process, enabling the review team to calculate scores and include them within the data extraction, Table 2.2. The questions covered various aspects, from a clearly defined inclusion criteria to understanding if confounding factors and statistical analysis was used appropriately.

Appraisals of the included studies were conducted independently by members of the review team (AI, CR and ZI), with any discrepancies resolved through discussion with AT, who had consensus. Despite the rigorous critical appraisal, no study was excluded or weighted based on the score obtained from the JBI tool. While some suggest that such tools are useful in assessing “poor quality” of a study and thereby be used as sensitivity analyses,^{247,248} this was not undertaken in this review. This decision was primarily due to the variability in quality assessment among different tools and the lack of consensus of what constitutes to “poor quality” across these tools.^{246,249} Furthermore despite the structured questioning provided by the JBI tool, with a series a question, this process across reviewers still remains challenging and subjective.

2.3.8 Synthesis of findings

A narrative synthesis was undertaken, and summary of the findings were reported in a data table. All studies were reported. In instances where a given article used the same data set, both studies and articles were reported in the data table and a note included to indicate were duplication of study occurred. Studies were heterogenous in the following: country of origin, ages of participants, reported socioeconomic measures and analytical approach. For example, some studies categorised education as: without studies, primary, secondary and university

level,²⁵⁰ whereas another study categorised education as 0-8 years or ≥ 8 years.²⁵¹ Other examples include occupation as white or blue collar,²⁵¹ or categorising as manual, non-manual and retired/never worked.²⁵² Therefore, unadjusted odds were calculated and imputed for meta-analysis. *Low* SES was referred to the lowest socioeconomic group in each study which was calculated as Quantile 1 (Q1) of the population and conversely Quantile 2 - Quantile 4 were combined to constitute those of *high* SES, for a given marker. This approach ensured all study population was considered, therefore preventing skewness of resulting by comparing only two extremities of the population.

A random effects meta-analysis was performed to understand the association between a given socioeconomic factor and polypharmacy. This statistical technique allowed for the combination of results from multiple independent studies, bringing the data together and producing an overall pooled estimate.²⁵³ The decision to select a random effects model was primarily due to the heterogeneity observed amongst the included studies and therefore making a fixed effects model not appropriate for this analysis.²⁵⁴⁻²⁵⁶ Both models have an overall arching goal of providing a pooled estimate for multiple studies however, they both differ with how they handle variability amongst the studies. Within a fixed effects model the assumption is that studies are homogenous, thereby sharing a common true effect size. Any differences observed will be solely due to random sampling and therefore studies are weighted according to how many individuals are involved. For example, a larger study will show to be having more weight, thereby having a larger effect size on overall odds. Whereas a random effects model acknowledges that true effect size can vary amongst the study, possibly due to the large degree of heterogeneity and partially due to random sampling error. Therefore, both factors are considered within the calculated pooled estimate. Considering that my review had studies with a large degree of heterogeneity, mainly due to studies being international and including various measures of SES, the random effects model was most appropriate. The inverse variance method further reflected the justification of this selection, with it allowing efficient utilisation of the information within the included studies, and essentially prioritising studies with a greater precision through allocating them with greater weight. For example, a study with a larger sample size that has a smaller standard error are allocated more weight than a smaller sample size with larger standard errors. Essentially this allows for robustness and reducing the impact of potential outliers on the overall effect size. Distributing the overall weights of the studies in this way allows for a more precise calculated pooled effect estimate. Overall, the methods were carefully selected to account for the predicted heterogeneity across the studies.²⁵³

2.3.9 Meta-analysis eligibility criteria

All included articles underwent further eligibility screening to meet the following criteria to be included into the meta-analysis:

- I. studies were required to present unadjusted data, to allow for an odds ratio to be calculated. This followed a calculation of a log odds ratio and standard error which were then imputed into Revman 5.4 to generate forest plots. All calculations were independently calculated by two reviewers (AI, FM).
- II. Studies were required to report or present their findings in a way where it was clear to identify the number of people in receipt of polypharmacy or not, this should be reported in line with any given SES marker. Where more than one SES marker was reported, data were extracted for all measures where it was clearly indicated which individuals have polypharmacy or not.

Like the narrative synthesis, the decision was taken not to restrict the meta-analysis to a specific SES measure but instead each factor was reported separately to understand how the relationship of polypharmacy and SES can differ across varying measures. Similarly placing such restrictions had the potential to exclude key literature. If multiple papers used the same datasets, then the article with the largest number of participants was included in the meta-analysis, if this was the same then it corresponded to the article that was published the latest. Furthermore, if a study⁹⁴ reported no polypharmacy as 1-4 medication this study would be excluded for meta-analysis, unless otherwise raw data were present which allowed recategorisation of no polypharmacy as individuals with 0-4 medicines.

Sensitivity analyses are an important component of all systematic reviews and subsequently a meta-analysis, to demonstrate the robustness of the outcome, however, there is no set strategy in how to perform a sensitivity analysis.²⁵⁴ Therefore two sensitivity analyses were carried out for this review, the first removing any studies that did not solely include participants 55 years and above and the second removing studies that performed *poorly* during the quality appraisal. Arbitrary cut off scores are often used to determine if the studies are considered, weak, moderate, or strong²⁵⁷ and this approach was replicated for my review. An arbitrary benchmark was agreed upon amongst the review team and studies performing <80% at quality appraisal was excluded for sensitivity analyses results. As previously discussed, the lack of a universal quality appraisal tool and the large degree of personal judgment exercised in assessing quality appraisal, meant that for the analyses of this review no study was excluded based on the quality appraisal. However, some authors argue that there is room for a study to be excluded based on

quality appraisal,²⁴⁷ whilst others are more pragmatic and suggest carrying out a sensitivity analyses on *poorer* quality studies,²⁵⁸ which is the method adopted for this review, to prevent any exclusion of studies based on an arbitrary benchmark thereby open to bias.

To understand the level of statistical heterogeneity (proportion of variability not attributable to chance) among the studies, an I^2 was calculated. The Cochrane handbook has suggested thresholds to decipher what high heterogeneity may constitute to. For example: 75-100% is seen as considerably high heterogeneity, but also 50-90% as substantial heterogeneity, demonstrating an overlap and thus no clear arbitrary values.²⁵³ Some suggest that more defined definitions should be in place, for example, Higgins has suggested: 25%, 50% and 75%, being assigned to low, moderate and high heterogeneity, respectively.²⁵⁹ Whereas others propose anything above 50% contributing to high heterogeneity.²⁶⁰ This review therefore opted for the average mark between the literature and used 75% as high heterogeneity. However, it is important to remember that all meta-analyses will produce some form of heterogeneity and such methods to assess this should not be used in isolation.²⁶¹ The I^2 particularly is only one of many tools that can be used but is one that has been suggested as a useful tool by quantifying heterogeneity.^{260,262}

2.4 Results

2.4.1 Literature search

Searches retrieved 20,064 citations. After de-duplication, 13,412 articles were screened for eligibility based on title and abstract. From this, 187 articles progressed to full text screening, which resulted in 54 articles meeting the inclusion criteria, 23 articles identified from other methods (Figure 2.1); 13 articles were excluded from the meta-analysis as they did not provide unadjusted data that could be extracted for an OR to be calculated. Therefore, a total of 54 articles were included in the narrative synthesis with 41 articles progressing to meta-analysis.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

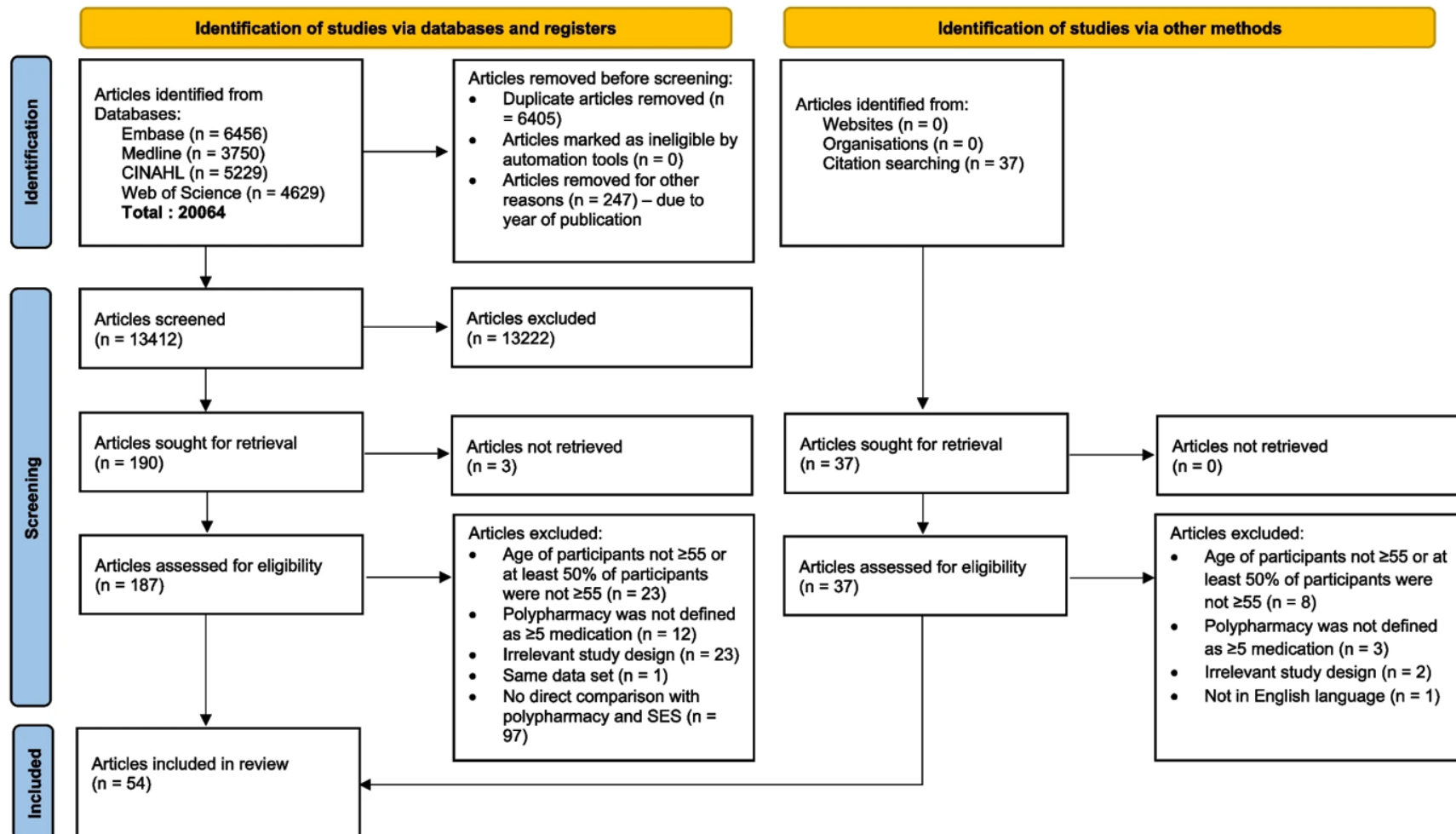


Figure 2. 1: Study selection and exclusion according to the PRISMA flow diagram.

2.4.2 Study characteristics

The 54 included studies included within the review reported multiple measures of SES. Specifically, 50 focussed on education,^{73–75,94,220,230,250–252,263–303} while 18 studies concentrated on income.^{94,220,251,269,271,272,274,278,282–284,286,289,297,299,300,302,304} Additionally, six studies examined wealth,^{73,266,281,293,303,305} four studies investigated occupation,^{251,252,284,293} seven studies concentrated on employment,^{220,229,285,294,296,299,302} five studies explored social class,^{75,229,250,275,296} two studies utilised SES categories^{270,306} and one examined area-level deprivation.⁷⁴

The included studies were conducted across a range of countries as follows: India,^{296,302} Jordan,²⁶³ the Netherlands,³⁰⁶ Sweden,^{230,251,276,288} Spain,²⁵⁰ Belgium,^{265,269} Pakistan,^{268,304} UK,^{74,75,229,305} China,^{94,252,295,301} Japan,^{282,303} Singapore,²⁷⁷ Kuwait,²⁷⁹ Malaysia,^{280,294} Poland,²⁸¹ Togo,²⁸³ Saudi Arabia,^{291,297} Taiwan,²⁹² Vietnam.²⁹³ Most studies were conducted within Brazil^{267,270,271,274,275,278,284,286,287,289,298,299} and the United States,^{220,264,266,272,273,285,290,300} while one study included participants from multiple European countries and Israel.⁷³

The size of the studies varied considerably from 59²⁶⁴ to 1,742,336²⁸⁸ participants. Most studies were longitudinal or cross-sectional design. Studies used a variety of data sources, mainly large databases such as National surveys,^{75,270} which extracted smaller populations for analysis. Three large ageing studies from the UK were used as data sources within the included studies, English Longitudinal Study on Ageing (ELSA).³⁰⁵ Cognitive Function and Ageing Studies (CFAS)²⁷⁵ and Newcastle 85+ study.⁷⁴ Studies collected primary data in the form of surveys, or questionnaires for analysis. Further details on the characteristics of the included studies and individual data sources can be found in Table 2.2.

Table 2. 2: Characteristics of included studies.

Sampling Frame		SES		Utilisation by SES		
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Al-Qerem W <i>et al</i> (2018)	Jordan	Prescriptions obtained from pharmacies and hospitals in Amman, Madaba and Zarqa (Jordan) : October 2017 - January 2018	- Total 367 - Age ≥ 60	Education	Education: OR 1.40 SE = 0.36	6/8
Midão L <i>et al</i> (2018)	Austria, Belgium, Croatia, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Italy, Luxembourg, Poland, Portugal, Spain, Sweden, Switzerland and Slovenia) and Israel	SHARE – Survey of Health, Ageing and Retirement in Europe - database	- Total 29,342 - Age ≥ 65	Education Wealth – shortage of money	Wealth/Shortage of money: OR 1.39 SE = 0.03 Education OR 1.03 SE = 0.14	8/8
Panda M <i>et al</i> (2020)	India	Primary Data – collected from rural health and training centres: December 2018 – July 2019	- Total 300 <i>analysis based on N=127</i> - Age ≥ 60	Education Income Employment	Education – OR 2.62 SE 0.48 Income – OR 1.75 SE 0.43 Employment – OR 0.18 SE 0.69	8/8
Sinnige J <i>et al</i> (2016)	Netherlands	Electronic Medical Records through NIVEL Primary Care Database (NIVEL-PCD)	- Total 45,731 <i>analysis based on N=45,496</i> - Age ≥ 55	'SES Category' combining Income Employment Education	SES OR 1.28 SE 0.03	8/8
Haider I, <i>et al</i> (2008)	Sweden	The SWEOLD (Swedish Panel Study of Living Conditions of the Oldest Old, 2002)	- Total 621 - Age ≥ 77	Education Occupation Income	Education OR 1.50 SE 0.18 Occupation – OR 0.89 SE 0.16 Income – OR 1.10 SE 0.16	8/8
Golchin N <i>et al</i> (2015)	United States	Survey – under the Cuyahoga County Board of Health	- Total 59 - Age ≥ 65	Education	Education OR 0.89 SE 0.77	6/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Carmona-Torres J <i>et al</i> (2018)	Spain	National Health Survey (2006, 2011 and 2012) and European Health Survey (2009 and 2014)	- Total 26,277 - Age ≥ 65	Education Social Class	Education – OR 1.61 SE 0.04 Social Class – OR 1.31 SE 0.04	7/8
Wauters M <i>et al</i> (2016)	Belgium	BELFRAIL Study – selection of participants from the BELFRAIL cohort	- Total 503 - Age ≥ 80 <i>analysis based on N=473</i>	Education	Education – OR 1.52 SE 0.20	8/8
Charlesworth C <i>et al</i> (2015)	United States	National Health and Nutrition Examination Survey (1988-2010) – restricted to those ≥ 65 years	- Total 13,869. <i>Data used for 2009-2010 N=1,523</i> - Age ≥ 65	Education Wealth	Education OR 1.22 SE 0.12 <i>Income poverty ratio taken from study analysis P 0.998</i>	8/8
Rozenfeld S <i>et al</i> (2008)	Brazil	Survey – Uso de medicamentos por aposentados brasileiros (Medication use by Brazilian retirees) – selection of 800 participants	- Total 577 - Age ≥ 60	Education	Education OR 0.86 SE 0.18	6/8
Sarwar M <i>et al</i> (2018)	Pakistan	Primary data collection across various healthcare settings (tertiary care, private and public hospitals) between 1 December 2017 – 28 February 2018	- Total 385 - Age ≥ 65	Education	Education OR 1.70 SE 0.23	6/8
Walekiers D <i>et al</i> (2015)	Belgium	Belgian Health Interview Survey (2008) – Face to face interviews and questionnaires. Analyses restricted to ≥ 65 years and older	- Total 2835 - Age ≥ 65	Education Income	Education OR 1.47 SE 0.08 Income – OR 1.17 SE 0.10	8/8
Thomas H <i>et al</i> (1999)	Wales	The Caerphilly Prospective Study 1979	- Total 1906 - Age $\geq 56-75$	Employment Social Class	Social class – OR 1.32 SE 0.21 Employment - OR 2.32 SE 0.17	6/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Ramos L <i>et al</i> (2016)	Brazil	National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM)	- Total 6844 - Age ≥ 60	SES Education	SES - OR 0.82 SE 0.07 Education: OR 0.97 SE 0.09	8/8
Carvalho M <i>et al</i> (2012)	Brazil	Primary data collection - <i>Saúde, Bem-Estar e Envelhecimento</i> : SABE Health, Wellbeing and Ageing study	- Total 2143 - Age ≥ 65	Income Education	<i>Taken from data table in paper</i> Income: Tercile 1: 1.0 Tercile 2: 1.5 (1.0-2.2) P 0.057 Tercile 3: 1.3 (0.9-1.9) P 0.090 Education Year 0: 1.0 Year 1 to 3: 0.8 (0.5 – 1.3) 0.339 Year 4 to 11 : 1.0 (0.6 – 1.7) 0.859 Year 12 to 22 1.4 (0.6 – 3.1) 0.380	8/8
Lu J <i>et al</i> (2014)	China	Project of Longevity and Aging in Dujiangyan Study: April 2005. Aged 90+	- Total 859 - Age ≥ 90	Income Education	Income: OR 1.01 SE 0.43 Education OR 0.60 SE 0.37	7/8
Assari S <i>et al</i> (2019)	United States	Primary data collection - Sacramento Area Latino Study	- Total 632 - Age ≥ 65	Income Education Employment	<i>Taken from data table in paper</i> Education: OR 0.97 P 0.414	7/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
		on Aging (SALSA, 1996-2008)			Income: OR 1.15 <i>P</i> 0.296 Employment OR 0.21 <i>P</i> 0.042	
Perry B <i>et al</i> (2001)	United States	National Health and Nutritional Examination Survey III 1988-1994	- Total 5249 - Age ≥65	Income Education	<i>Taken from data table in paper</i> Beta weights Income: 0.07 Education: 0.28	7/8
Prithviraj G <i>et al</i> (2012)	United States	Collected from ambulatory oncology clinics at an academic centre (February 1 st 2008 - September 30 th 2009)	- Total 117 - Age ≥65	Education	Education OR 1.34 SE 0.49	7/8
Rawle M <i>et al</i> (2018)	England, Scotland and Wales	Survey - MRC National Survey for Health and Development	- Total 2122 - Age ≥69	Education Social Class	<i>Taken from data table in paper</i> Education None (ref) <i>P</i> 0.010 Social class Manual (ref) <i>P</i> 0.592	8/8
Filho A <i>et al</i> (2008)	Brazil	BambuÍ Project 1997	- Total 1544 - Age ≥60	Education Income	Education – OR 1.06 SE 0.12 Income OR 1.15 SE 0.13	8/8
Davies L <i>et al</i> (2021)	England	Newcastle 85+ study- data – collected from general practices in Newcastle or North Tyneside	- Total 845 - Age ≥85	Area - level Deprivation	<i>Taken from data table in paper</i> (75th centile IMD) OR 1.04, 95% CI: 0.76– 1.42 and people living in socioeconomic disadvantage (<25th centile IMD) OR1.03, 95% CI: 0.76–1.39	7/8
Chen Y <i>et al</i> (2001)	England and Wales	Cognitive Function and Ageing Study 1991- 1994	- Total 12,489 - Age ≥65	Social Class Education	<i>Taken from data table in paper</i>	8/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Doheny M <i>et al</i> (2021)	Sweden	Sample of data from - All registered inhabitants aged ≥65 31 st December 2014, 2014-2015	- Total 291,800 - Age ≥65	Education	Social class (ref: class I & II) Class I&II 1.00 (0.90±1.12) Class IIIa 1.21 (1.04±1.42) Class IIIb 1.22 (1.12±1.34) Class IV&V 1.30 (1.15±1.47) Education (ref: ≥10 y) ≤ 8 years 1.08 (0.88-1.31) 9 years 1.00 (0.93-1.07) ≥ 10 years 1.00 (0.90-1.11) <i>Taken from data table in paper</i> Education level: Post-secondary OR 1.00 Primary OR 1.60 Secondary OR 1.28	8/8
Slater N <i>et al</i> (2020)	England	The English Longitudinal Study of Ageing (ELSA) – Wave 6 (2012-2013)	- Age ≥50 years Total 7730 - Age ≥60 - Total 6035	Wealth	Wealth – OR 1.40 SE 0.07	8/8
*Slater N <i>et al</i> (2018)	England	The English Longitudinal Study of Ageing (ELSA) – Wave 6	- Age ≥50 years Total 7730 - Age ≥60 - Total 6035	Wealth	N/A	N/A
Masumoto S <i>et al</i> (2018)	Japan	Data – collected from Japanese outpatient primary care clinics: January to March 2016	- Total 740 - Age ≥65	Wealth Education	Wealth – OR 1.12 SE 0.20 Education – OR 1.15 SE 0.16	8/8
Tan Y <i>et al</i> (2019)	Singapore	National sample – wave 3 of the Panel on Health and Ageing of Singaporean Elderly (PHASE)	- Total 1499 - Age ≥66	Education	Education OR 1.08 SE 0.15	8/8

Sampling Frame		SES		Utilisation by SES		
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Neves S et al (2013)	Brazil	Primary data from those living in urban areas covered by the Family Health Strategy program in Recife	- Total 432 - Age ≥ 60	Education Income	Education OR 2.69 SE 0.33 Income OR 0.82 SE 0.63	7/8
Badawy N et al 2020	Kuwait	Questionnaire based Survey March to July 2017	- Total 500 - Age ≥ 65	Education	Education OR 1.53 SE 0.19	7/8
Ong S et al (2018)	Malaysia	Data from The National Medical Care Survey	- Total 22,832 - Age ≥ 65	Education	<i>Taken from data table in paper</i> Education – reference no formal education Primary – OR 1.61 (1.12-2.32) Secondary – OR 1.44 (0.93-2.23) Tertiary – OR 1.08 (0.47-2.5)	7/8
Li J et al (2019)	China	Data from an existing computerised medical record database 2012-2017	- Total 3370 ≥ 60 <i>n=2122</i> - Age ≥ 18	Education Occupation	Occupation OR 1.96 SE 0.08 Education OR 1.37 SE 0.11	7/8
Neumann-Podczaska et al (2022)	Poland	PolSenior - nationwide multidisciplinary project conducted by International Institute of molecular Cell Biology	- Total 4793 - Age ≥ 65 years	Education Self-reported poverty/Wealth	<i>Polypharmacy 5+ vs 1-4</i> Education – OR 1.09 SE 0.08 Wealth – OR 0.95 SE 0.09	7/8
Aoki T et al (2017)	Japan	Using the Primary care practice-based research network (PBRN) , self-administered questionnaires were distributed in 28 primary care clinics between October 2015-February 2016	- Total 544 - Age ≥ 20 years, ≥ 61 <i>n=454</i>	Education Income	Education OR 1.58 SE 0.21 Income OR 1.85 SE 0.20	8/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Gbeasor-Komlanvi (2020)	Togo	Primary data- Interview and questionnaires - March to June 2017	- Total 370 ≥60 years	Education Income	Education OR 0.45 SE 0.37 Income OR 0.65 SE 0.30	7/8
Sarwar M et al (2017)	Pakistan	Primary data collected from December 2015 to March 2016. Tertiary care public and private hospitals across Punjab	- Total 3129 ≥60 years	Income	<i>Taken from data table in paper</i> Income <i>P</i> 0.592 (low-income class) <i>P</i> 0.716 (middle income class)	7/8
Almedia N et al (2017)	Brazil	Data taken from previous study conducted in Cuiabá	- Total 573 ≥60 years	Education Income Occupation	Education OR 0.71 SE 0.39 <i>Taken from data table in paper</i> Income <i>P</i> 0.006 Occupation <i>P</i> 0.542	7/8
Murphy C et al (2018)	United States	Data from Medical Expenditure Panel Survey (MEPS, 2008-2014)	- Total 24,804 ≥18 years ≥60 years <i>n</i>= 13804	Education Employment	<i>Taken from data table in paper</i> Education less than high school PR 1.13 (CI 1.07-1.20) College degree or higher PR 0.98 (CI 0.92-1.04) Employment unemployed PR 0.68 (CI 0.64-0.73)	7/8
Marques P et al (2019)	Brazil	Data from the Brazilian Older Adults Frailty (Fibra) study	- Total 2217 ≥65	Education Income	Education – OR 1.32 SE 0.12 Income – OR 1.01 SE 0.10	7/8
Silva M et al (2018)	Brazil	Household survey January - February 2014 in Minas Gerais	- Total 2619 - All ages ≥60 <i>n</i>=1597	Education	Education OR 1.57 SE 0.08	6/8
Morin L et al (2018)	Sweden	Registered data November 1 st , 2010 – December 20 th 2013	- Total 1,742,336 - Aged ≥65 years	Education	Education OR 1.45 SE 0.00	8/8
Pereira K et al (2017)	Brazil	Data collected in Florianopolis – 2009-2010	Total 1705	Education Income	Education OR 1.21 SE 0.10	8/8

Sampling Frame		SES		Utilisation by SES		
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Bazargan M et al (2017)	United States	Interviews carried out 2013-2014, African Americans	- Aged ≥ 60 years - Total 400	Education	Income OR 0.95 SE 0.12 Education OR 1.55 SE 0.29	7/8
Salih S et al (2013)	Saudi Arabia	Medical outpatients at internal medicine clinics King Abdulaziz Medical city Riyadh 1 st March 2009- 31 December 2009	- Total 766 - Aged ≥ 12 ≥ 61 $n=413$	Education	Education OR 3.48 SE 0.24	8/8
Haider S et al (2009)	Sweden	Three national registers : Swedish Prescribed Drug Register, the national inpatient register and the national Education Register	- Total 626,258 - Aged 75-89	Education	Education OR 1.29 SE 0.01	8/8
Chan D et al (2009)	Taiwan	Longitudinal observational study – disabled Taiwanese elderly from the ANLTCNT (Assessment of National Long-Term Care Need in Taiwan) June 2001 – June 2002	- Total 11,788 ≥ 65 years	Education	<i>Taken from data table in paper</i> Education 1-6 years 1.37 ≥ 7 years 1.33	7/8
Bui D et al (2021)	Vietnam	Survey for Type 2 Diabetic patients in district hospital (3 districts hospitals within Quynh Phu District and Vu Thu District).	- Total 806 - Aged ≥ 40 $n=714$ ≥ 55	Education Occupation Wealth	Education OR 0.73 SE 0.18 Occupation OR 1.03 SE 0.19 Wealth OR 1.23 SE 0.23	8/8
Lim L et al (2017)	Malaysia	Malaysian Elders Longitudinal Research (MELoR) cohort	- Total 1256 - Aged ≥ 55 years	Education Employment	Education OR 0.75 SE 0.13 Employment OR 1.36 SE 0.15	8/8
Zhang X et al (2021)	China	Nationwide prospective cohort study – randomly selected from six tertiary level hospitals survey	- Total 9062 - Aged ≥ 65	Education	Education OR 0.70 SE 0.07	8/8

Sampling Frame				SES	Utilisation by SES	
Study	Country	Study Data	Participant Characteristics	Socioeconomic Measure	Main Data Extraction in relation to SES and Polypharmacy	Quality Appraisal
Nitya S et al (2021)	India	Geriatric Health Clinics across rural health centres	- Total 207 - Aged ≥ 60	Education Social Class Employment	Education OR 1.23 SE 0.30 Social class OR 1.35 SE 0.33 Employment OR 1.75 SE 0.30	7/8
Aljawadi M et al (2022)	Saudi Arabia	Using the Saudi National Survey for Elderly Health (SNSEH) – June 2006 – June 2007	- Total 2946 - Aged ≥ 60	Education Income	Education OR 1.21 SE 0.08 Income OR 0.94 SE 0.08	8/8
Rezende G et al (2021)	Brazil	Survey conducted April – September 2014	- Total 1,016 (<i>sample taken</i>) - Aged ≥ 60	Education	<i>Taken from data table in paper</i> Education <i>P</i> 0.620	7/8
Gomes M et al (2019)	Brazil	Prescriptions provided to older patients at primary health care units September 2016 – July 2017	- Total 386 - Aged ≥ 60	Education Income Employment	Education OR 0.97 SE 0.26 Employment OR 1.13 SE 0.32	8/8
Rasu R et al (2019)	United States	Medical Expenditure Panel Survey Data (MEPS) 2005-2008	- Total 4775 - Aged ≥ 65	Education Income	Education OR 1.14 SE 0.07 Income OR 1.24 SE 0.09	7/8
Yang M et al (2015)	China	Data from the Comprehensive Geriatric Assessment and Health care Service System in Chinese Elderly Project	- Total 717 - Aged ≥ 60	Education	Education OR 0.59 SE 0.22	7/8

2.4.3 Quality appraisal

The included 54 studies scored in the range 6-8, out of a possible 8 (mean=7.4, median= 7) as summarised in Table 2.3. Articles often scored poorly on identifying and reporting confounders. For example, 26 studies scored poorly on questions relating to confounders. A large proportion of the studies failed to coherently provide explanation for confounder selection and the analysis undertaken. The majority scored well on displaying inclusion criteria, using appropriate statistical analysis, and describing subjects and setting. For example, 26 articles scored full marks on quality appraisal, with all studies scoring 100% for questions 1-4. Table 2.3 showcases the quality appraisal of all studies by question, and Appendix (F) includes the quality appraisal tool used.

Table 2. 3: Quality appraisal of included studies, using the JBI checklist for cross sectional studies.

Paper	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Al-Qerem W <i>et al</i> (2018)	1	1	1	1	0	0	1	1
Midão L <i>et al</i> (2018)	1	1	1	1	1	1	1	1
Panda M <i>et al</i> (2020)	1	1	1	1	1	1	1	1
Sinnige J <i>et al</i> (2016)	1	1	1	1	1	1	1	1
Haider I, <i>et al</i> (2008)	1	1	1	1	1	1	1	1
Golchin N <i>et al</i> (2015)	1	1	1	0	1	0	1	1
Carmona-Torres J <i>et al</i> (2018)	1	1	1	1	0	1	1	1
Wauters M <i>et al</i> (2016)	1	1	1	1	1	1	1	1
Charlesworth C <i>et al</i> (2015)	1	1	1	1	1	1	1	1
Rozenfeld S <i>et al</i> (2008)	1	1	1	1	0	0	1	1
Sarwar M <i>et al</i> (2018)	1	1	1	1	0	0	1	1
Walckiers D <i>et al</i> (2015)	1	1	1	1	1	1	1	1
Thomas H <i>et al</i> (1999)	1	1	1	1	0	0	1	1
Ramos L <i>et al</i> (2016)	1	1	1	1	1	1	1	1
Carvalho M <i>et al</i> (2012)	1	1	1	1	1	1	1	1
Lu J <i>et al</i> (2014)	1	1	1	1	0	1	1	1
Assari S <i>et al</i> (2019)	1	1	1	1	0	1	1	1
Perry B <i>et al</i> (2001)	1	1	1	1	0	1	1	1
Prithviraj G <i>et al</i> (2012)	1	1	1	1	0	1	1	1
Rawle M <i>et al</i> (2018)	1	1	1	1	1	1	1	1
Filho A <i>et al</i> (2008)	1	1	1	1	1	1	1	1
Davies L <i>et al</i> (2021)	1	1	1	1	0	1	1	1
Chen Y <i>et al</i> (2001)	1	1	1	1	1	1	1	1
Doheny M <i>et al</i> (2021)	1	1	1	1	1	1	1	1

Paper	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Slater N <i>et al</i> (2020)	1	1	1	1	1	1	1	1
Masumoto S <i>et al</i> (2018)	1	1	1	1	1	1	1	1
Tan Y <i>et al</i> (2019)	1	1	1	1	1	1	1	1
Neves S <i>et al</i> (2013)	1	1	1	1	0	1	1	1
Badawy N <i>et al</i> 2020	1	1	1	1	0	1	1	1
Ong S <i>et al</i> (2018)	1	1	1	1	0	1	1	1
Li J <i>et al</i> (2019)	1	1	1	1	0	1	1	1
Neumann-Podczaska <i>et al</i> (2022)	1	1	1	1	0	1	1	1
Aoki T <i>et al</i> (2017)	1	1	1	1	1	1	1	1
Gbeasor-Komlanvi (2020)	1	1	1	1	0	1	1	1
Sarwar M <i>et al</i> (2017)	1	1	1	1	0	1	1	1
Almedia N <i>et al</i> (2017)	1	1	1	1	0	1	1	1
Murphy C <i>et al</i> (2018)	1	1	1	1	0	1	1	1
Marques P <i>et al</i> (2019)	1	1	1	1	0	1	1	1
Silva M <i>et al</i> (2018)	1	1	1	1	0	0	1	1
Morin L <i>et al</i> (2018)	1	1	1	1	1	1	1	1
Pereira K <i>et al</i> (2017)	1	1	1	1	1	1	1	1
Bazargan M <i>et al</i> (2017)	1	1	1	1	0	1	1	1
Salih S <i>et al</i> (2013)	1	1	1	1	1	1	1	1
Haider S <i>et al</i> (2009)	1	1	1	1	1	1	1	1
Chan D <i>et al</i> (2009)	1	1	1	1	0	1	1	1
Bui D <i>et al</i> (2021)	1	1	1	1	1	1	1	1
Lim L <i>et al</i> (2017)	1	1	1	1	1	1	1	1
Zhang X <i>et al</i> (2021)	1	1	1	1	1	1	1	1
Nitya S <i>et al</i> (2021)	1	1	1	1	0	1	1	1

Paper	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Aljawadi M et al (2022)	1	1	1	1	1	1	1	1
Rezende G et al (2021)	1	1	1	1	0	1	1	1
Gomes M et al (2019)	1	1	1	1	1	1	1	1
Rasu R et al (2019)	1	1	1	1	0	1	1	1
Yang M et al (2015)	1	1	1	1	1	0	1	1

JBI checklist for analytical cross-sectional studies. Checklist questions - 1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were the confounding factors identified? 6. Were strategies to deal with confounding factors started? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used?

2.4.4 Association between education and polypharmacy

Fifty studies^{73–75,94,220,230,250–252,263–303} investigated the association between education and polypharmacy, with 38 studies^{73,94,230,250–252,263–270,273,274,277–279,282–284,286–291,293–297,299–303} eligible for meta-analysis giving a pooled OR of 1.21 (95% CI 1.15-1.28; $I^2=94\%$) for receipt of polypharmacy in those of low education when compared to higher education (Figure 2.2). Studies were excluded from the meta-analysis if they did not report unadjusted data for individuals with and without polypharmacy for a given SES measure as it would prevent an OR to be calculated (see exclusion criteria for meta-analysis Section 2.3.9). Results suggested that individuals with a low SES had 21% higher odds to be in receipt of polypharmacy. Results were significant. Heterogeneity was considered high, with the combination of all studies yielding a 94% heterogeneity. However, this is expected with the meta-analysis combining a broad range of studies of which originated from a wide range of countries. Despite this, the overall direction of effect and statistically significant P values indicated that SES (in this instance, measured as education) appears to be an important factor in contributing to polypharmacy.

To validate the robustness of the results obtained from the above meta-analysis, sensitivity analyses were carried out firstly removing any studies generating a low-quality appraisal score ($<80\%$), OR 1.20 (95% CI 1.13-1.27, $I^2=94\%$ $P<0.00001$) 38 studies, Appendix G. A second analysis was carried out excluding any studies that did not solely include participants ≥ 55 years, OR 1.18 (95% CI 1.11-1.25, $I^2=94\%$ $P<0.00001$), Appendix H. Both tests confirmed robustness of the findings (Appendix G and H).

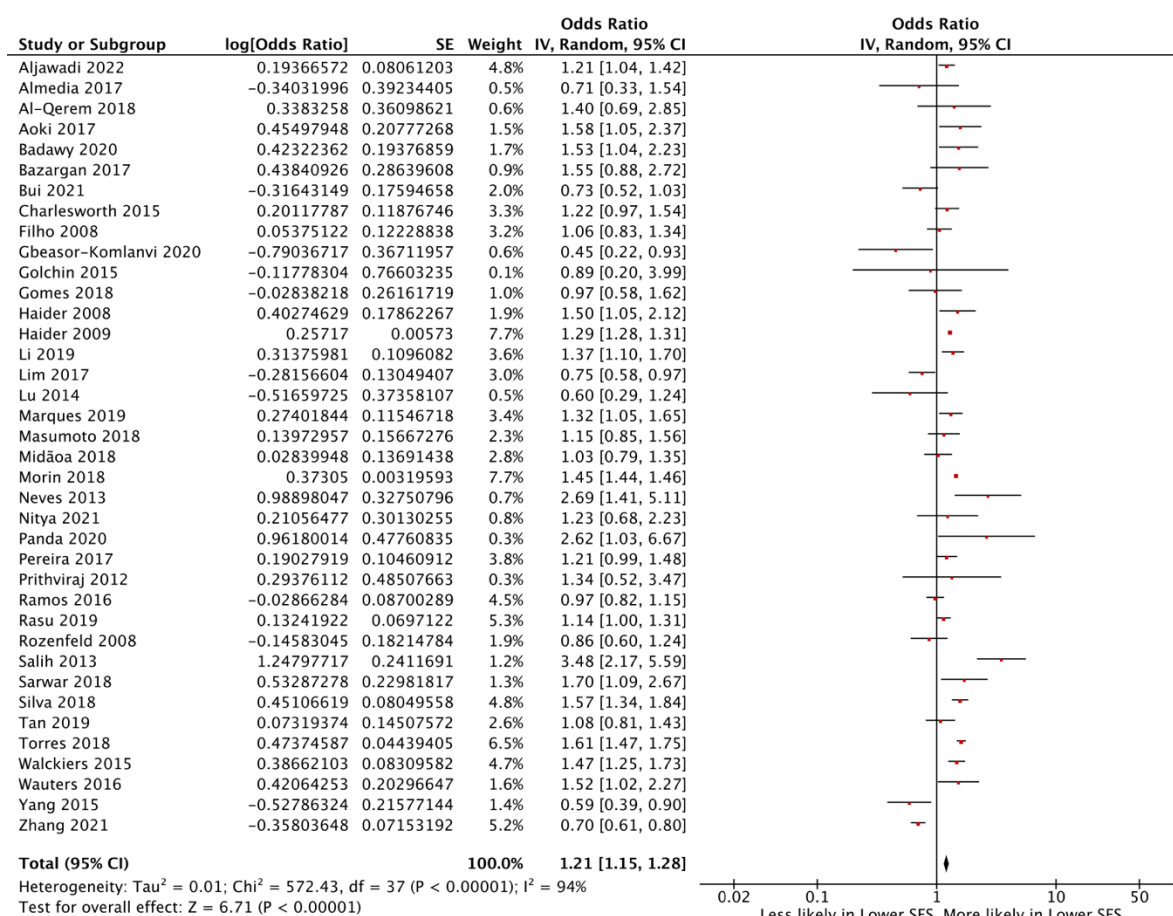


Figure 2. 2: Forest plot showing the likelihood of polypharmacy according to education for low compared to high SES.

Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance.

2.4.5 Association between income and polypharmacy

Eighteen studies^{94,220,251,269,271,272,274,278,282–284,286,289,297,299,300,302,304} investigated the association between income and polypharmacy, 12 studies^{94,251,269,274,278,282,283,286,289,297,300,302} were eligible for meta-analysis giving a pooled OR of 1.10 (95% CI 0.98-1.23; $I^2 = 46\%$) for receipt of polypharmacy in individuals from low income when compared to individuals from higher income (Figure 2.3). Unadjusted results therefore suggest individuals from low SES were 10% more likely to be in receipt of polypharmacy, with heterogeneity considered as being low (46%).

None of the included studies were excluded for the criterion on the sensitivity analysis, as all studies achieved an appraisal of 80% or higher. (Appendix I) However the second sensitivity analysis test (Appendix J) showed results of a similar magnitude and direction of effect, when excluding studies that included participants under 55 years, OR 1.06 (95% CI 0.97-1.16, $I^2 = 22\%$ $P < 0.19$). The I^2 value decreased, which was expected following the removal of only one

study. In the original analysis, this study had a higher OR than the other included studies and contributed significantly to the overall weight of the analysis.

2.4.6 Association between wealth and polypharmacy

Six studies^{73,266,281,293,303,305} investigated the association between wealth and polypharmacy, four studies^{73,293,303,305} were eligible for meta-analysis, giving a pooled OR of 1.38 (95% CI 1.31-1.46) for receipt of polypharmacy in those of less wealthy backgrounds (Figure 2.3). Results demonstrated no heterogeneity, with P values demonstrating statistical significance ($P < 0.00001$). Like income, no study was removed on the basis of poor-quality (Appendix I). However, excluding studies with participants < 55 years as a sensitive test (Appendix J) confirmed robustness (OR 1.37, CI 1.24-1.51, $I^2 = 8\%$ $P < 0.00001$).

2.4.7 Association between occupation, employment and polypharmacy

Four studies^{251,252,284,293} reported the association between occupation and polypharmacy, and seven^{220,229,285,294,296,299,302} reported the association between employment and polypharmacy. Three studies^{251,252,293} assessing occupation and five studies^{229,294,296,299,302} assessing employment were eligible for meta-analysis (Figure 2.3). A pooled OR of 1.23 (95% CI 0.70-2.17; $I^2 = 92\%$) was calculated for those in receipt of polypharmacy from lower occupations. Similarly, the pooled OR was 1.34 (95% CI 0.85-2.13; $I^2 = 76\%$) for receipt of polypharmacy in unemployed, compared to employed, individuals. Heterogeneity was considered high for both occupation and employment. Sensitivity analysis yielded no obvious differences. Excluding studies with poor quality was applicable to employment only (OR 1.12, CI 0.66-1.89, $I^2 = 67\%$ $P < 0.69$) (Appendix I). Second analysis (Appendix J) on excluding studies of which included participants < 55 years also yielded a significant degree of difference (OR 0.89, CI 0.64-1.22, $I^2 = 100\%$ $P < 0.46$). However, results observed can strongly be attributed to the fact this analysis removed all but one study in the meta-analysis.

2.4.8 Association between social class, SES and polypharmacy

Five studies^{75,229,250,275,296} reported the association between social class and polypharmacy, and two studies^{270,306} focused on SES and polypharmacy. Three studies^{229,250,296} assessing social class were eligible for meta-analysis and the pooled OR was 1.31 (95% CI 1.21-1.42; $I^2 = 0\%$) for receipt of polypharmacy in those of lower social class compared to higher social class (Figure 2.3). Two studies^{270,306} assessing SES were eligible for meta-analysis and the pooled OR was 1.03 (95% CI 0.67-1.59; $I^2 = 97\%$) for receipt of polypharmacy for those of lower, compared to higher, SES. Excluding studies was only applicable to social class with poor

quality only, which had no effect on odds (OR 1.31, CI 1.21-1.42, $I^2 = 0\%$ $P < 0.00001$). (Appendix I)

Results for the other SES factors displayed varying outcomes, with some P values being of significance, for example with wealth and social class. Whereas income, occupation, employment, SES categories were not statistically significant, suggesting the possibility of results were obtained by chance. However, the overall trend and direction of effect indicated that there were similar observations across the reported SES measures, with odd ratios suggesting individuals with lower SES were more likely to experience polypharmacy. Again, the degree of heterogeneity varied among the SES measure, from low to high. However, such results are expected due to the variability across the studies and the differing number of studies for each measure – for example four studies used wealth as a measure but 12 studies used income. Additionally, factors such as sample size can also influence the P value observed, thus both results should not be assessed in isolation but rather collectively. Sensitivity analysis revealed no obvious differences. Funnel plots were also conducted for the original meta-analysis, displaying no evidence of publication bias (Appendix K and Appendix L).

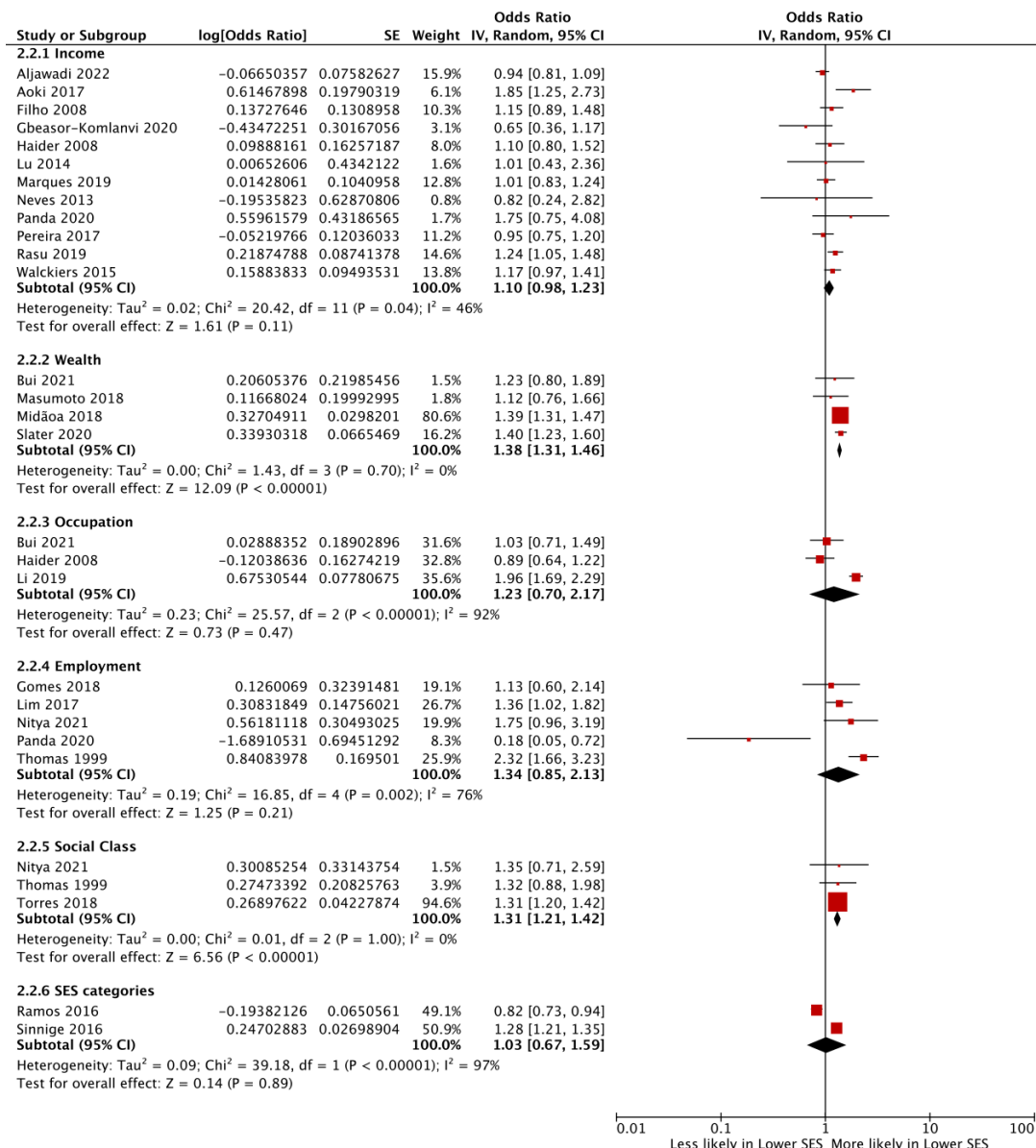


Figure 2. 3: Forest plot showing the likelihood of polypharmacy according to income, wealth, occupation, employment, social class and SES categories.
Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance.

2.5 Discussion

2.5.1 Main finding

This systematic review and meta-analysis concluded that people with lower socioeconomic status are more likely to experience polypharmacy. Most of the studies included in this review primarily used education as an indicator of socioeconomic status, while fewer studies employed measures such as occupation, income, and social class. Pooled estimates revealed a significant association when using education as a marker of SES: individuals with lower educational attainment had 21% increased odds of being in receipt of polypharmacy when compared to

those with a higher education level. Significant associations were observed when wealth and social class were used as SES measures. Although similar trends were observed for income, occupation, employment and SES categories, the results did not reach statistical significance.

2.5.2 Interpretation of findings and comparison with the literature

To the best of my knowledge this is the first systematic review and meta-analysis that has been carried out exploring the relationship between polypharmacy and socioeconomic status; focusing on an ageing population irrespective of co-morbidities or drug class. My work has demonstrated that SES and polypharmacy are associated whereby people of lower SES are more likely to be in receipt of polypharmacy. However further work is needed to understand the reasons behind this finding. Therefore, I will discuss some key aspects to this paradigm, the first being the complex relationship between polypharmacy and multimorbidity.

Firstly, as discussed in Chapter 1, the interplay between multimorbidity and polypharmacy is often complex, and while one should naturally follow the other, evidence suggests instances of inappropriate medication use.³⁰⁷ This has resulted in a range of problems associated with using multiple medications such as; poorer quality of life, frailty, adverse drug events and increased mortality.^{43,70,308} Furthermore, the literature has highlighted people of lower SES have higher risk of developing multimorbidity, which may help explain – at least in part – some of my findings. For instance, a systematic review and meta-analyses by Pathirana *et al*³⁰⁹ identified three key findings: (1) low education levels were associated with a 64% increased likelihood of multimorbidity OR 1.64 (95% CI 1.41-1.91, $I^2 = 89.3\%$); (2) higher deprivation correlated with a statistically significant risk of multimorbidity; and, (3) the relationship between income as a SES indicator and multimorbidity varied across the studies. While, this study did not specifically focus on polypharmacy or older people, it offers an important insight into the associations between multimorbidity and SES and possibly providing context for the observed increase in medication use amongst individuals from lower SES.

Although I acknowledge that the relationship between multimorbidity and polypharmacy is complex, it raises questions around the prescribing of multiple medications for managing complex health needs and whether socioeconomic factors may influence inappropriate prescribing practices. Some have commented on this discourse and have showed multiple instances where SES may have a role in contributing to inequitable access to healthcare services. For example, a study showed even after adjusting for multiple LTCs, individuals with lower SES were more likely to utilise healthcare services, including general practitioners,^{310,311}

which are often the initial point of contact for obtaining a prescription. Conversely, individuals with higher SES may potentially better manage their conditions, have access to better healthcare services, experience reduced waiting times to see healthcare professionals, all of which could influence medication usage.^{312–315} Essentially the evidence is suggesting that SES can both directly and indirectly influence medication usage.

In a broader context, evidence has shown that socioeconomic status significantly influences healthy ageing³¹² thus aligning with the concept of the “wealth health” gradient, discussed earlier in Chapter 1. This concept describes the relationship between socioeconomic status and health outcomes and suggests individuals from higher SES backgrounds tend to experience better health outcomes compared to those of lower SES backgrounds. This can be attributed to a range of factors. For example, McMaughan *et al* discuss some of the challenges encountered by individuals from lower SES, such as “out of pocket” expenses coupled with the inability to afford medications, for managing co-existing health conditions. While the extent of this divide may vary depending on the country and welfare systems, it exemplifies the health inequalities between SES groups. Another example can include access to healthcare services, where individuals with higher SES have often been shown to better navigate both public and private healthcare systems, obtaining multiple clinical opinions for their concerns, and accessing specialised healthcare services.³¹⁰ Furthermore, evidence suggests that individuals with higher SES are more likely of being prescribed the medications they want or believe they need,^{315,316} reflecting a possible direct influence on prescribing practices. In addition, Prosser *et al*³¹⁷ showcase that prescribing of medication is often patient mediated, leading to more costly, beneficial treatment being prescribed to those that are more proactive in their health, often individuals of higher SES. Further work has also shown inequalities in treatment choices based on SES, with individuals from lower SES backgrounds being less likely to receive preventative medication, when compared with those with higher SES.³¹⁸ This is inevitable in having a direct impact on quality of life and health outcomes. Further work that has shown the disparity in health outcomes has been carried out around treatment adherence, of which has highlighted individuals of lower SES are less likely to be adherent to their treatment.^{319–322} Adherence of medication plays a large contributor to treatment success and thus poor adherence inevitably results in poorer health outcomes.

The results of my review identified that education was a commonly used measure, when assessing socioeconomic status at individual level. Results suggested a strong statistical

relationship between education and polypharmacy. Fifty of the included studies used education to measure SES, and the overall findings highlighted that older people with lower education levels are more likely to be in receipt of polypharmacy. There are several possibilities that may help provide some justification to the results observed. Education plays an important role in shaping an individual's attitude toward their health, as discussed in Chapter 1. Usually, individuals from higher levels of education have shown to practice better health behaviours and therefore have greater knowledge and awareness of their health. This has resulted in such individuals being more receptive to preventative care and actively making better long term health choices.^{323,324} Similarly, adapting such health behaviours allows for the initiation of appropriate medical treatment within a timely manner³²⁵ thereby possibly reducing the need to result to multiple medications or displaying worse health outcomes. Furthermore, evidence has suggested those of a lower education attainment are often less likely to challenge healthcare professionals and be less involved with shared decision making.^{326,327} This, therefore, may have the potential for people to take additional medication without requiring a detailed explanation or challenging their healthcare professional.^{328,329} Similarly, shared decision making has shown to overall improve both treatment adherence and patient satisfaction in some circumstances.³³⁰ Adherence is most certainly a key contributor to treatment success, and health outcomes, adhering to prescribed medicine regimens potentially reduces the likelihood of further interventions (medications) for the same condition.^{331–333} While education may be an important contributor in outcomes and shaping of health behaviour, there are also many other elements outlined in the determinants of health, such as income, employment, access to healthcare services - all of which are important factors when thinking about health outcomes.

My review demonstrated employment, and income was used across studies as a marker of SES, both demonstrating a lower income, or unemployed individuals were more likely to be in receipt of polypharmacy. While again there may be tangible interplay between factors to provide possible justification to the results observed, the literature has touched on a few key aspects as to why such factors may cause inequalities in healthcare. Firstly, the ability for an individual to access free medications, may contribute to higher levels of polypharmacy.³³⁴ In most instances, unemployed individuals, or individuals with lower income are likely be entitled to free prescription coverage. With this resulting in no direct cost to the patient, thereby having the possibility of increased medicine utilisation. However, access to free medication incentives vary across healthcare systems globally. For example, in the United Kingdom (UK) there is universal health coverage, through the NHS individuals often have access to free medications, or subsidised costs, of which those of low income are most commonly eligible for. Whereas, in

contrast, privatised healthcare systems such as that in the United States (US), are an example of where individuals often experience out of pocket expenses for medication. This can be problematic especially if an individual lacks health insurance or access to finances; here, lower levels of medication use may occur in those from a lower SES, but an increase in inequalities in healthcare access, contributing to health inequities.⁸⁷

2.5.3 Strengths and limitations

This systematic review and meta-analysis showcased comprehensive findings in relation to the association of socioeconomic status on polypharmacy in older people. Whilst my approach was comprehensive and the methodology robust, I do acknowledge that my work has limitations.

Firstly, the definition I used to conceptualise older people (≥ 55 years) was arbitrary – the appropriateness of which can be debated. As discussed previously in this chapter, justifiable rationale was in place for the selection of this arbitrary threshold. For instance, previous work was used to inform this definition; initial scoping searches also supported using the ≥ 55 years value. This approach enabled the inclusion of key literature while preventing articles to be excluded by being too narrow in the inclusion criteria. However, this approach also comes with limitations. The selected age range therefore included anyone from 55 years and above, resulting in a diverse age. This can lead to variation in how individuals respond to medication, for example a 55-year-old is physiologically different from an 80-year-old. This can affect drug metabolism, and the susceptibility individuals have to adverse effects, both of which subsequently influence medicine utilisation. Similarly using an arbitrary cut off precludes the ability to understand if an individual has had a negative response to a medication, which can often be impacted by multimorbidity. In such instances often people will assess frailty, a consideration which was not addressed in this review.³³⁵

A further methodological limitation was the marker used to measure SES. My review did not limit the included studies to a specific marker for SES, partly to acknowledge the breadth of literature and to identify commonly used markers for future analyses of this thesis. However, this approach resulted in inconsistency across the data. For example, the assessment of each marker varied across studies and where two studies may have referred to education level, the approach to measure differed, *i.e.* primary level, degree level, and higher than degree – whereas others used more simpler cut off such as ≤ 12 years or > 12 years. In addition to this, the assessment of income across studies varied considerably, whereby some studies referred to household income opposed to individual level. This raises questions in regard to its applicability

to all family members, particularly in scenarios where we have an individual that is retired, or as evidence has showcased females earn typically less than men.³³⁶ As a result, the variability in defining high vs low SES makes it challenging to compare across studies. Finally, some of the included studies used area level measures such as SES categories as a marker. Similar to the variability of among the other markers, it is difficult to ascertain how accurate an area level marker can be in capturing the socioeconomic status of all individuals in a given area, especially when they include a broad range of factors. Essentially in doing so, we are introducing ecological fallacy leading to erroneous assumptions of individuals and potentially misleading conclusions.³³⁷ However, my review included a large proportion of studies that evaluated SES at the individual level. In order to improve reliability and accuracy in comparing studies for the meta-analysis participants were re-grouped into quintiles, facilitating odds to be calculated for individuals in Q1 in comparison to those in Q2-Q4, as previously discussed in this chapter. While this approach does not remove all limitations, it does contribute to mitigating them.

Further limitations were also acknowledged during the review process. All screening of titles and abstracts were carried out by one reviewer independently and a randomly allocated subsection was screened by a second reviewer. While this approach aligns with the Cochrane handbook guidelines, there is still a possibility relevant studies may have been excluded as the second reviewer did not screen all titles and abstracts. However, with the extremely large search that was generated (13,412 hits), it was impractical to get a second reviewer to screen all titles and abstracts. Secondly, the inclusion and exclusion criteria, which excluded non-English text and conferences abstracts, may have resulted in the possibility that not all articles were captured. Due to the lack of resources for translation, articles only in English language were considered. Similarly, grey literature was not searched, despite some suggesting searching grey literature can reduce publication bias and offer a more comprehensive overview of the literature.^{233–235} However, given the extensive scope of my review I decided that it would be very unlikely that many relevant studies will be found in grey literature search. I did, however, carry out both forward and backward citation searching to explore a breadth of literature. Nevertheless, these factors could have still contributed to the possible exclusion of key literature. However, I took precautions to mitigate overlooking eligible papers. For example, all titles and abstracts were screened with caution, and any that were unclear progressed to full text screening. While full texts were screened by one reviewer, 25% were independently reviewed by the review team. Furthermore, quality appraisal was carried out independently by all members of the review team. Nevertheless, there always remains potential for undetected systematic errors that can influence outcomes.

Lastly, I acknowledge there may be limitations in how my meta-analysis was conducted. Firstly, ORs were calculated using unadjusted raw data, this allowed for the re-grouping of participants in order for fairer comparisons to be made across the studies. Using unadjusted data does not account for the confounding relationships. However, the magnitude of effect and overall direction can still suggest that SES is an important factor in individuals being in receipt of polypharmacy. Most studies did account for confounders and provided multiple adjusted models in their analysis; overall, across the studies it was observed that such trends remained whereby people with lower SES were more likely to be in receipt of polypharmacy. However, I will still have to be mindful that results obtained in the meta-analyses could be a result of uncontrolled confounders. Secondly, post hoc sensitivity analyses were conducted to identify potential sources of bias and therefore should, if possible, be planned in advance and implemented into the study protocol,³³⁸ however this is not always feasible. This review took the decision to do post hoc sensitivity analysis, which is a potential limitation - this approach can be permissible, particularly in cases where unplanned issues begin to surface as the review progresses.²³²

2.6 Conclusion

This chapter findings demonstrate, for studies published up to, July 2021, there are significant socioeconomic inequalities in polypharmacy among older people, whereby people with lower SES have higher odds of being in receipt of polypharmacy. SES was mostly measured by education, suggesting its significance as a measure of SES, in understanding inequalities in healthcare access and medication use. The results from this chapter will provide the foundation for analyses in subsequent chapters. Despite not limiting this review to a particular country, a large proportion of studies originated from the United States and Brazil. While the included studies added valuable insights to this review, the general social and economic structure of such countries differs considerably from that of the UK. The presence of the NHS, with healthcare free at the point of access and accessibility of means tested medication payments, may have a distinct impact on prescribing practices. It will therefore be important to conceptualise such findings within an English setting, particularly as very few studies were included from the UK. Understanding socioeconomic inequalities in polypharmacy, in a UK context, will be significant in developing evidence-based policy with the overall aim to improve equitable healthcare practices. This will be the focus of my work for the subsequent chapters of this thesis.

Chapter 3. Cognitive Function And Ageing Studies

3.1 Introduction

Chapter 1 introduced the challenges facing older people and the ranging health inequalities present within today's society. It further demonstrated the potential harms that can be attributed to polypharmacy, particularly in an older population. Chapter 2 added to this knowledge by showcasing the body of evidence available to demonstrate how socioeconomic inequalities are present in individuals with polypharmacy. It suggested education is commonly used across the literature as a measure for SES, with approximately 93% of the included literature using this marker as a measure. However, to date, much of the published literature exploring this topic is from North and South America,¹⁹⁶ and subsequently there are limited studies from the UK.^{74,219,305,339} Therefore, before I sought to understand the extent of polypharmacy in relation to SES, and how this has changed over time in an English setting, this chapter sets out to describe the data set(s) that I have chosen to carry out the aforementioned analysis.

Chapter aim:

Describe the Cognitive Function and Ageing Study (CFAS) and the creation of variables for the analysis in subsequent chapters.

Objectives:

- I. Describe the CFAS studies in relation to the rationale, sampling and recruitment.
- II. Describe the key variables created that will be used in my subsequent analyses.

This chapter will set out to provide background to this study, alongside the steps taken to prepare for the analyses outlined in Chapter 4 and 5.

3.2 Longitudinal cohort study

CFAS are longitudinal cohort studies in their design, which therefore allows for repeated observations of the same variables over a given time period, which can often be years or even decades.^{340,341} Following participants in this way is particularly useful in understanding long-term effects, establishing casual relationships and provide a comprehensive picture on how such variables evolve.³⁴¹ This is therefore of particular advantage in helping to inform public health strategies. Typically observational in nature, longitudinal studies collect either qualitative or quantitative data, with no external influence and thereby allowing for researchers to observe and collect data naturally over time.³⁴¹ Data is often gathered from predefined groups, for

example in the CFAS cohort this included individuals aged 65 years and above. This approach allows for appropriate statistical tests to analyse changes for the entire population, selected groups, or at individual level. Such study types are therefore set aside from other designs, for example, cross sectional which only allow for analyses at a given time point, lacking the depth that can be provided through examination findings over time, particularly useful in understanding cause and effect relationships.³⁴¹ Therefore, in order to understand the extent of polypharmacy changing over time in relation to SES, a longitudinal data set was important to use.

3.3 Rationale of CFAS

The Medical Research Council, Multicentre Study of Cognitive Function and Ageing Study (MRC-CFAS) set out to focus on estimating the prevalence and incidence of cognitive decline and dementia. The principle epidemiological aim of the study was to i) estimate the prevalence and incidence of cognitive decline and dementia ii) understand the geographical variations, iii) determine the natural history of dementia, in particular the rate of cognitive decline and including the interval between identification of cognitive impairment and death iv) and identification of factors associated with differing rates of cognitive decline and risk of dementia.³⁴² Policy aims set out to focus on evaluating disability that is associated with cognitive impairment and thereby such resulting service needs. Overall, the study longed to set the foundation for long term studies in cognitive decline. This is well supported with the breadth of data that had been collected allowing for investigations into different states of health, such as depression and subsequent symptomatology. Therefore, four main themes have emerged from this study including: i) dementia (including cognition and all other aspects) ii) depression iii) disability and healthy life expectancy iv) health policy and health. The study also acted to support further sub studies and European wide initiatives such as EURODEM³⁴³ and EURODEP.³⁴⁴

3.4 Study population: sampling and recruitment

CFAS are a series of multidisciplinary multiphase design studies with baseline interviews starting from 1989 (CFAS I) and 2008 (CFAS II) with a population including individuals aged ≥ 65 years. Both studies will be used for the analysis of this PhD, all data discussed will be taken from baseline interviews. Participant background information in relation to demographics was collected through the Office of Population Census and Surveys (OPCS) 1990-1991 census, now referred to as the Office of National Statistics (ONS). CFAS participants were recruited from six centres across the UK (Cambridgeshire, Newcastle upon Tyne, Nottingham, Oxford,

Liverpool, and Gwynedd- (Figure 3.1), baseline in 1991, with Liverpool recruitment occurring in 1989. Follow up interviews were conducted in all participants in 1993-1995, and with a subset of participants in 1997, 1999 and 2001. Three of these centres, Cambridgeshire, Newcastle upon Tyne, and Nottingham were then used to recruit for CFAS II. CFAS II data was collected in 2008-2009, with a follow-up wave two years later. The study design and methods were adopted from CFAS I, to facilitate comparison over the twenty-year interval. All participants were recruited using identical methods across the sites, apart from methods used in Liverpool. Figure 3.2 shows a visual representation of the recruitment and retention of participants during the study, at baseline and assessment.

Family Health Service Authority (FHSA) lists were used to help with obtaining representative samples of the population with such lists being reflective of patients registered at a general practitioner (GP) and other healthcare providers in the area. Each centre defined the area, and subsequently the given population was drawn for the corresponding area. There were however some limitations from this method of sampling, for example, individuals that had moved from the area or passed away would still be on such lists, however, such issues were resolved through cross checking with GP surgeries. Each centre contributed to 2500 participants, to ensure a sufficient geographical spread. Sampling was stratified by age – 65-74 years and ≥ 75 years. Oversampling occurred to account for factors such as death, incorrect registration, or ineligibility. FHSA lists were not used in Gwynedd, due to being inaccessible and, therefore, GP surgery records were searched with ascertainment reflective on surgery size.³⁴⁵

Participants were assessed through detailed interviews, physical health assessment and cognitive tests. Multiple waves of data collection allowed the research team to compare health trajectories and help identify patterns and or predictors of cognitive decline and functional impairment. All interviews were conducted in the interviewees place of residence, if for reasoning such as agitation, frailty or tiring then shorter set of questions were prioritised and asked. All initial screening interviews were carried out by lay members, with all screening being completed in two years. All assessment interviews were carried out by a professional allied to medicine, carers or relatives were approached with consent whereby need be to help with the information collected.

At different points of the study various study information was collected, for example at screening, this included question on age, gender, marital status, residence, education, occupation, living circumstances, social support (including family, friend contact), self-

reported physical health, functional ability (*via* instrumental activities of daily living/activities of daily living measured using a modified Townsend ADL score), cognitive impairment (measured *via* the Mini Mental State Examination and augmented cognitive tests recommended by MRC guidance), mental state using the Geriatric Mental State Examination which would help identify major psychiatric disorders in older adults such as dementia, depression, anxiety and psychosis. It also incorporated questions from CAMDEX (Cambridge Examination for Mental Disorders and CAMCOG – longer cognitive assessment. Self-reported chronic diseases such as cardiovascular diseases, endocrine disorders, respiratory disorders, cerebrovascular disease, (detailed in Chapter 5) and self-reported medication usage including OTC items purchased were reported. Additional information can be found in the following citations.^{342,346}



Figure 3. 1: Map of Great Britain highlighting the location of centers that were used for recruitment of CFAS.

Adapted from.³⁴²

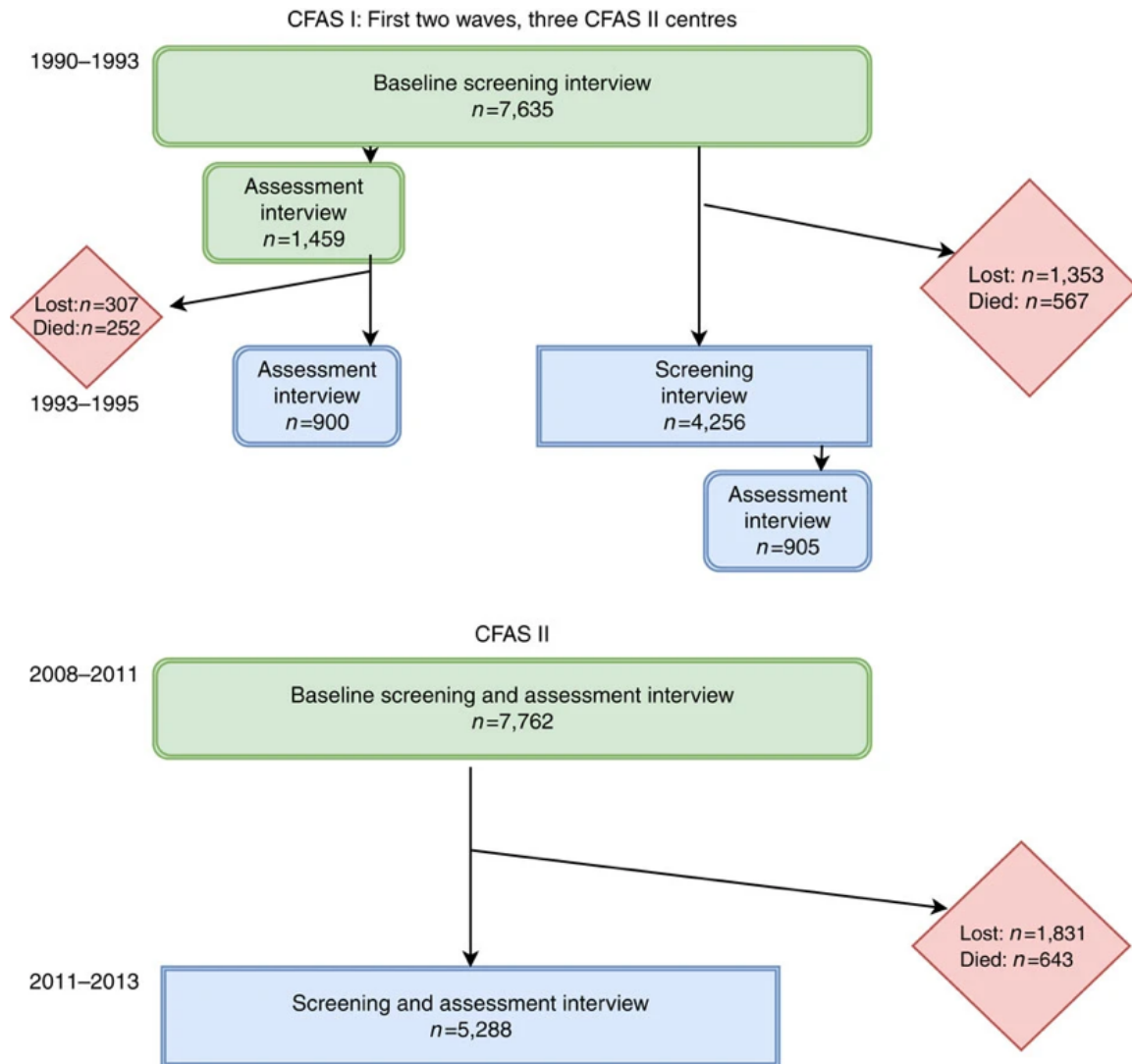


Figure 3. 2: highlights the flow of participants in CFAS I and II through baseline and 2 years follow up, including those died or were lost to follow up between the waves.
Adapted from Matthews *et al.*³⁴⁷

3.5 Key findings

Key findings from the studies highlighted the incidence and prevalence of dementia across the study sites, including rising with age and approximately 180,000 new cases of dementia occurring in England and Wales each year.^{348,349} With data being collected in relation to housing status, 4.4% of individuals resided in institutional care, prevalence of dementia across this setting was 62% (95% CI: 52; 71),³⁵⁰ slightly higher in women than man and no increase in prevalence with age. There was also no variation in the type of prevalence by the type of care home. Longitudinal analysis across the studies highlighted that incidence of dementia across the two decades decreased by 20% (95% CI 0; 40), with a reduction of age specific incidence thereby demonstrating the number of people estimated to develop dementia in any year remained relatively stable.³⁴⁷

Although primary aims of the CFAS were around investigating dementia and other cognitive related functions, the depth of data allowed and led to research in other areas, of which are important to the work of my thesis. This includes ageing and closely related to healthy life expectancies, medication usage and disability free life, key findings of this work are discussed below.

3.5.1 The burden of diseases on disability-free life expectancy in later life

This study³⁵¹ focused on total life expectancy (TLE) and disability free life expectancy (DFLE), highlighting that at the equal age of 65, women had a higher TLE – 19.4 years, 11.0 years DFLE (57%), whereas men had a TLE of 15.3 years, 12.1 years DFLE (79%).³⁵¹ Analyses further demonstrated more DFLE were gained than TLE in persons free of stroke, cognitive impairment, arthritis, and/or visual impairment at baseline. Elimination of such conditions would result in compression of disability.

3.5.2 A comparison of health expectancies over two decades in England: results of the CFAS I and II

Further work demonstrated over the two decades while there is an increase in life expectancy, 4.5 years for men and 3.6 years for women, years lived without disability (healthy life expectancy) did not increase proportionally.³⁵² Overall, despite people living longer, they are spending more years with disability – a finding which emphasised the need for better health interventions to improve quality of life.

3.5.3 Is late-life dependency increasing or not? A comparison of CFAS

This study³⁵³ demonstrated while there was an increase in life expectancy, more adults are living longer with some level of dependency, but predominately in the community opposed to care homes; however, there is a need for additional care home place predicted with an increase in both low and high dependency over the years. The majority extra years of life for men were spent independent (36.3%) or with low levels of dependency (36.3%), whereas for women the majority were spent with low dependency (58.0%) and only 4.8% were independent.³⁵³

3.5.4 Medication usage change in older people (65+) in England over 20 years: findings from the CFAS I and CFAS II

CFAS data collected self-reported medication allowing for this study to highlight the increase in medication usage among participants over the two decades.⁶⁵ The proportion of individuals taking five or more medicines quadrupled from 12% to 49%. A medicine included all prescribed and purchased products. Cardiovascular medications were noted as the most commonly used medicine, and subsequently polypharmacy was associated with an increased number in diagnosed long term conditions. Age, number of LTCs and living in a care setting were strongly associated with increased medication usage. This study is a useful starting point for my analysis, given it highlighted changed in medication usage over time; it also included some medication groups that can be used to help focus my analyses.

3.5.5 Is frailty a stable predictor of mortality across time? Evidence from the CFAS

This study³⁵⁴ focused on frailty, a measure to quantify health status, and highlighted across CFAS, mean frailty was slightly higher in CFAS II, but mortality associated with frailty remained relatively stable.

3.5.6 Healthy ageing for all? Comparisons of socioeconomic inequalities in health expectancies over two decades in the CFAS I and II

Similar to the previous findings discussed, the work here focused on health expectancies but through an inequality perspective. Results showcased while overall life expectancy had increased, gains in DFLE were significantly greater for the most advantage socioeconomic groups compared to the least - men RRR 4.7 years (95% CI, 3.3; 6.2), women RRR 2.8 years (95% CI, 1.3; 4.3).³⁵⁵ In the given two-decade comparisons, the most advantaged women experienced a reduced risk of incident disability RRR 0.7 (95% CI 0.5; 0.8), while more advantaged men had a greater likelihood of recovering from disability RRR 1.8 (95% CI 1.0; 3.2) and a reduced risk of disability free mortality RRR 0.4 (95% CI 0.3; 0.6) than in 1991. Whereas least advantaged men and women saw minimal changes in the percentage of life spent

disability free or independence in the same period. Therefore, the study highlights such increase in life expectancies are not equally distributed, and those from more advantaged socioeconomic groups are experiencing better health outcomes and fewer years in disability. These findings emphasise the importance of focusing on most disadvantages groups to help address such gaps.

3.6 Data management and data cleaning

Multiple files were provided and therefore required review to determine which variables were beneficial for the subsequent analyses that were required. Data files for CFAS I and CFAS II were organised to ensure that they were kept separate, and therefore cleaning of the data differed across both studies. Data cleaning began with CFAS II, as the data was provided first by the CFAS Research Team. Below is a brief summary of the methods used to prepare the data for the analyses as described in Chapter 4 and 5 of this thesis.

Step 1: Requested files were provided by the CFAS team as .dta files for compatibility with STATA. All files were cross referenced with the study questionnaires, and further information available across the data portal.^{342,346} During this process, key demographic data was identified from the data that will be useful in the analyses, such as: age, number of years of education, centre number. Also, questionnaires were scanned to identify which LTCs could be identified throughout the data, of which were then located in their respective variable. The rationale in relation to the selection of MLTCs is discussed further in Chapter 5.

Step 2: Once the relevant files containing the required variables were identified, files were merged using IDENT, a prepopulated variable in the CFAS data of which was a unique number provided to each participant.

Step 3: During this stage key cut offs were devised to help with the process, this therefore included identifying the appropriate stratification for age groups, and the stratification for the number of years of education, all further discussed below.

Step 4: All participants medication records were included in this study. Medicines were identified, and regrouped into an appropriate category, as discussed further in Chapter 5. Once the allocation of medicines to a specific group was completed in CFAS II, the coding was used as the foundation for CFAS I, with some additional medicines identified that were prescribed during that earlier time period.

Step 5: Coding was developed to identify people with and without polypharmacy, in specific medication groups and with multimorbidity. Appropriate analyses were carried out, to address the questions in hand.

3.7 Selection of variables

Variables were selected and created to carry out the analyses reported in Chapter 4 and 5, as are discussed below.

3.7.1 Education

Education was collected and recorded for each participant, as the number of years of full-time education, and thereby a categorical variable was created to help make comparisons across the level of education. The categories were designed to reflect statutory school ages, and in reflection of the time periods investigated. Therefore, 9 years of compulsory school ages (5-14 years) reflected individuals in the 1991 cohort (Covered by Balfour Acts of 1902 and Fisher Act 1918). Whereas for 2011 cohort, mandatory school ages were longer mainly due to most births being after the Fisher Act, 10 years, applicable to those born after 1947 (approximately those ages 65-80 years in the 2011 cohort). As a result, the following categorical variables for education were created:

- i. Category 1: 0-9 years
- ii. Category 2: 10-11 years
- iii. Category 3: ≥ 12 years

3.7.2 Age

Age of participants was recorded at screening, and participants with cognitive impairment, a secondary source was used to confirm their age. The purpose of the age categories ensured that during all analysis comparisons could be made across categories, particularly with CFAS being a large study. Participant ages were organised into six groups (65-69, 70-74, 75-79, 80-84, 85-89 and 90+).

3.7.3 MLTCs

All participants had been asked if they have experienced a list of conditions, varying from cardiovascular to metabolic disorders, for example, heart attack, stroke or diabetes, full inclusion list of LTCs used in this analysis can be found in Appendix M. Study questionnaires were reviewed to identify which questions correlated to demonstrating the presence or a comorbidity, this was then treated as a binary variable and multimorbidity count was developed,

as two or more conditions, in line with current research and guidelines. Further discussion around multimorbidity and polypharmacy is present in Chapter 5.

3.7.4 Medication

The CFAS data collection recorded all medicines, prescribed and purchased by an individual, a strength of this study. Participants were asked a series of questions in relation to medication usage, for example to list name, dosage, duration and frequency. All products had been coded using an NHS Read Code which are a set of pre-defined codes reflective of drug classification and an indication of clinical use. While this was a useful foundation to help construct reflective medication groups (required for subsequent analysis in Chapter 5) further work was required to ensure medications were allocated to a suitable group, again discussed further in Chapter 5. After the creation of medication groups, a binary variable was created to identify individuals that had polypharmacy, use of five or more prescribed medications.

3.8 Ethics

All projects intending to access CFAS data are required to submit a data application form in order to gain the necessary ethical approval for data. Therefore, information was required to be provided in relation to study background and the objectives for accessing data. Furthermore, any collaborators involved in funding the project were also requested, of which in this case was the National Institute of Healthcare Research, Applied Research Collaboration Northeast North Cumbria, funders of my PhD work. In addition, with the longitudinal design of the study, it was requested to provide information of which interview stage was required for the analyses. Data was requested for Wave 1 of both CFAS I and II, however, as multiple variables would be required for analyses, all interview data was requested at baseline waves. All investigators involved in the project were also required to be provided. All data provided was anonymised, using ID numbers to protect participant confidentiality. Ethical approval was granted within one month of requesting the data and subsequently shared as encrypted files allowing for full access. Data that requested for both CFAS I and CFAS II, wave 1, was granted.

3.9 Conclusion

In conclusion, this chapter has introduced CFAS, its design, methodology and rationale for commissioning the study. The chapter has discussed and introduced the variables required to carry out the intended analysis of my PhD, laying a foundation for more in-depth discussions in later chapters of this thesis. There has also been discussion around some of the literature arising from CFAS, particularly those deemed important for this work.

Chapter 4. Education Effect on Polypharmacy Across CFAS

4.1 Introduction

The work of previous chapters has highlighted the broad presence of socioeconomic inequalities across the literature and the pressing issues of multiple medication usage in an ageing population. Therefore, the work of this chapter will use CFAS (detailed in Chapter 3) to understand the association at baseline and then longitudinally present relationships observed. It will also demonstrate public health implications of the findings.

Chapter aim:

Determine the association of SES (measured as the number of years of education for an individual) on polypharmacy in an ageing population in England.

Objectives:

- I. Determine the demographic characteristics of CFAS, particularly in relation to the prevalence of polypharmacy at baseline across CFAS I and CFAS II.
- II. Determine if there is a relationship between education and polypharmacy and, if so, how the relationship has changed over time.
- III. Determine how observed relationships between education and polypharmacy are affected by confounders.
- IV. Understand and describe the wider public health impact of the observed relationships.

4.2 Background

Polypharmacy is most commonly defined in the literature as the use of five or more medications,⁸⁹ although there are many other variations to its definition. For example, it has been suggested to use the additional measurement of appropriateness¹⁰³ while others are of the opinion that this arbitrary value does not take in the complexities of multiple health conditions, and while five medications may be appropriate for one individual it may not be for another.^{89,356} The discourse around its definition is discussed in depth in Chapter 1 Section 1.4.3. This being said in healthcare research the most commonly used definition is five or more medicines⁸⁹ and polypharmacy has become a growing public health burden.³⁵⁷ Multiple medication use has raised many concerns due to the undesirable effects it can often cause, such as drug-drug interactions and an increased risk of falls.^{43,70} This concern is particularly pertinent for the older population, who are most at risk of polypharmacy.³⁵⁸ There is growing discourse amongst

healthcare professionals in ensuring patients with polypharmacy are reviewed and safer prescribing occurs.³⁵⁹ The interplay between multimorbidity and polypharmacy is of great interest as they often follow each other. Whilst in some instances polypharmacy may be appropriate and reflective of treatment need, there have also been instances of inappropriate polypharmacy, and thus multiple tools are available for prescribers to ensure that polypharmacy is appropriate.^{360,361}

Inequalities in polypharmacy prevalence, whereby different socioeconomic factors such as income and education can be associated with multiple medication usage, are another area of interest. The work of Chapter 2 has shown there are potential inequalities in being in receipt of polypharmacy,¹⁹⁶ whereby education was used as a common socioeconomic marker. Further work has also suggested such inequalities remain despite adjusting for variables such as multimorbidity.⁷⁵ Therefore subsequent aims of this PhD are to determine if there are associations between education and polypharmacy, and, if so, how such inequalities have changed over time, focusing on an English setting.

4.3 Methods

4.3.1 Statistical analysis

The purpose of the primary analysis was to understand the relationship between SES and polypharmacy. Studying this relationship presents several methodological challenges, that will be discussed throughout the subsequent chapters, however, do warrant early consideration to direct the analyses undertaken. Confounding is a key concern, particularly whereby SES may be associated with other factors such as comorbidities, healthcare access or more by in general with health-seeking behaviours that all have the potential in affecting the use of medication, such concepts introduced in Chapter 1. The issues of reverse causality should also be considered, for instance individuals with higher medication usage may experience reduced education attainment, due to illness, thereby complicating further the direction of observed associations. There are further issues around selection bias, whereby, individuals with lower SES or poorer health outcomes may be underrepresented, particularly with data attrition. As mentioned in Chapter 3, education categories were created and clinical cut off points were chosen for example the use of ≥ 5 medication to define polypharmacy. Whilst justification has been provided throughout this thesis for the use of dichotomisation it does still have the potential to mask more nuanced gradients of medication use. Similarly, SES has the potential in itself to be measured using various markers such as, continuous indicators (number of years

of education), ordinal categories (low, medium, high education) and composite indices (index of multiple deprivation). Each approach carries implications for interpretations and are addressed throughout this thesis. Such challenges in particular have been used to inform the selection of analytical methods, particularly in interaction models that are present in Chapter 5. Secondary analysis then aimed to understand how this has relationship changed over time and to determine the public health impact of this association. Baseline demographics were reported for the whole cohort, including the contributions of participants from each centre. Descriptive statistics were used to report all variables of interest, including polypharmacy reported by gender, age and SES (measured by the number of years of education). Logistic regression modelling was then developed to understand the association between polypharmacy and SES, with and without adjustments for confounders. This regression was appropriate given that the outcome variable of interest was binary: the presence or absence of polypharmacy. Multivariable models were then developed in order to help account for potential confounders and provide a clearer understanding of the factors that potentially influence the outcome.³⁶²

4.3.2 Logistic regression

Logistic regression is often used in epidemiology as a mathematical modelling approach, to describe relationships between variables with dichotomous or binary outcomes.³⁶³ This model is designed to produce a probability of an event(s) occurring between 0 and 1, and thereby providing a reflective odds ratio.³⁶³ Using this method in epidemiology allows the ability to quantify risk factors, assess effectiveness of interventions and control for confounders. Unlike linear regression, which predicts a continuous outcome, and therefore not suitable for this analysis with an outcome of being or not being in receipt of polypharmacy.³⁶⁴ In addition Poisson regression was further deemed unsuitable, whilst commonly used for count data, the focus of this study was not on modelling the number of medications as a count variable, but rather on estimating the odds of having polypharmacy. Logistic regression is therefore appropriate for binary outcomes and offers an interpretable framework for odds ratios. Additionally, Poisson regression has the potential to overestimate standard errors³⁶⁵ when used with binary data, whereas logistic regression is more robust for this outcome structure.

There are several types of logistic regression that can be used including:

- i. Binary – response or dependent variable is dichotomous, therefore with two possible outcomes.
- ii. Multinomial – dependent variable has three possible outcomes.
- iii. Ordinal – response variable has three or more possible outcomes, with a defined order.

In relation to this thesis and to answer the first question at hand – if there is a relationship between education and polypharmacy and, if so, how this relationship has changed over time, the most appropriate model would be a binary logistic regression allowing for a dichotomous outcome.

4.3.3 Multivariable analysis

In order to answer the second part of the analysis (how observed relationships are affected by confounders) variables that would be adjusted required to be selected.^{378,379,378,379} These were selected through which variables may influence outcomes based on existing research within the area. I selected this approach for selecting my confounders, as it ensures that my analyses will be informed by past research and my own expertise.

Potential confounders were therefore selected through expertise knowledge and relevant literature that has shown notable associations with polypharmacy, for example:

- i) age, often individuals that are older are more likely to be in receipt of polypharmacy.^{366,367}
- ii) Gender differences amongst medication use, and where females are often more likely to use more medications than males.³⁶⁸
- iii) Large interplay between multimorbidity and polypharmacy,⁶¹ a concept discussed in greater depth in Chapter 1 and further discussed in Chapter 5.

4.3.4 Linear trend analysis

A linear trend analysis was undertaken amongst the education categories to investigate the potential of a *dose response effect*. While another way to approach this analysis would be to consider education as a continuous variable opposed to categorical, providing a more detailed analysis into how such incremental changes in an individual's education level are associated with polypharmacy,³⁶⁹ this method was not chosen for several reasons. Firstly, large extremities were present in the data, which may obscure findings and skew results. Secondly, the additional year or so in earlier school life can often be more beneficial than the same additional years in later years of education. Earlier years of education often set the foundations for an individual's cognitive and lifelong development, thereby is often more significant.^{370,371} Lastly, this additional analysis was conducted to assess the strength of the results from the univariable and multivariable analyses, and to observe the distinct association between the categories – a more robust insight into the relationship between education and polypharmacy.

4.3.5 Population attributable fraction

To answer the final question of this analyses, of what the public health impact is of the results obtained, the population attributable fraction (PAF) was calculated. This measure is used to estimate the proportion of cases for a given outcome that can be attributed to specific risk factors, with the assumption of a causal relationship. It therefore allows to help direct and prioritise public health interventions, through estimating the potential reduction of a given outcome if such risk factors were removed from the population. In my analysis, a regression-based model was used to calculate PAF, focussing on understanding how the level of education affects the likelihood of polypharmacy.^{372,373} The model also adjusted for potential confounders associated with polypharmacy, which were to be identified from prior knowledge, logistic and multivariable models. In calculating PAF in such a way this has allowed for the appreciation of multiple factors that can be attributed to polypharmacy. However, it is important to note that PAF assumes a direct causal relationship, which may not fully reflect the complexity of the underlying associations. Therefore, the estimates should be interpreted with caution. Alternative causal inference methods, discussed further in Chapter 6 section 6.7 could offer more robust means of assessing causality in future studies

All statical analysis as carried out using STATA version 17.0 and 18.0 (StataCorp, College Station, Texas (TX)).

4.3.6 Polypharmacy definition

As explained in Chapter 1, polypharmacy refers to the use of multiple medications and despite its definition lacking consensus, it is most commonly referred to as the use of five or more medications,⁸⁹ which was adopted in my analysis. Although this arbitrary value can present challenges, for example, whether five medications is an appropriate cut off¹⁰³ and its inability to understand the appropriateness of the medication, it was necessary to have a specific marker, when handling large data to allow for the identification of individuals with polypharmacy. Alternative measures could have included a categorical variable such is 0-4 (no polypharmacy), 5-9 (polypharmacy), and ≥ 10 medications (hyper-polypharmacy).⁸⁹ However, this categorical outcome was ill suited for my analysis, particularly given that a large proportion of participants in CFAS I were using less than five medications.

In order to be reflective of the daily burden of taking medications, for example adverse effects, social burden and poor adherence,³⁷⁴ items that where *one time use* or *non-drug* were excluded. This included vaccines, wound management products, catheters and stoma care. In addition to this, anything that did not have systemic absorption were excluded, including topical

creams/ointments, ear drops, nasal sprays and eye drops. These exclusions were based on the rationale that they have no or little systemic effect^{375–378} and therefore limited interactions with other medications (*i.e.* through an oral route – a key concern in relation to potential harms with polypharmacy); they also limited systemic adverse effects.

A strength of CFAS was the identification of OTC purchases. However, as it was unclear what exactly was purchased by the participants, and therefore such items could potentially include topical products or herbal preparations, OTC items were excluded from the analysis. Another commonly purchased OTC product are vitamins and were able to be identified and therefore they were categorised and included in analyses as a separate category. A full list of all categories of medications created for this analysis can be found in Appendix N.

4.4 Results

4.4.1 Demographic characteristics of the CFAS at baseline across both studies

There were 7,639 participants in CFAS I during wave 1 of analysis (Figure 4.1). Of these participants, 60.1% were female and most individuals were aged between 65-69 years old, 25.9%. Participants used between 0-8 medications, median 2 (Figure 4.2), full cohort characteristics can be found in Tables 4.1 and 4.2. A total of 10.5% of the study participants displayed polypharmacy, of which 64.3% were female and most were aged between 75-79 (26.1%). People with polypharmacy tended to have 10-11 years of education. Despite low levels of polypharmacy, 53.9% of the total cohort displayed multimorbidity, with individuals being mostly female and aged between 65-69 (25.0%).

For CFAS II, there were 7,762 participants during wave 1 of analysis. Of these participants, 54.5% were female and most individuals were again aged between 65-69 years old, 25.0%. The percentage of individuals in the total study across each education category was as follows: 25.5% for 0-9 years (Category 1), 49.8% for 10-11 years (Category 2), and 21.3% for 12 years and more (Category 3) Table 4. Participants used between 0-23 medicines, median 4 (Figure 4.2). A total of 45.1% of the study participants displayed polypharmacy, of which 55.0% were female and, similarly to CFAS I, most were aged between 75-79 (23.9%). Again, a large proportion of individuals with polypharmacy had 10-11 years of education. A total of 65.7% displayed multimorbidity, of which 56.1% were female, and most individuals with multimorbidity were aged between 70-74 (24.2%). In CFAS I polypharmacy across the education categories was fairly consistent, unlikely that of CFAS II (Figure 4.3).

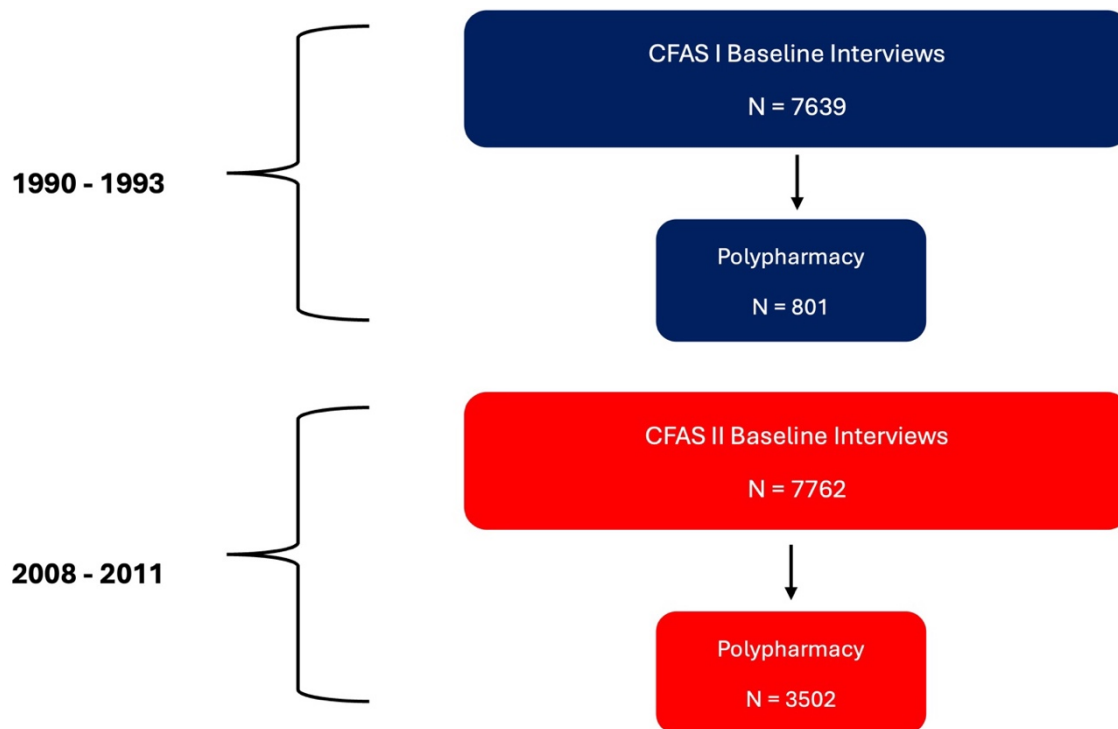


Figure 4. 1: Study design of CFAS I and II, with participants displaying polypharmacy.

Table 4. 1: Baseline demographic characteristics of participants in CFAS I and CFAS II at wave 1.

	CFAS I		CFAS II	
N	7639		7762	
Centre				
Cambridgeshire	2601	(34.0)	2558	(33.0)
Newcastle	2524	(33.0)	2582	(33.3)
Nottingham	2514	(32.9)	2622	(33.8)
Sex				
Female	4594	(60.1)	4228	(54.5)
Male	3045	(39.9)	3534	(45.5)
Age Group				
65-69	1982	(25.9)	1939	(25.0)
70-74	1778	(23.3)	1873	(24.1)
75-79	1725	(22.6)	1624	(20.9)
80-84	1309	(17.1)	1278	(16.5)
85-89	615	(8.1)	737	(9.5)
≥90	230	(3.0)	311	(4.0)
Education (Years)				
0-9	5706	(74.7)	1976	(25.5)
10-11	1240	(16.2)	3863	(49.8)
≥12	693	(9.1)	1653	(21.3)
Unavailable			270	(3.5)

Key: Data are n (%). CFAS=Cognitive Function and Ageing Study.

Where N does not add up to CFAS I: 7639 or CFAS II: 7762 data is missing.

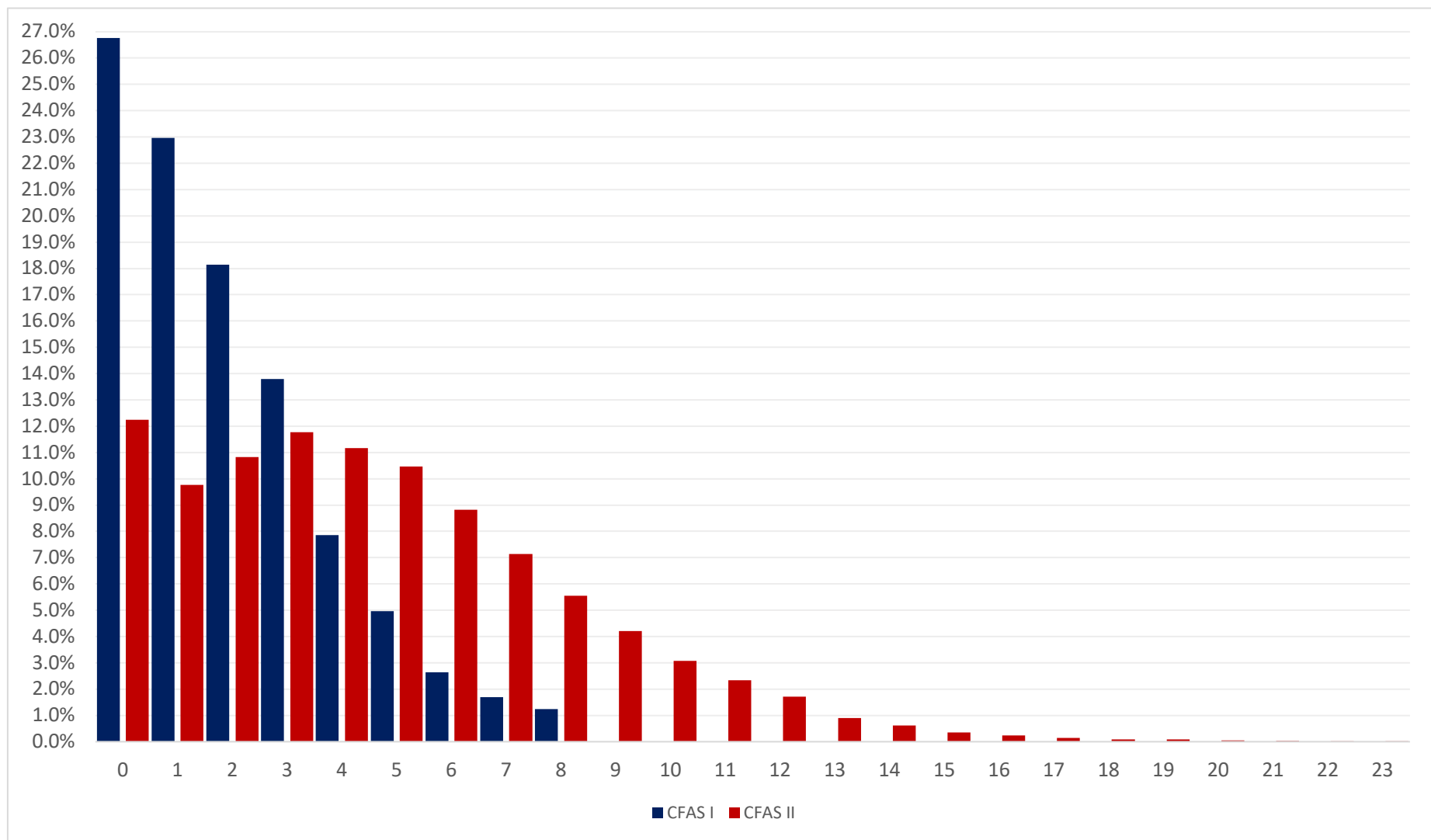


Figure 4. 2: Distribution of the number of medicines administered by participants across CFAS I and II at baseline waves.

Table 4. 2: Baseline demographic characteristics of participants with and without polypharmacy in CFAS I and CFAS II at wave 1.

Total cohort population	CFAS I				CFAS II			
	7639				7762			
	Yes		No		Yes		No	
Polypharmacy	801	(10.5)	6838	(89.5)	3502	(45.1)	4066	(52.3)
Polypharmacy across the number of years of education								
0-9 years	610	(76.2)	5096	(74.6)	1102	(31.5)	855	(21.0)
10-11 years	130	(16.3)	1110	(16.3)	1691	(48.3)	2162	(53.2)
≥12 years	61	(7.6)	632	(9.3)	600	(17.1)	1049	(25.8)
Sex								
Polypharmacy across females	515	(11.2)	4079	(88.8)	1936	(45.8)	2288	(54.2)
Polypharmacy across females and number years of education								
0-9 years	391	(76.0)	3034	(74.4)	659	(34.0)	461	(20.1)
10-11 years	83	(16.1)	660	(16.2)	891	(46.0)	1147	(50.1)
≥12 years	41	(8.0)	385	(9.4)	310	(16.0)	564	(24.7)
Polypharmacy across males	286	(9.4)	2759	(90.6)	1566	(44.7)	1934	(55.2)
Polypharmacy across males and number years of education								

0-9 years	219	(76.6)	2062	(74.7)	443	(9.7)	394	(20.4)
10-11 years	47	(16.4)	450	(16.4)	800	(51.1)	1015	(52.5)
≥12 years	20	(7.0)	247	(9.0)	290	(18.5)	485	(25.0)

Multimorbidity

Participants with and without multimorbidity, but with polypharmacy	707	(20.7)	94	(11.7)	3026	(86.4)	476	(13.6)
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*Key: Data are n (%). CFAS=Cognitive Function and Ageing Study.
Where N does not add up to CFAS I: 7639 or CFAS II: 7762 data is missing.*

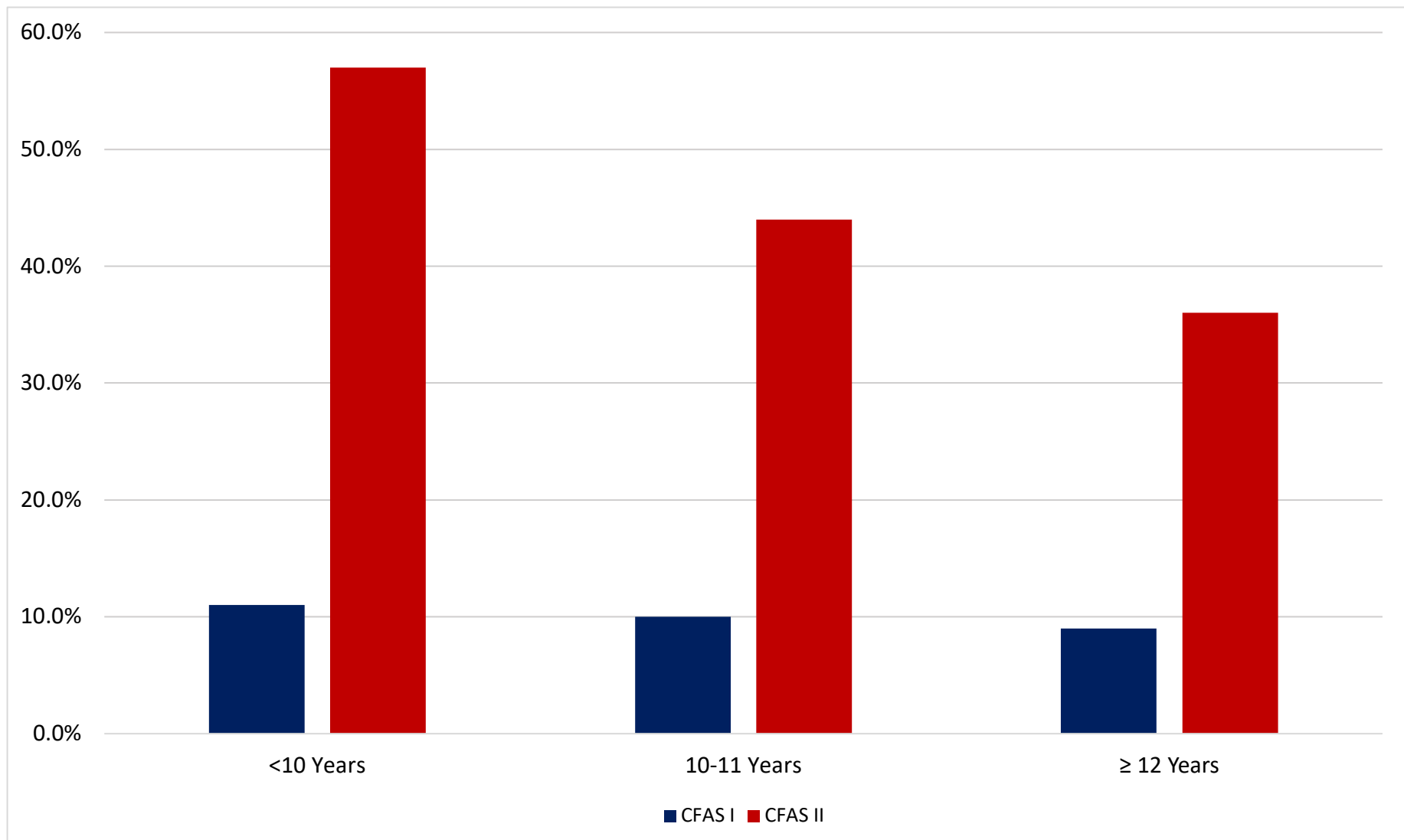


Figure 4. 3: Percentage of people with polypharmacy across CFAS I and II at baseline waves by years of education.

4.4.2 Relationship between education and polypharmacy

Table 4.3 includes analysis of each variable of interest, showing the odds of being in receipt of polypharmacy across both CFAS I and II. Odds presented for CFAS I highlighted an increased likelihood of being in receipt of polypharmacy for individuals with <10 years of education, OR 1.03 (95% CI 0.84; 1.27) when compared to those with 10-11 years of education. Whereas a much lower odds, OR 0.83 (95% CI 0.60; 1.14) if presenting with ≥ 12 years of full-time education. Similar observations were shown for CFAS II, but overall demonstrating an increased odds of being in receipt of polypharmacy for individuals that have lower number of years of education.

Over the two decades, there was more than a 4-fold increase in polypharmacy, with over 2500 more individuals being in receipt of polypharmacy for CFAS II compared with CFAS I, Table 4.2. Individuals with less education had much higher odds of being in receipt of polypharmacy in CFAS II, OR 1.61 (95% CI 1.44; 1.80). Those that had ≥ 12 years of education had reduced odds of polypharmacy, OR 0.73 (95% CI 0.64; 0.82), of which reached a significant difference. Observing the data over the two time points (1990-2010), highlights two key points: i) the education effect on being in receipt of polypharmacy remained present over the two time periods. ii) The presence of widening inequalities is evident over the time periods, with a greater difference of polypharmacy between <10 years and ≥ 12 years of education.

4.4.3 Relationship between education and polypharmacy in the presence of confounders

To understand the relationship between education and polypharmacy, confounders were identified and implemented into the model. These variables have the ability to affect the outcome (polypharmacy) or exposure (education), as discussed in Chapter 3. Multivariable models (Table 4.3) were built to assess the influence of the aforementioned confounders, adjusting for age, sex and a combination of both variables. Figure 4.4 presents visual representation of results for model 1 (adjustment for age and sex). In CFAS I when adjusting for age and sex, the odds of being in receipt of polypharmacy decreased minimally for both <10 years of education OR 1.01 (95% CI 0.82; 1.24) and ≥ 12 years OR 0.79 (95% CI 0.57; 1.09), in respect to the univariable analysis. Considerable overlap was present in confidence intervals with those observed in univariable analysis for being in receipt of polypharmacy, thereby showcasing the observed relationships from univariable analysis remained fairly consistent after adjusting for age and sex in combination.

The results obtained for adjustments of confounders for CFAS II differed. In the combination model of age and sex, the odds of being in receipt of polypharmacy decreased substantially from univariable analysis: <10 years OR 1.61 (95% CI 1.44; 1.80) to 1.17 (1.03; 1.33), with no overlap in confidence intervals thereby suggesting both age and sex have a considerable confounding affect in this cohort, and associated relationships between lower education and being in receipt of polypharmacy have become weaker. However, for individuals with ≥ 12 years similar observations with that of CFAS I were observed, with the protective effect of higher education against polypharmacy remaining consistent, OR 0.73 (95% CI 0.64; 0.82) to 0.71 (95% CI 0.63; 0.80). Overall, results consistently indicated that higher education is associated with a reduced likelihood of being in receipt of polypharmacy, and the contrary was observed for lower education.

The final model constructed for analysis was to investigate the association between the number of years of education and polypharmacy, adjusting for age, sex, and multimorbidity across the studies. Overall, across both CFAS I and II, minimal differences were seen on odds of being in receipt of polypharmacy with the addition of multimorbidity as a confounder: the protective effect of higher education remained consistent and significant, Table 4.3 ≥ 12 years OR 0.83 (95% CI 0.60; 1.14), adjusted OR 0.81 (95% CI 0.58; 1.14) (CFAS I); OR 0.73 (95% CI 0.64; 0.90), adjusted OR 0.79 (95% CI 0.69; 0.90) (CFAS II). However, for individuals with <10 years of full-time education, age, sex and multimorbidity combined presented confounding relationships in multivariate analysis, with a decreased in odds and thereby a weaker association: For CFAS II, OR 1.61 (95% CI 1.44; 1.80), adjusted OR 1.13 (95% CI 0.98; 1.30). For CFAS I, the confidence intervals overlap between adjusted and non-adjusted models: <10 years overall odds reduced OR 1.03 (95% CI 0.84; 1.27) to OR 0.97 (95% CI 0.79; 1.20) despite minimal change in odds, overall associations remained.

Table 4. 3: Univariable and multivariable analysis for variable of interest and polypharmacy CFAS I and CFAS II at wave 1.
Variable of interest includes education (years full time), age group, sex. Model 1 adjusted for age and sex and Model 2 adjusted for age, sex and multimorbidity.

Unadjusted odds ratio (95% CI)								Adjusted odds ratio (95% CI)									
CFAS I				CFAS II		CFAS I				CFAS II		CFAS I				CFAS II	
Variable of Interest						Model 1						Model 2					
Education:																	
<10 years	1.03	(0.84; 1.27)	1.61	(1.44; 1.80)		1.01	(0.82; 1.24)		1.17	(1.03; 1.33)		0.97	(0.79; 1.20)		1.13	(0.98; 1.30)	
10-11 years (referent)	1.00		1.00			1.00			1.00			1.00			1.00		
≥12 years	0.83	(0.60; 1.14)	0.73	(0.64; 0.82)		0.79	(0.57; 1.09)		0.71	(0.63; 0.80)		0.81	(0.58; 1.14)		0.79	(0.69; 0.90)	
Age Group																	
65-69 (referent)						1.00			1.00			1.00			1.00		
70-74						1.25	(1.00; 1.57)		1.50	(1.31; 1.72)		1.23	(0.97; 1.55)		1.39	(1.21; 1.61)	
75-79						1.63	(1.31; 2.03)		2.02	(1.75; 2.34)		1.58	(1.26; 1.97)		1.81	(1.55; 2.11)	
80-84						1.62	(1.29; 2.05)		2.41	(2.04; 2.83)		1.58	(1.24; 2.00)		2.21	(1.85; 2.65)	
85-89						1.83	(1.37; 2.43)		2.01	(1.70; 2.51)		1.86	(1.38; 2.49)		1.88	(1.52; 2.32)	
≥90						1.44	(0.92; 2.43)		2.17	(1.62; 2.90)		1.73	(1.09; 2.76)		2.11	(1.52; 2.94)	
Sex																	
Female(referent)						1.00			1.00			1.00			1.00		
Male						0.87	(0.74; 1.01)		0.98	(0.89; 1.08)		0.96	(0.82; 1.13)		1.08	(0.97; 1.20)	
Multimorbidity																	
												7.41	(5.92; 9.27)		6.89	(6.08; 7.80)	

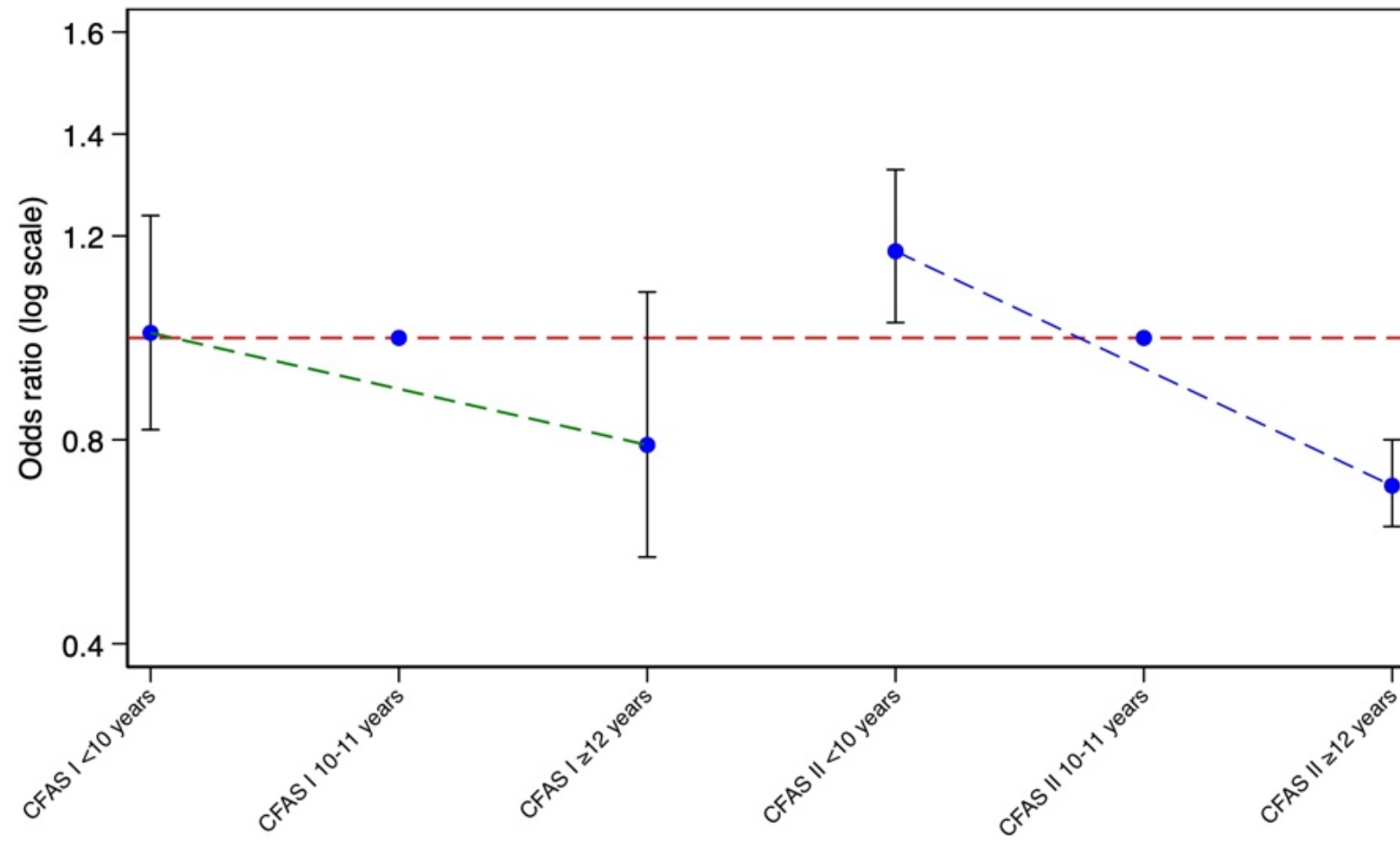


Figure 4. 4: Forest plot showing odds ratio of polypharmacy across CFAS, in relation to the number of years of education. Adjusted for age and sex

4.4.4 Linear trend analysis

A final test was carried out, conducting a linear trend analysis and thereby treating the education categories as a continuous variable, to understand if a linear relationship was present. CFAS I and II results mimic observations discussed above. For every step increase (moving from <10 years, to 10-11 years, to ≥ 12 years) there was a decrease in odds of being in receipt of polypharmacy, Table 4.4. Results from CFAS II demonstrate the protective effect of education – with much steeper decline in odds with every step increase in education, and at the 95% CI indication of statistical significance – OR 0.78 (95% CI 0.72; 0.84). Other observations from these analyses showed, a higher odd of polypharmacy with increased age, as expected, but the effect of sex was not as pronounced: males were displaying lower odds of polypharmacy compared to females in CFAS I, and close to equal in CFAS II.

4.4.5 Understanding wider public health implications of the observed relationships

PAF was calculated to estimate the proportion of cases of polypharmacy that were attributed to risk factors, in this instance modifiable risk factor (education) and non-modifiable risk factors (age and sex). To carry out this analysis, individuals were placed in the most desirable characteristic, *i.e.* such that would be estimated to cause the least risk, therefore, in this instance, a greater number of years of education have been attributed to individuals being less likely in receipt of polypharmacy. Therefore, subsequent analysis carried out, education category 3 (≥ 12 years) became the referent. In CFAS I, 12.5% of people with polypharmacy were attributed to education category 1 (<10 years) and 2.7% attributed to education category 2 (10-11 years), Figure 4.5 and Table 4.5. In CFAS II, 7.2% of polypharmacy cases were attributed to having less than 10 years of education, and 8.9% to having 10-11 years of education, Figure 4.6. While both studies attribute higher proportion of cases to lower years of education, much higher cases were attributed to the middle education category in CFAS II compared to CFAS I, suggesting education level having a more substantial association in being in receipt of polypharmacy in CFAS II than I. An indication in a shift in socioeconomic factors / dynamics between the two times period is evident.

Table 4. 4: Linear trend analysis of variable of interest (using education categories as a continuous variable) and polypharmacy, CFAS I and II at wave 1.

Variable of Interest	Adjusted Odds Ratio (95% CI)	
	CFAS I	CFAS II
Education	0.91 (0.81; 1.03)	0.78 (0.72; 0.84)
Age group		
65-69 (referent)	1.00	1.00
70-74	1.25 (1.00; 1.57)	1.51 (1.32; 1.73)
75-79	1.62 (1.30; 2.02)	2.00 (1.72; 2.30)
80-84	1.62 (1.28; 2.04)	2.31 (1.98; 2.71)
85-89	1.82 (1.37; 2.42)	2.00 (1.64; 2.40)
≥90	1.43 (0.92; 2.23)	2.10 (1.57; 2.79)
Sex		
Female (referent)	1.00	1.00
Male	0.87 (0.74; 1.01)	0.98 (0.89; 1.01)

Table 4. 5: Population attributable fraction for both CFAS I and CFAS II at wave 1. Modifiable risk (education) and non-modifiable risk (age and sex).

CFAS I					CFAS II				
Variable of Interest	Participants with polypharmacy (%)	Odd ratio		PAF	Variable of Interest	Participants with polypharmacy (%)	Odd ratio		PAF
Modifiable risk factor					Modifiable risk factor				
E1	10.7	1.26	(0.96; 1.67)	12.5		56.3	1.66	(1.43; 1.91)	7.2
E2	10.5	1.27	(0.92; 1.74)	2.7		43.9	1.40	(1.23; 1.57)	8.9
E3	8.8	1.00				36.4	1.00		
Non modifiable risk factor					Non modifiable risk factor				
<i>Age group</i>					<i>Age group</i>				
65-69		1.00					1.00		
70-74		1.24	(1.00; 1.56)	3.9			1.54	(1.34; 1.76)	5.4
75-79		1.60	(1.29; 2.00)	9.1			2.07	(1.80; 2.38)	8.1
80-84		1.61	(1.27; 2.03)	7.0			2.45	(2.09; 2.88)	7.8
85-89		1.82	(1.37; 2.42)	4.3			2.12	(1.75; 2.57)	3.6
≥90		1.43	(0.92; 2.23)	0.9			2.27	(1.72; 3.00)	1.5
Sex				20.7	Sex				
Male		1.00					1.00		
Female		1.17	(1.00; 1.36)				1.01	(0.92; 1.10)	0.5

Key: E1 <10 years of education, E2 10-11 years of education and E3 ≥12 years of education. Population attributable fraction (PAF)

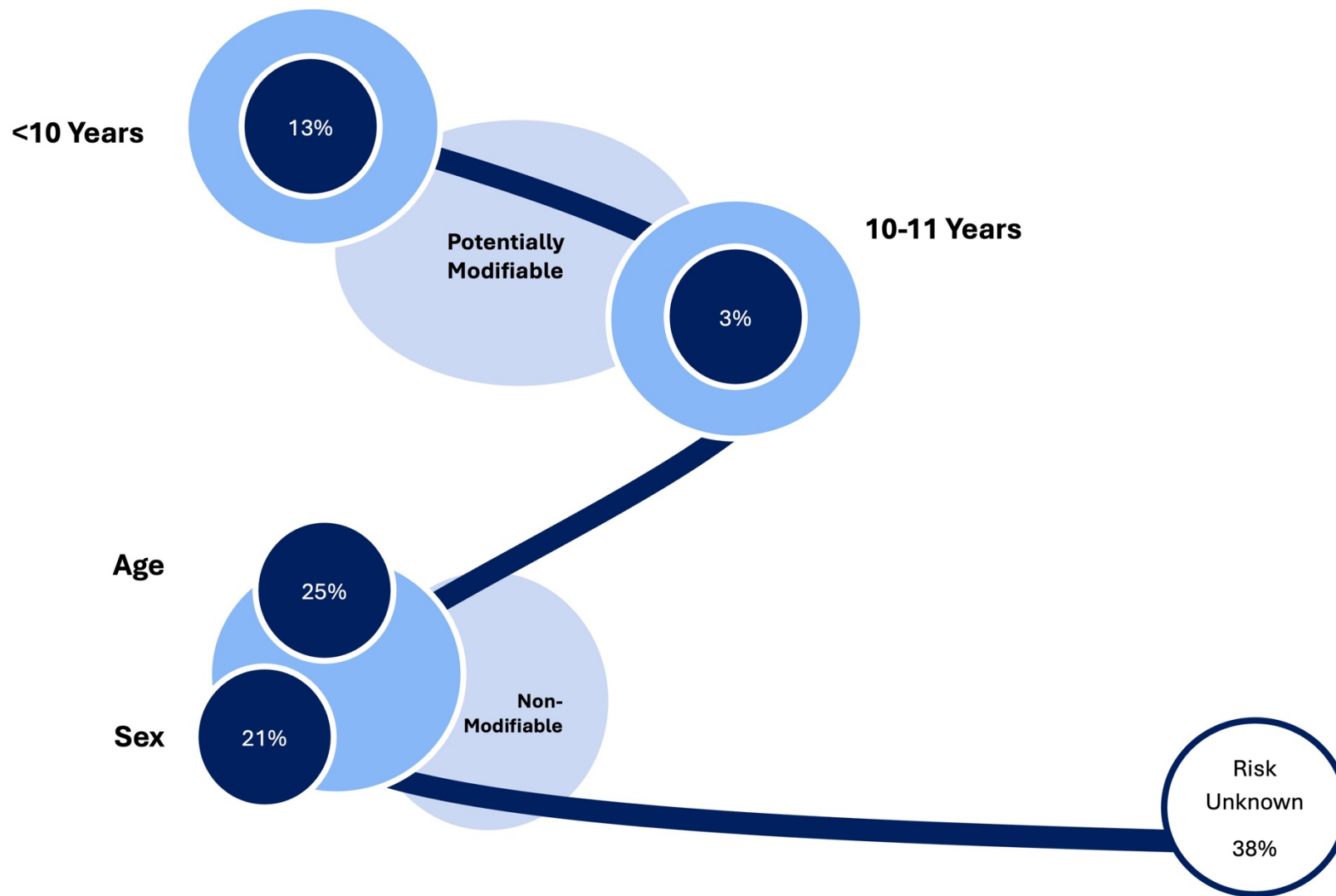


Figure 4. 5: Visual representation of population attributable fraction for CFAS I.

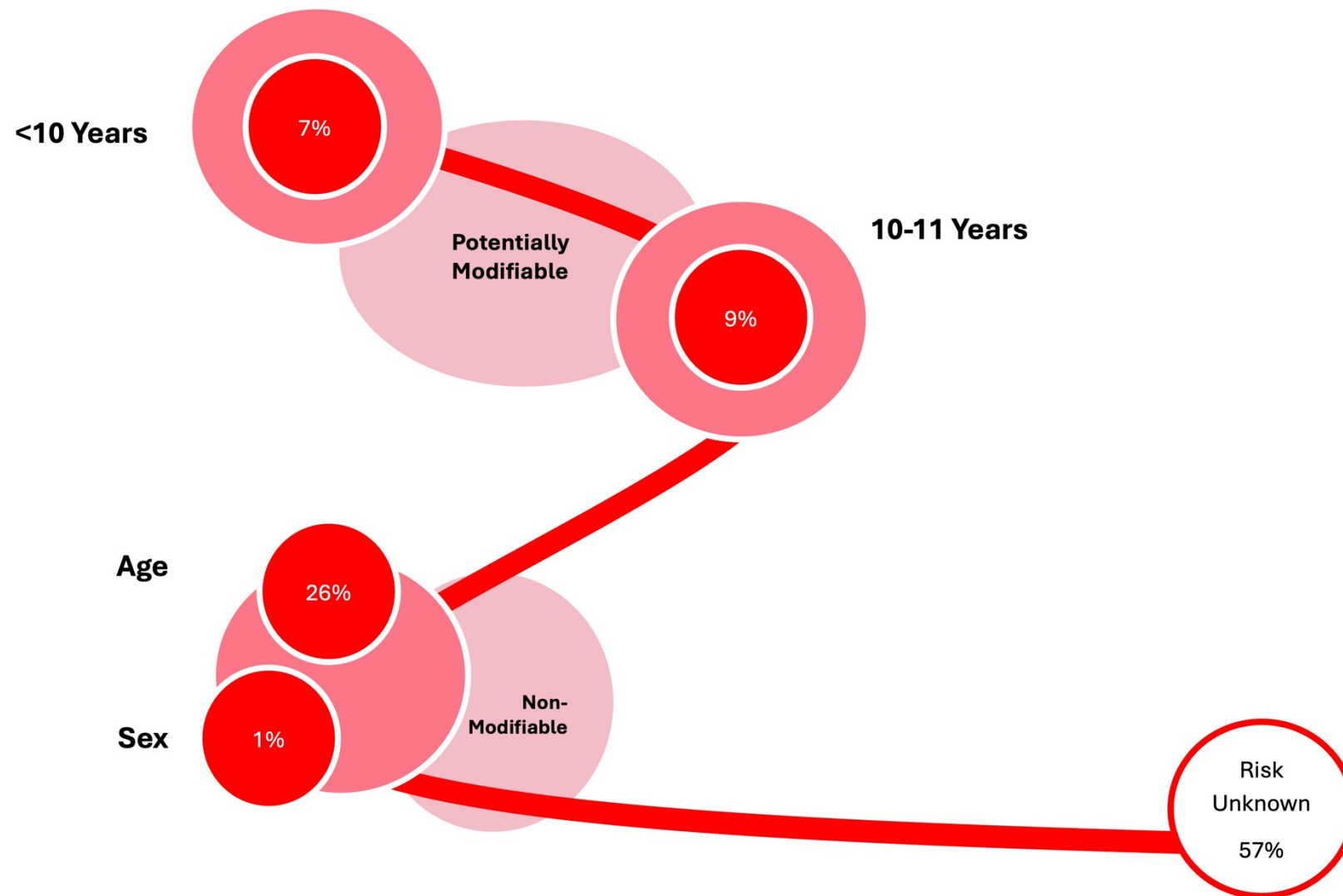


Figure 4. 6: Visual representation of population attributable fraction for CFAS II.

4.5 Interpretation of findings

Overall, my findings have suggested the likelihood of being in receipt of polypharmacy is associated with an individual's SES, in the context of education. The results support the wider literature that demonstrates an increased utilisation of medications in individuals with lower SES¹⁹⁶ in addition to wider healthcare inequalities present in the UK.^{4,5,159} This chapter has provided novel findings to the literature, through leveraging two waves of cohort data, collected 20-years apart, in order to examine changes in the association of SES and polypharmacy among older adults in England. Whilst some of the literature has showcased the relationship between low SES and medication usage, little work has been done around how such inequalities have evolved over time. The chosen methods for this analysis, provided a nuance understanding how socioeconomic factors can shape medication usage in an ageing population, with the potential to inform public health strategies.

My analysis revealed that individuals with lower years of education were more likely to be in receipt of polypharmacy. The increased receipt of polypharmacy among those with lower levels of education could, in part, be explained by limited health literacy. This concept is around an individual's ability to process and understand basic health information in order to make an informed decision.³⁷⁹ Education has shown to directly improve health literacy, through enabling individuals to make better informed decisions in relation to their health and use of medication.^{380–382} Having an appreciation of such factors plays a critical role, particularly in polypharmacy, being able to understand a complex medication regimen, which has the potential to increase drug interactions and present challenges with adherence. Such inequalities are pronounced in the UK, whereby those with lower education attainment have shown to display low health literacy.³⁸³ Education is also a critical determinant of health and has the potential to influence access to healthcare, health behaviours and the ability to navigate complex healthcare systems,^{224,384} some of which has been discussed in Chapter 1. The increasing inequalities in utilisation of medications, between different levels of education underscores the need for targeted public health interventions to help address such growing inequalities.

The observed inequalities in polypharmacy can also be reflective of broader socioeconomic inequalities that have been reported across the literature.³⁸⁵ In other words, the results observed in this thesis could be because of an indirect effect of education as discussed in greater depth in Chapter 1. For example, income and general employment prospects have shown to be better for those with a higher education level.^{386,387} In turn, such differences can provide people with the platform to afford better healthcare and healthier lifestyles.³⁸⁸ Conversely, those with lower

levels of education are more susceptible to economic hardship and poorer health outcomes, including an increased likelihood of having MLTCs, and therefore increased utilisation of medications.³⁸⁹

My results have suggested there is a widening gap in polypharmacy inequalities. For example, in CFAS I, the difference in being in receipt of polypharmacy between low and high educational categories was modest. However, in CFAS II, this gap became more pronounced, with a higher OR for polypharmacy in education category 1(<10 years) and a significantly lower OR in education category 3. In addition, results from the PAF analysis, highlighted the potential public health affect that education attainment on polypharmacy can have. The reduced PAF value for lower education level can somewhat suggest some improvement in health care practices in mitigating the risk of the utilisation of multiple medications for individuals from less affluent backgrounds. For example, across the literature there has been work around the importance of health literacy and raising awareness.³⁹⁰ Such health literacy has shown to be crucial in ensuring understanding of treatment and help to make informed decisions. However, the PAF results also demonstrated a larger proportion of cases attributed to the middle education category in CFAS II than I, suggesting education level having a more substantial association in being in receipt of polypharmacy in CFAS II. Results also highlighted the importance of age and medication utilisation, a relationship not surprising with increasing age being strongly associated in increased medication utilisation.⁸⁸ Older people are also more likely to have multiple chronic conditions, and thereby leading to an increase in medication, this therefore further reinforces the importance of ensuring such age groups are targeted for medication reviews and deprescribing practices to mitigate risks that are often associated with polypharmacy.

Other broader possible explanations to the observed results, more specifically to the UK are as follows. Firstly, in relation to widening inequalities economic austerity measures that have been implemented have disproportionality affected individuals within society, particularly those from lower SES backgrounds. Cuts to healthcare budgets have inevitably made it more difficult for individuals to access healthcare services, particularly those from lower SES.^{391,392} Housing inequality remains a persistent widening issue in the UK,³⁹³ coupled with poor housing conditions particularly affecting lower income families are associated with poor health outcomes. Such conditions have shown to exacerbate chronic illnesses, inevitably leading to an increase in medication use and polypharmacy.^{393,394} Tackling such inequalities require a multifaceted approach, discussed both in Chapter 1 and 2 of this thesis. Essentially addressing

broader social determinants, such as employment and housing, can be critical in reducing such inequalities and such comprehensive policies can help create a more equitable society, in order to allow all to achieve optimal health outcomes despite socioeconomic background.³⁹⁵

In relation to gender, differences in CFAS I showcased a reduced odds for men compared to women in being receipt of polypharmacy. However, results in CFAS II showed a minimal shift over time, whereby little difference was present between men and women. Similarly, the results from the PAF analysis further showcased the effect of gender diminishing between the two time periods - 20.7% risk attributed to gender in CFAS I, and near to negligible in CFAS II (0.5%). The results indicated the potential shift of gender on polypharmacy over time. The literature has indicated women are more likely to use healthcare services and medications.³⁹⁶⁻³⁹⁹ With polypharmacy often being more likely in women than men.^{72,400} However, a study carried out in Canada,⁴⁰¹ demonstrated whilst women were more likely to be in receipt of polypharmacy, absolute increase over time was greatest in men. For example, polypharmacy prevalence in men increased from 55.7% in 2003 to 62.3% in 2016, whereas for women the figures were 64.2% to 65.1%, respectively.⁴⁰¹ Similarly, hyper-polypharmacy increased from 21.7% to 26.1% (men) and 27.7% to 29.0% for women. Such findings indicate a reduction in the gender gap over time, and therefore whilst women may have traditionally demonstrated higher prevalence of polypharmacy, more recent increases among men have narrowed such a gender gap in prevalence. Nevertheless, results from my findings could warrant further investigation to understand further such relationships with gender.

4.6 Strength and limitations

This study has utilised data from CFAS I and CFAS II, some of the largest longitudinal population datasets in the UK to understand the relationship between SES and polypharmacy, and how this relationship has changed over time. The study acknowledged some methodological limitations, which are discussed below.

Firstly, polypharmacy was defined using an arbitrary threshold of five or medications. As discussed in Chapter 1, an arbitrary cut off does not account for the nuances of appropriate medication usage, however, it remains as the most clinically used definition. Secondly, to meet the requirements of the definition of a medicine in my work, systemic absorption should be present, and, therefore, common medicines, such as eye, ear, nose drops, and topical applications were excluded. This was primarily due to the limited potential for drug-drug interactions and adverse effects such medications can have. However, such medications can

still have systemic adverse effects and interact with systemically absorbed medication; for example, topical NSAIDs combined with oral anticoagulants can increase the risk of a bleed. Thirdly, in regard to data, it was not possible to determine with absolute certainty the indication for each medication in this study. Whilst NHS read codes and some clinical information, for example, the presence of MLTCs and dosage provided guidance to help correct allocations of medicines. It is also important to acknowledge that medication use in this cohort was self-reported which presents some challenges; for example, interviewees only recorded what participants were willing to share with them. Finally, the measure of SES used in this study was a limitation in itself. Education levels were categorised in order to reflect statutory schooling, and as detailed earlier in this chapter, care was taken to avoid ecological fallacy through using an individual level measure as opposed to area based measures, as discussed in Chapter 2. However, it cannot still be assumed that the number of years of education accurately reflect an individual's SES. In addition, the categories devised were reflective of a British cohort and therefore, may not be a reflective marker for ascertaining an individual's SES in other countries, or in other time periods. However, the Index of Multiple Deprivation (IMD) varied across the three sites included: Cambridgeshire, Nottingham and Newcastle. Cambridgeshire presents a mix of less deprived areas alongside some significantly deprived areas, in particular, areas of Fenland.^{402,403} Newcastle upon Tyne is identified as an area of substantial challenges in income and employment, with deprivation across the city.^{404,405} It is ranked in one of the most deprived quartiles in England with 76 out of 176 of its neighbourhood ranked among the 20% most income deprived in England.⁴⁰⁵ Whereas Nottingham is ranked as the 11th most deprived in England, with 30.8% of its Lower Super Output Areas (LSOAs) in the top 10% most deprived nationally,⁴⁰⁶ similar to Cambridgeshire with pockets of deprivations. This spread of IMD highlights the richness of data and subsequently varied socioeconomic background of the included participants.

There was also the presence of missing data, particularly in CFAS II, however such cases are expected in large cohort studies and the option to choose solely to report missing data was selected, a plausible approach when missing data accounts for less than 5%.⁴⁰⁷ However, other approaches⁴⁰⁸ were considered such as multiple imputation, creating imputed values through various statistical analyses that reflect both observed data variability in the data were ill suited. Primarily due to the complexity and therefore challenges^{408,409} with the presentation of results, particularly the multiple presumptions that would be made. In addition, wave 1 of CFAS II was conducted in 2008, almost 15 years ago, which may raise questions in relation to the relevance of the data. Nevertheless, to understand polypharmacy has changed over time and the broader

aspect of polypharmacy inequalities, CFAS was the only British study in older people that would allow for this level of analysis. Finally, this study used data from the baseline waves of CFAS I and II. As a result, it is important to note that the analyses cannot determine the direction of causality between socioeconomic status and polypharmacy. It is possible, for example, that individuals with higher medication burden may experience downstream effects on income or educational attainment due to health-related limitations. While longitudinal analysis would be ideal to explore these temporal relationships, the cross-sectional design is still valuable for identifying population-level associations and informing public health priorities.

4.7 Conclusion

To conclude, using CFAS I and CFAS II, this chapter provides an analysis of the association between SES (in respect to education) and polypharmacy. The work demonstrates that people of lower SES were more likely to be in receipt of polypharmacy and these inequalities have appeared to have widened over time. Furthermore, polypharmacy has increased across the 20 years between CFAS I (1990-1993) and CFAS II (2008-2011). Further work now needs to explore whether such inequalities are observed across different groups of medications, particularly those that have generated interest in increased utilisation over the years, for example the use of opioids. This forms the basis of the next chapter in my thesis.

Chapter 5. Association Between Education And Polypharmacy Across Medication Categories

5.1 Introduction

Chapter 4 set out to understand the relationship between education and polypharmacy and appreciate the prescribing practices across CFAS. Through the work in Chapter 2, globally education was identified as a commonly used individual measure of SES, and therefore appropriately selected for my analyses. A focus of Chapter 4 was to understand how both inequalities and polypharmacy were changing over time, therefore as CFAS presented longitudinal data, the studies were appropriate data sources to help answer these questions. The results from Chapter 4 highlighted the steep rise of polypharmacy over time, among older people. In relation to inequalities in polypharmacy, the findings from CFAS I demonstrated subtle changes in polypharmacy across the different education levels, however, this was not the case for CFAS II. The findings from CFAS II demonstrated that individuals with lower years of education were far more likely to be in receipt of polypharmacy than those with a greater number of years of education. To add further statistical weight to the findings, PAF was calculated to appreciate the wider public health impact. The overall results observed in Chapter 4 highlighted inequalities in polypharmacy whereby people of lower SES were more likely to be in receipt of polypharmacy and these inequalities have widened over time. However, these findings do not consider individual classes of medications, which presents an important knowledge gap to address. This chapter considers this subject further and sets to explore the relationship between education and polypharmacy among specific groups of medications, of which if identified could help direct policy for medication prescribing and optimisation.

Chapter aim:

Determine if the association of SES (measured as the number of years of education for an individual) and being in receipt of polypharmacy is consistent across varying groups of medication.

Objectives:

- I. Determine the demographic characteristics of CFAS, in relation to the prevalence of different medication groups.
- II. Determine the relationship between polypharmacy and education across different medication groups and whether this relationship differs.

III. Determine how such relationships are affected by confounders.

5.2 Background

Socioeconomic inequalities continue to be a persistent issue within the access to healthcare services and prescribing patterns.^{4,5} For example, individuals from lower socioeconomic backgrounds are more likely to be prescribed medications such as analgesics and antibiotics.^{410–412} Whilst these findings could be potentially explained as a result of higher health needs in such communities, there may also be broader underlying issues, such as complex mental health problems or higher dependency on pharmacological treatment among individuals from different backgrounds.⁴¹³ There are however some medications which are more likely to be prescribed to individuals from higher SES. For example, treatment related to the reduction of cholesterol, such as statins, as well as an increase usage of vitamins are shown to be more likely in women of higher SES.^{414,415} Such observations may be attributed to better health seeking behaviours^{416,417} or the ability to afford to purchase OTC products among higher SES groups. While it is evident that inequalities among specific medication groups may exist, it would be important to understand how this is reflective of an English setting, and by using an individual measure for SES. Therefore, this chapter aims to address these knowledge gaps and to build on the findings from Chapter 4 by examining the relationship between education and polypharmacy across different medication groups.

5.3 Descriptive epidemiology

5.3.1. Introduction

The purpose of the analysis for this chapter is to understand if the relationships observed in Chapter 4 were consistent across different medication groups, therefore methods that were used in this chapter replicated many of that were described in Chapter 4, Section 4.3. Baseline demographics were first reported for the whole cohort, to highlight the presence of each medication group across both CFAS I and CFAS II. Further descriptive statistics were then used to report all variables of interest in CFAS II, including individuals using medication from the corresponding group reported by gender and SES (measured by the number of years of education). The decision to progress with analysis for CFAS II alone was primarily due to the lower levels of medication usage across CFAS I (which inevitably would present challenges to carry out refined analysis across each medication category such as during the logistic regression). In addition, with prescribing practices changing extensively since CFAS I (1989-1993), conducting analysis with CFAS II (2008-2011) alone was sufficient to help provide

recommendations more in line and reflective to current practices. Furthermore, given that the aim of this chapter was to understand observations in relation to specific medication groups and no longer reporting observations over time, analysing CFAS II was an appropriate data source to use.

5.3.2 Medication groupings

A series of codes were developed in order to categorise all medications participants were using, into specific groups, based on the British National Formulary (BNF). Other studies have explored the epidemiology of specific drug classes, such as cardiovascular polypharmacy,^{418,419} or medications to treat diabetes,⁴²⁰ also providing a foundation for the categorisation. As previously discussed in Chapter 3, the work of Gao *et al*,⁶⁵ was an important starting point in helping formulate appropriate medication groups for my analysis. Gao's work highlighted some key findings: for example, the overall usage of medication increasing across the CFAS studies, and the increased prescribing of certain medication group, such as those used to treat cardiovascular conditions. However, this work did not focus on education as a marker of SES or polypharmacy among participants. Whilst Gao's approach resulted in fourteen broad medication groups (including dressings and appliances), my analyses required a more nuanced categorisation; for example, for medications with known socioeconomic inequalities, some of which will be discussed below. Given the familiar and wide usage of the BNF among healthcare professionals, it was appropriate to create my medication groups reflective of this, providing both relevance and accuracy. Using my clinical expertise, I ensured all medications could be grouped appropriately, with the creation of sub-groups for medication that were of particular interest, i.e. those potentially influenced by SES. Figure 5.1 presents the medication groups created for the analyses and further detail is provided in Appendix N. All participants had pre-coded NHS read codes allocated to each of their medications. Therefore, this was used to make an informed decision as to the indication for the medication, if not known by other interview questions.

The BNF⁴²¹ is a comprehensive reference guide that provides information to healthcare professionals around prescribing and administering medication. The resource includes common dosage suggestions, adverse drug reactions, contraindications, and drug interactions, to ensure safe prescribing practices. It also includes both prescription and OTC medications. All guidance on prescribing is reflective of evidence-based recommendations and national guidelines within the UK. Treatment guidance on specific conditions that are commonly presented by patients is also discussed, to help healthcare practitioners make informed decisions. The BNF is reviewed

regularly and updated to ensure best practice. The BNF 82⁴²¹ was used for the work in this thesis, which included sixteen chapters. As previously stated, the medication groups created for my analysis did overall reflect the BNF, but some additional subgroups were created to allow for more detailed analysis. For example, specific groups were created for antiplatelet, antihypertensive, and opioids, which across the literature have shown significant increase in usage over the years.^{422–425}

Antiplatelet prescribing has shown to have increased substantially over the years, with a rise from 28.1% (2000-2001) to 47.1% (2006-2007), in the US⁴²⁶ and similar observations in the UK.⁴²⁷ In 2021, the NHS Business Service Authority (NHS BSA) reported 10.5 million prescriptions for clopidogrel, up from around 6 million in 2011.⁴²⁷ Many possible factors have attributed to this, for example key clinical trials including, CREDO, (Clopidogrel for Reduction of Events During Observation)⁴²⁸ and CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events)⁴²⁹ both highlighting the possible clinical advantages of using such treatment. Similarly, guidance around the use of dual antiplatelet therapy (Chapter 1, Section 1.4.5) to reduce mortality have become adopted in prescribing practices, and supported by NICE guidelines, in emphasising the importance of antiplatelet therapy in secondary prevention of myocardial infarction.⁴³⁰ There has also been a rise in LTCs, such as hypertension and diabetes, both with additive effects on increasing the risk of cardiovascular disease.⁴³¹ SES has also shown to be a key contributor in the trends observed with the use of oral anticoagulation therapy. The work of Lunde *et al* demonstrated, individuals with lower education and income were less likely to be in receipt of preventative treatment, when compared to those of higher SES.^{432,433} Similarly, a study carried out in England, investigated the incidence of non-valvular atrial fibrillation and oral anticoagulants prescribing patterns, between 2009-2019.⁴³⁴ Authors found that those from lower SES were less likely to be prescribed oral anticoagulant and thereby more likely to be at risk of stroke. In addition, a further systematic review demonstrated socioeconomic inequities in both treatment and knowledge of Atrial Fibrillation (AF). Such evidence strongly reiterates how health inequalities play a critical role in contributing to adverse health outcomes.

Similarly, opioid prescribing has risen substantially both in the UK^{422,435,436} and globally,⁴³⁷ raising concerns with potential misuse and dependency. In the UK between 2008-2018, prescribing of opioids increased by 34%⁴³⁸ with over 231 million opioid prescriptions dispensed between 2018 to 2019.⁴³⁸ There are also geographical inequalities in opioid prescribing,²⁴ with regions such as the Northwest, Yorkshire and the Humber and the Southwest exhibiting the

highest levels of long-term opioid use in England. Such rises were also prominent before 2008; for example, between 1998 and 2010 the prescribing of strong opioids such as morphine, oxycodone and fentanyl significantly increased.⁴²² Further work has also demonstrated regional inequalities in the prevalence and intensity of pain,⁴³⁹ with higher prevalence in the northern regions than the south, a so-called “pain divide.” The study has also demonstrated positive correlation between severe chronic pain and opioid usage and thereby demonstrating whilst prescribing correlates to an increase in health need, there is a pronounced divide across the country. Such results may be attributed to wider issues such as the lack of access to healthcare resources and or limited access to non-pharmacological treatment.

5.3.3 Prevalence of different medication groups across CFAS

There were 7,639 participants in CFAS I wave 1. Of these, cardiovascular medications were most commonly used 27.5%, followed by analgesic non-opioids 22.8%, and gastrointestinal 16.5%. Medications belonging to the hyperlipidaemia category was the least common, 0.3%. Full cohort characteristics for individuals using medication from each category can be found in Appendix O. A graphical summary is provided in Figure 5.2.

In CFAS II 7,762 participants were present during wave 1. Of these participants, 49.9% were taking at least one antihypertensive medication, followed by hyperlipidaemia (45.4%) and cardiovascular (33.3%) being the most commonly used medication groups. Females were most likely to be using medications that belonged to the endocrine category (74.8%) whereas males were most likely to use antiplatelet (53.9%) and antidiabetic (56.2%) medicines. Male and Female characteristics can be found in Table 5.1. In relation to SES (measured as the number of years of education), participants from a lower number of years of education (<10 years), were most likely to use medications from the category hypnotics/anxiolytics/benzodiazepines (34.4%) and blood and nutrition (36.6%). Whereas individuals from higher education (≥12 years) were most likely to use OTC preparations (32.2%), despite how uncommon they are in the overall dataset. Full cohort characteristics respective of SES can be found in Table 5.2.

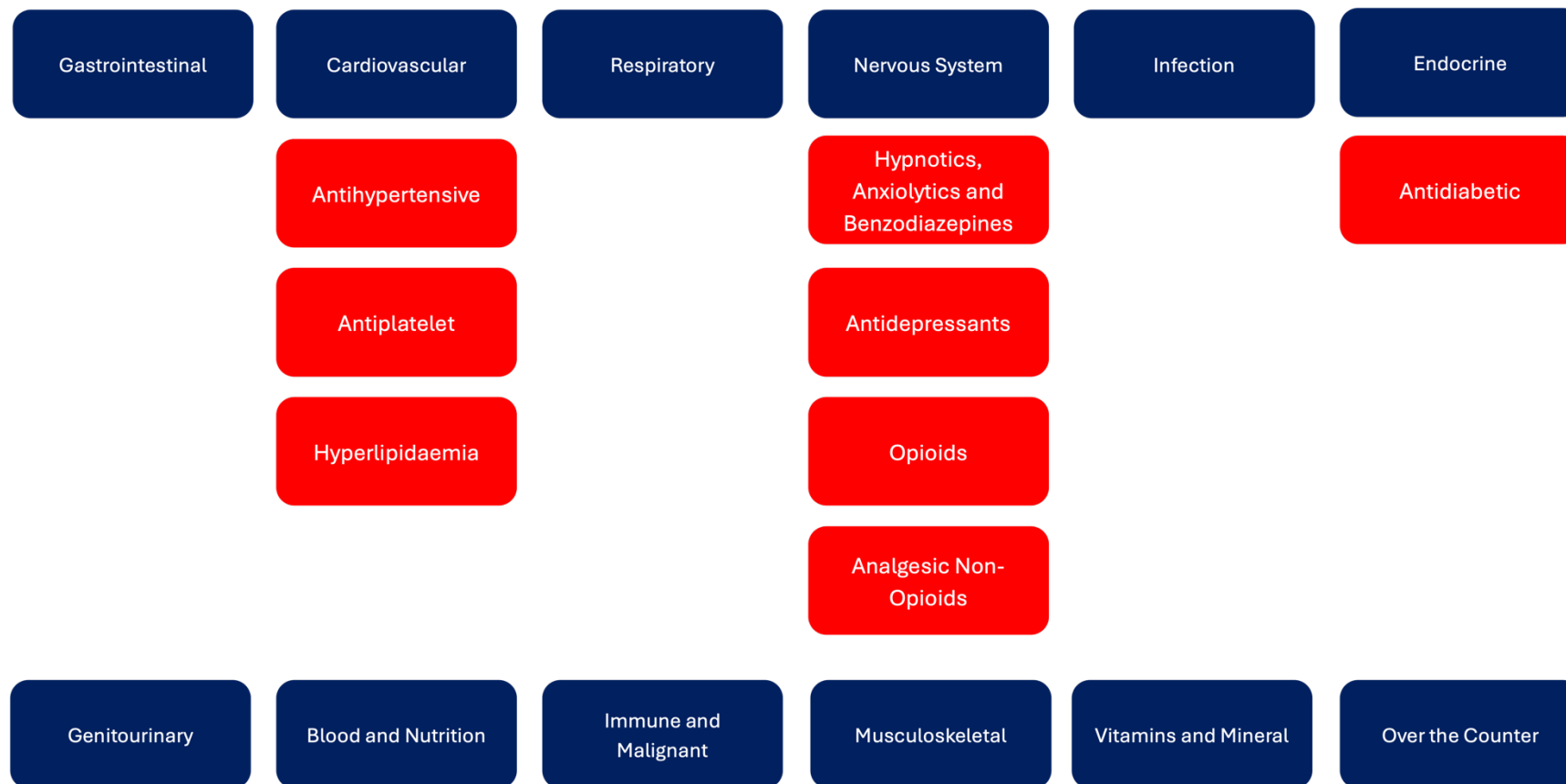


Figure 5. 1: Categorisation of the medication groups for the analysis.
Blue boxes represent main category, and red boxes correspond to sub groups that have been created.

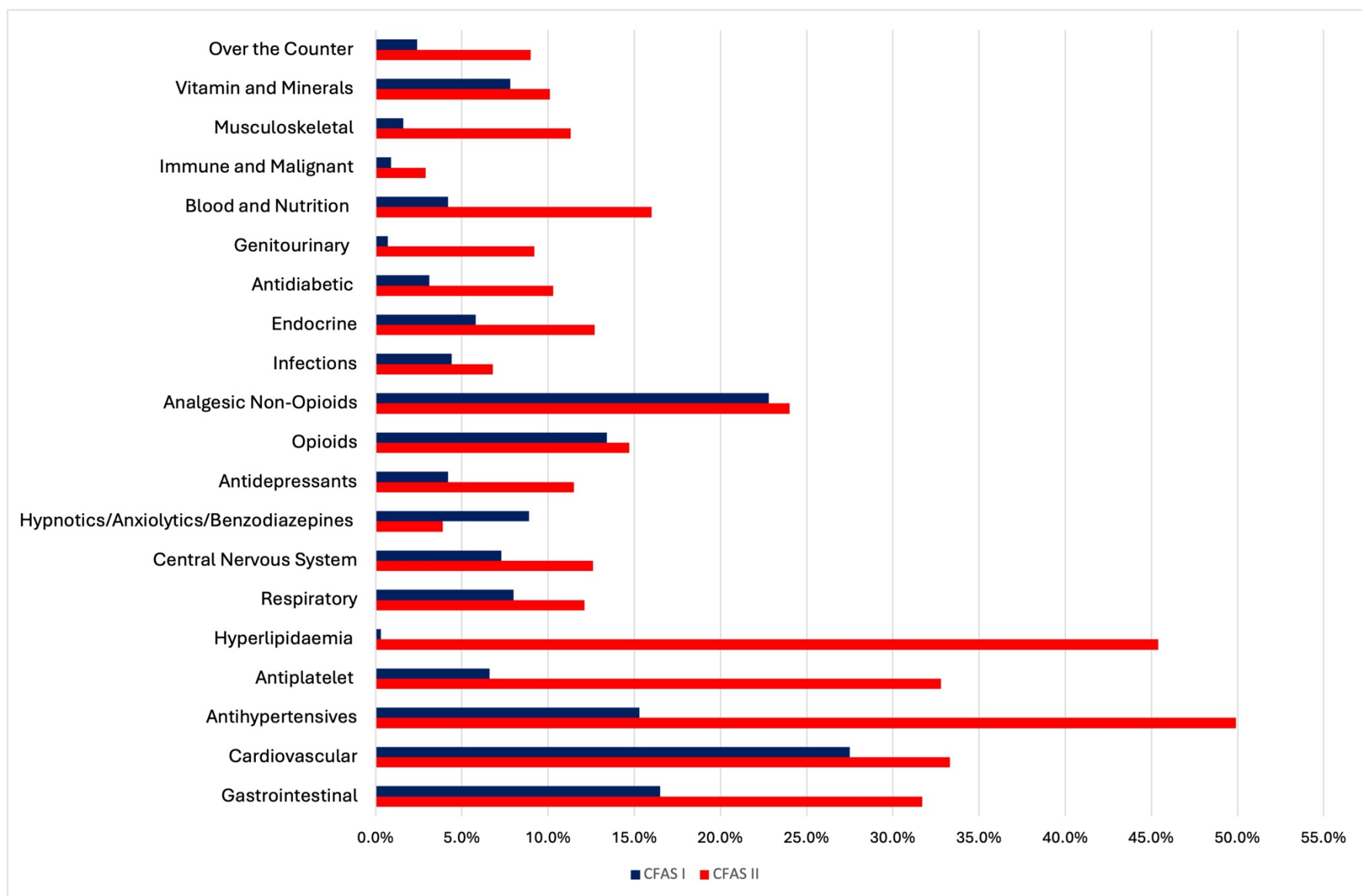


Figure 5. 2: Comparison of medication use across CFAS I and II.

Table 5. 1: Baseline demographics showing participants taking at least one medication within each medication group in CFAS II wave 1. Results are presented in respect to gender. Total cohort population included. Characteristic (n (%)) including medication group).

<i>Total Cohort Population</i>	7762			
Medication Group(s)	Male		Female	
Gastrointestinal	1084	(44.0)	1378	(56.0)
Cardiovascular	1215	(47.1)	1366	(52.9)
Antihypertensives	1828	(47.2)	2047	(52.8)
Antiplatelet	1370	(53.9)	1174	(46.2)
Hyperlipidaemia	1783	(50.7)	1737	(49.4)
Respiratory	401	(42.8)	537	(57.3)
Central Nervous System	377	(38.5)	603	(61.5)
Hypnotics/Anxiolytics/Benzodiazepines	87	(29.1)	212	(70.9)
Antidepressants	264	(29.5)	632	(70.5)
Opioids	392	(34.5)	746	(65.6)
Analgesic (non-opioids)	702	(37.7)	1159	(62.3)
Infections	234	(44.6)	291	(55.4)
Endocrine	249	(25.2)	739	(74.8)
Antidiabetic	450	(56.2)	351	(43.8)
Genitourinary	491	(68.9)	222	(31.1)
Blood and Nutrition	367	(29.6)	873	(70.4)
Immune and Malignant	74	(33.3)	148	(66.7)
Musculoskeletal	306	(35.0)	568	(65.0)
Vitamins and Minerals	351	(44.7)	435	(55.3)
Over the Counter	260	(37.3)	438	(62.8)

Where N does not add to total population, data is missing

Table 5. 2: Baseline demographics showing participants taking at least one medication within each medication group in CFAS II wave 1. Results are presented in respect to number of years of education. Total cohort population included. Characteristic (n (%)) including medication group.

Medication Groups	<10 years		10-11 years		≥12 years	
Gastrointestinal	746	(31.4)	1193	(50.2)	436	(18.4)
Cardiovascular	821	(32.6)	1233	(49.0)	461	(18.3)
Antihypertensives	1108	(29.1)	1962	(51.5)	738	(19.4)
Antiplatelet	745	(30.2)	1248	(50.5)	478	(19.3)
Hyperlipidaemia	919	(26.7)	1852	(53.7)	677	(19.6)
Respiratory	271	(29.8)	495	(54.5)	144	(15.8)
Nervous System	280	(30.7)	455	(49.9)	177	(19.4)
Hypnotics/Anxiolytics/Benzodiazepines	97	(34.4)	120	(42.6)	65	(23.1)
Antidepressants	255	(30.5)	415	(49.6)	166	(19.9)
Opioids	365	(32.9)	572	(51.5)	173	(15.6)
Analgesic (non-opioids)	587	(32.6)	902	(50.0)	313	(17.4)
Infections	162	(31.9)	252	(49.6)	94	(18.5)
Endocrine	306	(31.9)	482	(50.3)	171	(17.8)
Antidiabetic	222	(28.5)	418	(53.7)	139	(17.8)
Genitourinary	205	(29.2)	336	(47.9)	160	(22.8)
Blood and Nutrition	427	(36.6)	523	(44.8)	218	(18.7)
Immune and Malignant	70	(32.3)	98	(45.2)	49	(22.6)
Musculoskeletal	286	(34.0)	396	(47.0)	160	(19.0)
Vitamins and Minerals	163	(21.0)	406	(52.4)	206	(26.6)
Over the Counter	128	(18.4)	343	(49.4)	224	(32.2)

5.3.4 Descriptive analysis of medication groups in respect to education

Descriptive analysis was carried out to understand how the relationship between education and polypharmacy changed across the medication groups. Results are shown in the collection of graphs presented in Figure 5.3. Similar findings were observed across most medication groups, whereby individuals with an increased number of years of education were less likely to use medication from each given group. Across most groups the likelihood of polypharmacy and using a medication decreased when moving across the education categories. Similarly for individuals that were not using a medication the likelihood of polypharmacy also decreased with higher education level, suggesting that a presence of a specific medication group may have little effect.

However, comparing both the navy and red segments of the graph allowed for focus on individuals that were using a medication from the given group, and to understand if there is an increased likelihood of polypharmacy amongst such individuals. The overall trend indicated that whilst a higher odd of being in receipt of polypharmacy was present amongst medication users, higher education reduced the likelihood of polypharmacy. Therefore, the protective role of education is somewhat still present. There were however some medication groups where a weaker education effect may be present such as genitourinary and immune and malignant, therefore further analysis was carried out to understand the extent of the relationship.

Figure 5. 3: Distribution of participants with and without polypharmacy, across medication groups in CFAS II at baseline.

Results were calculated as a proportion (%) in each given education category.

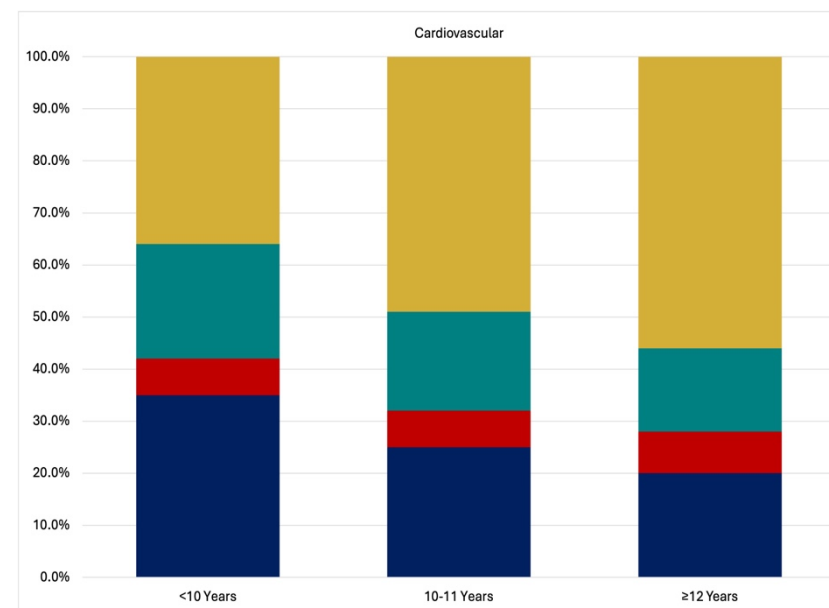
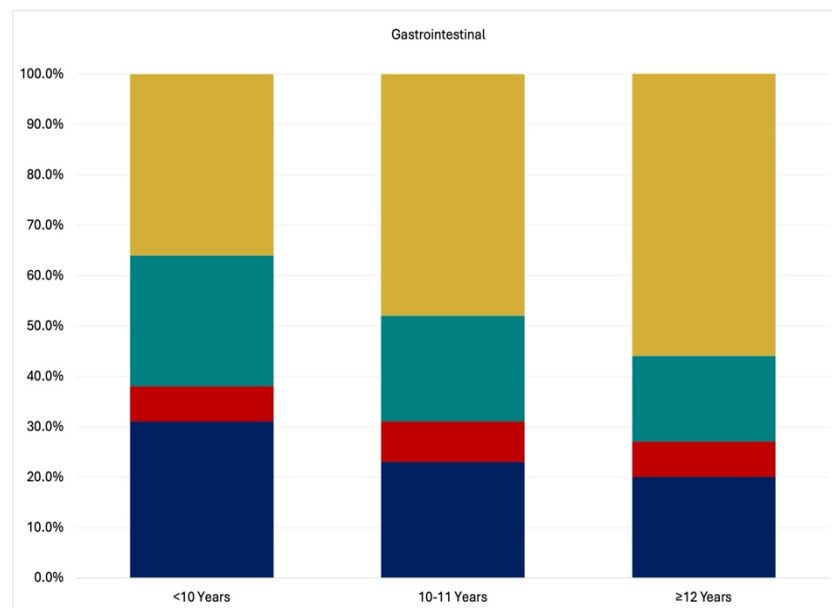
Key:

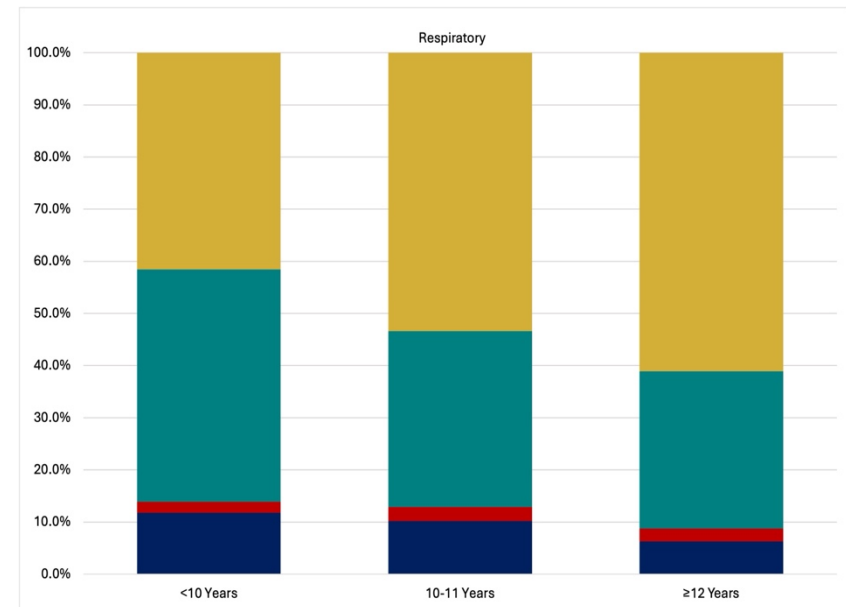
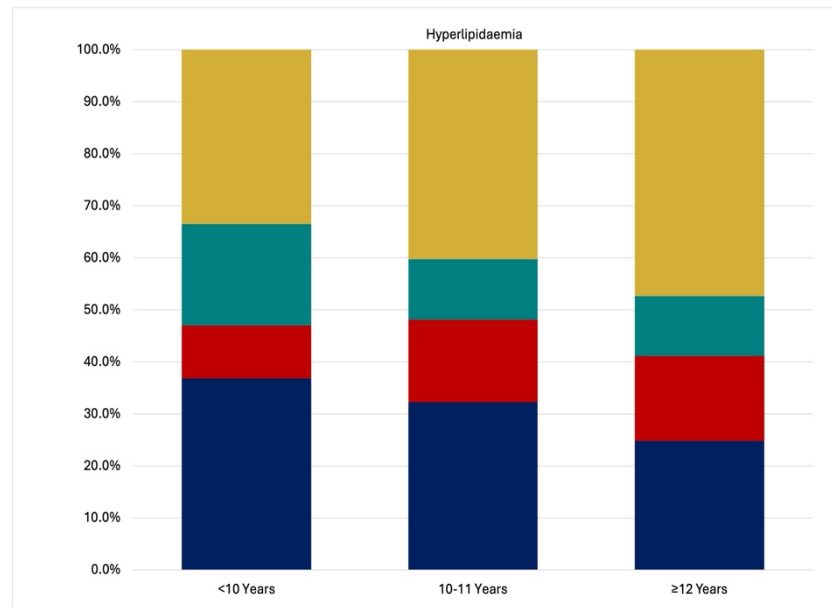
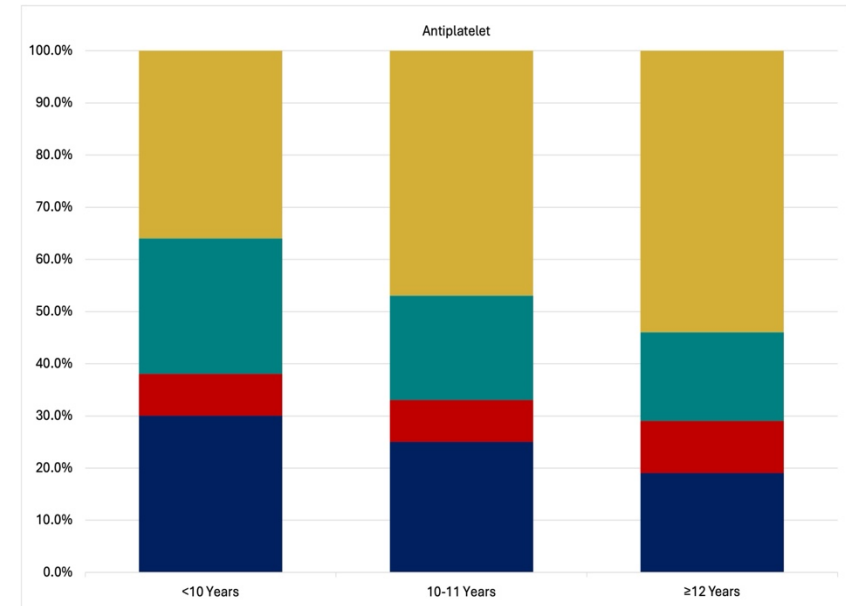
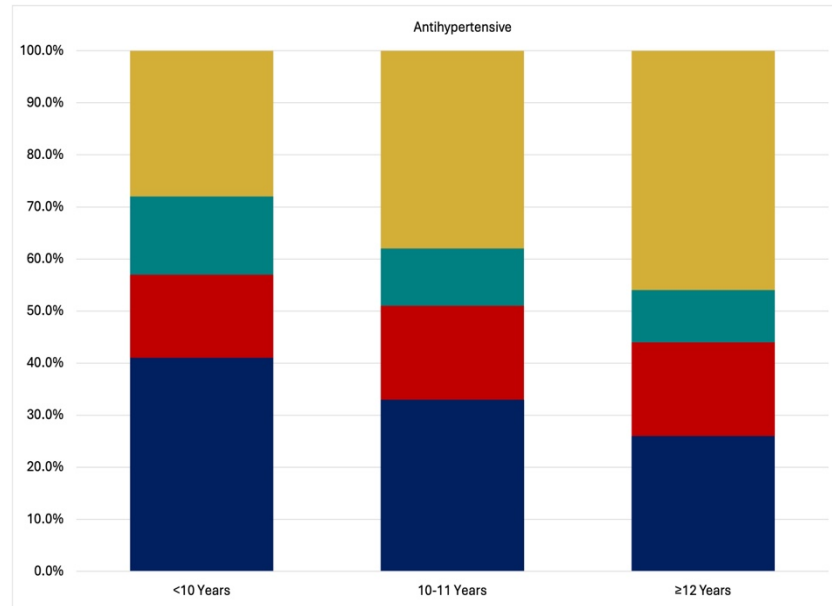
Navy - Participants with polypharmacy and using a medicine from the given medication group.

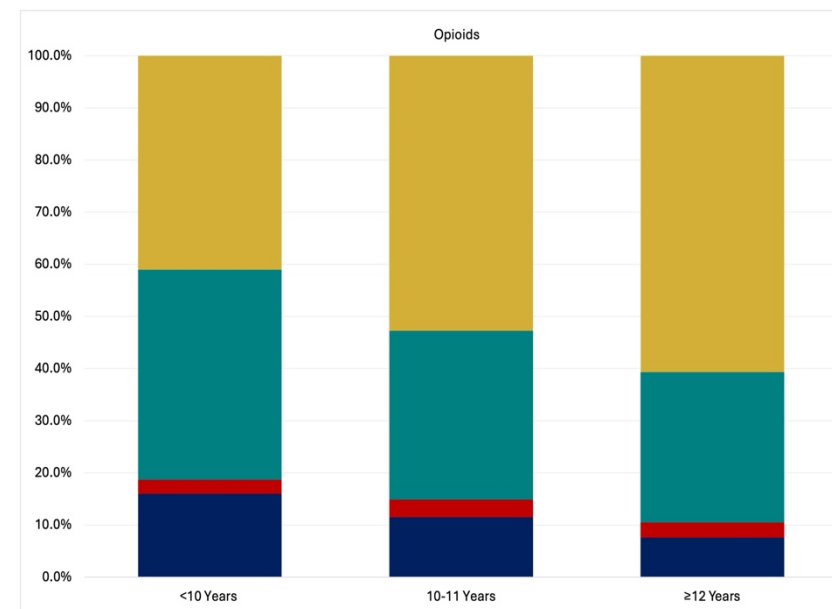
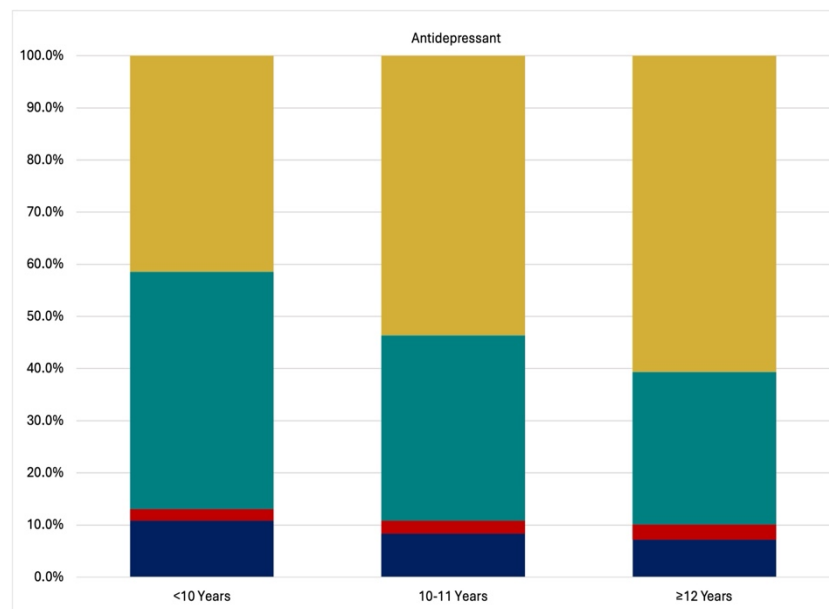
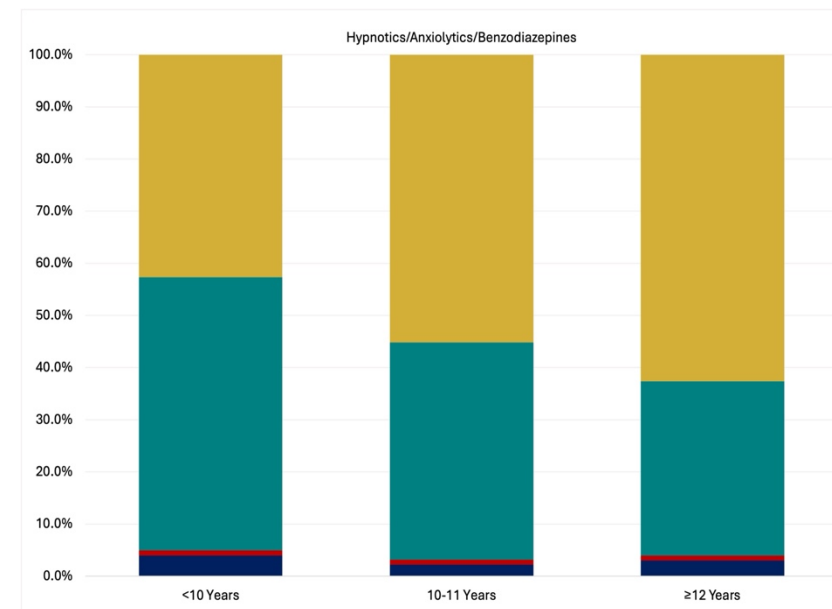
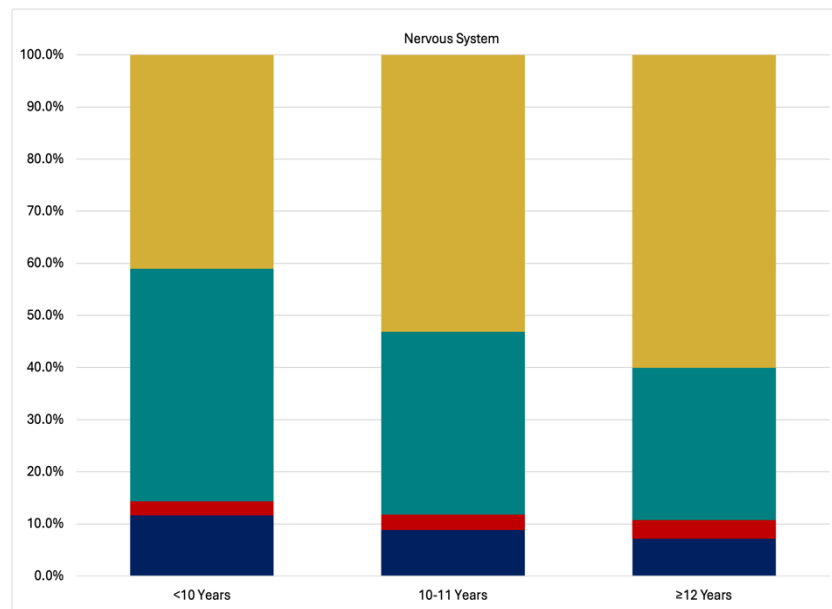
Red - Participants with no polypharmacy but using a medicine from the given medication group.

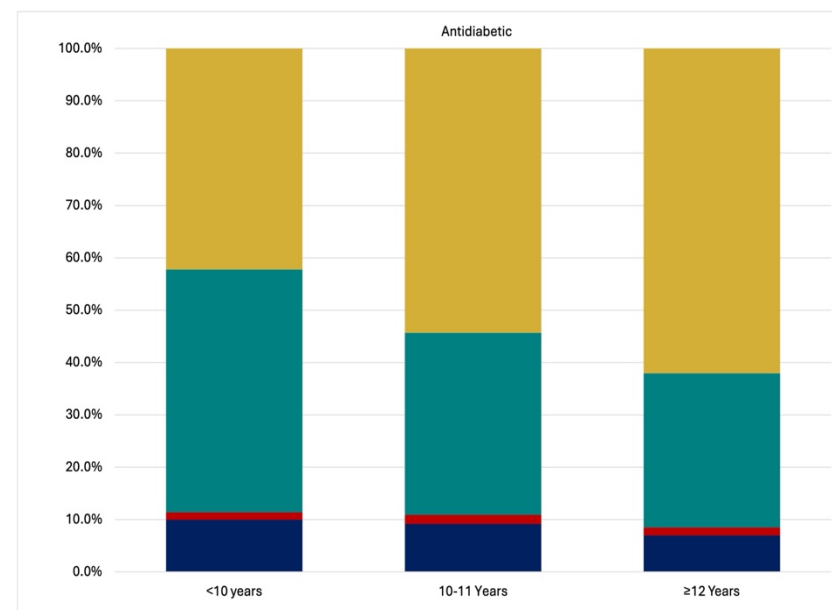
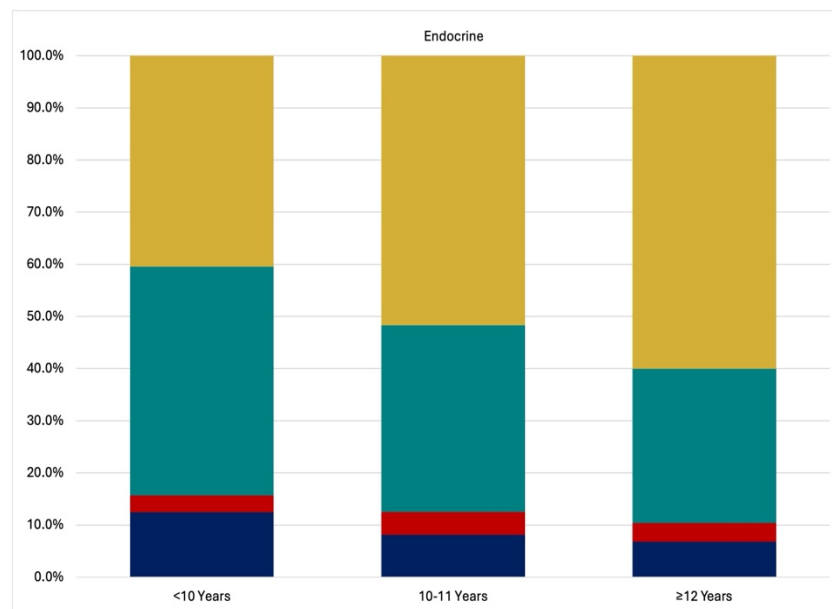
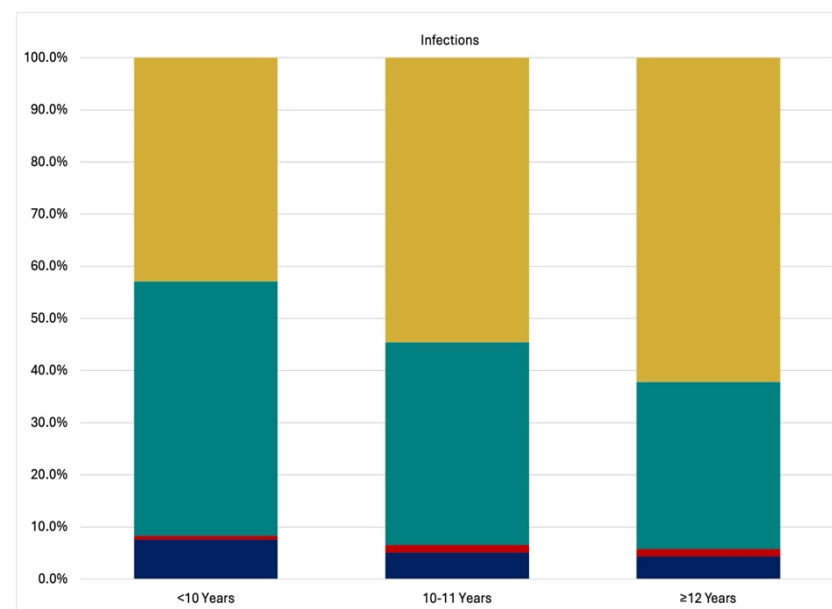
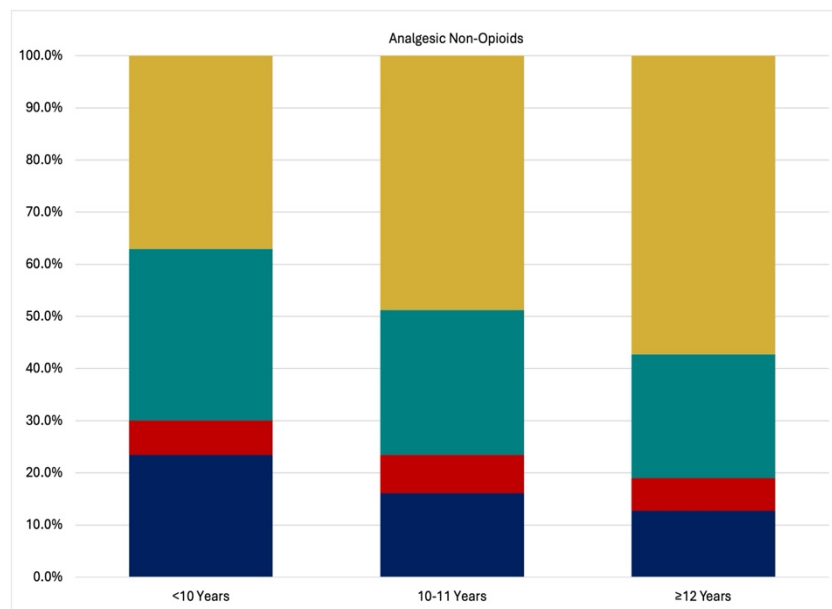
Teal - Participants with polypharmacy and not using a medication from the given medication group.

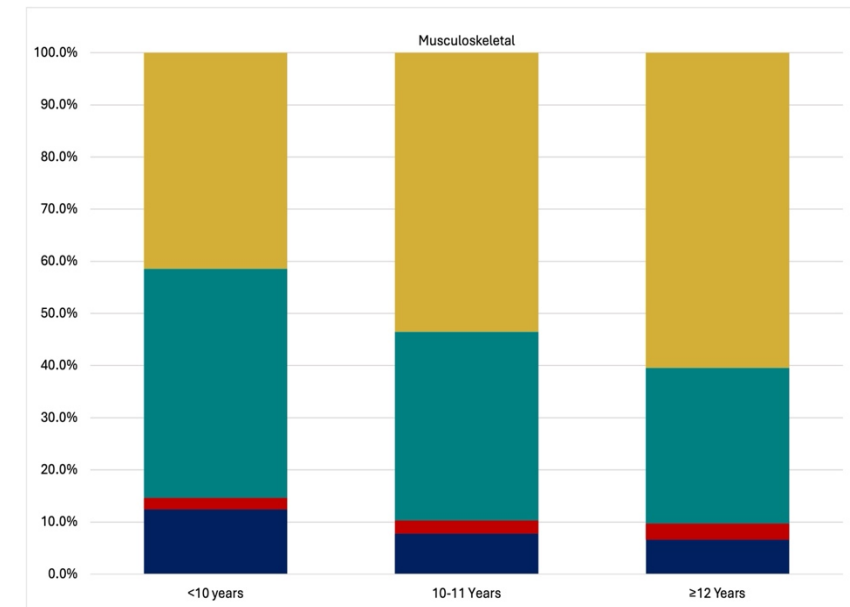
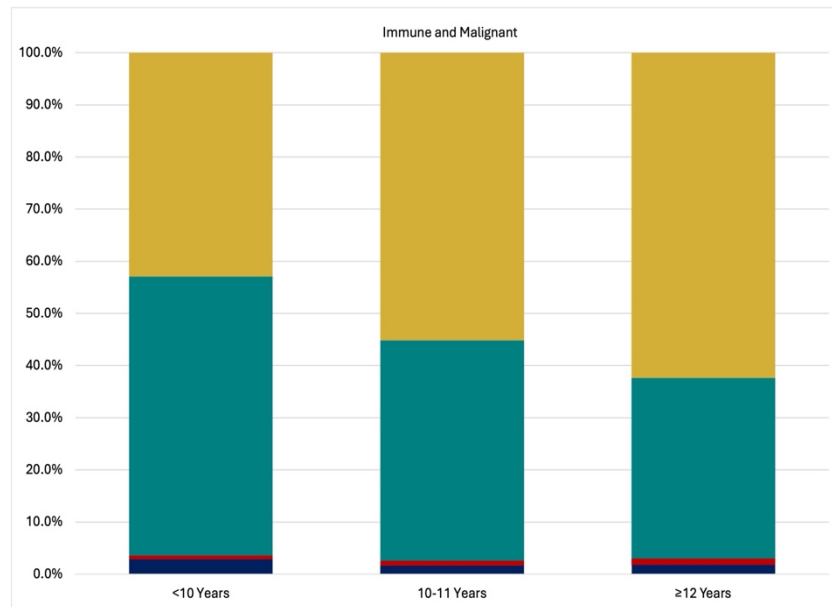
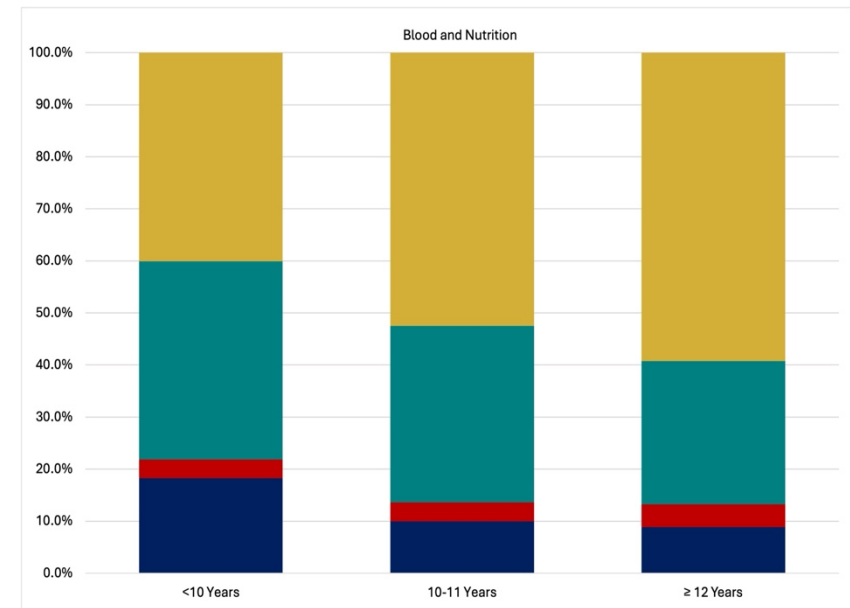
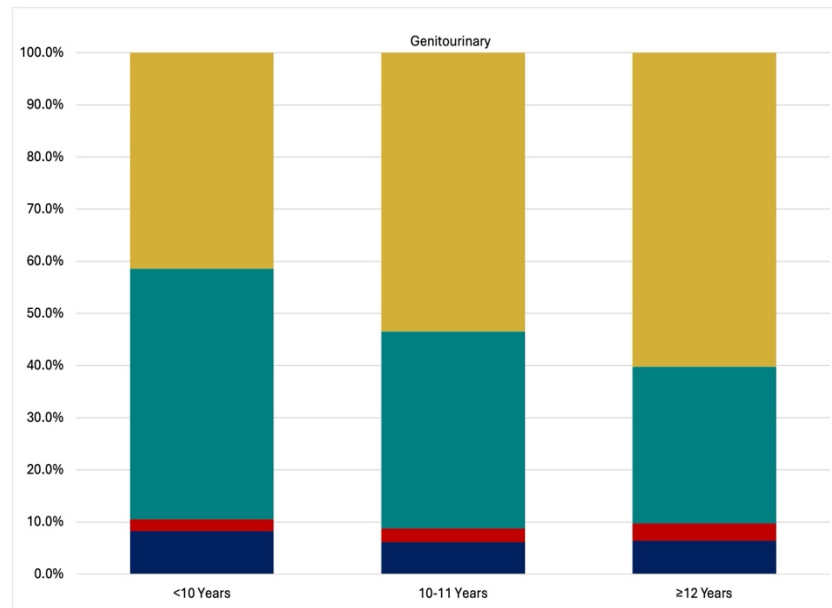
Gold - Participants with no polypharmacy and not using a medication from the given medication group.

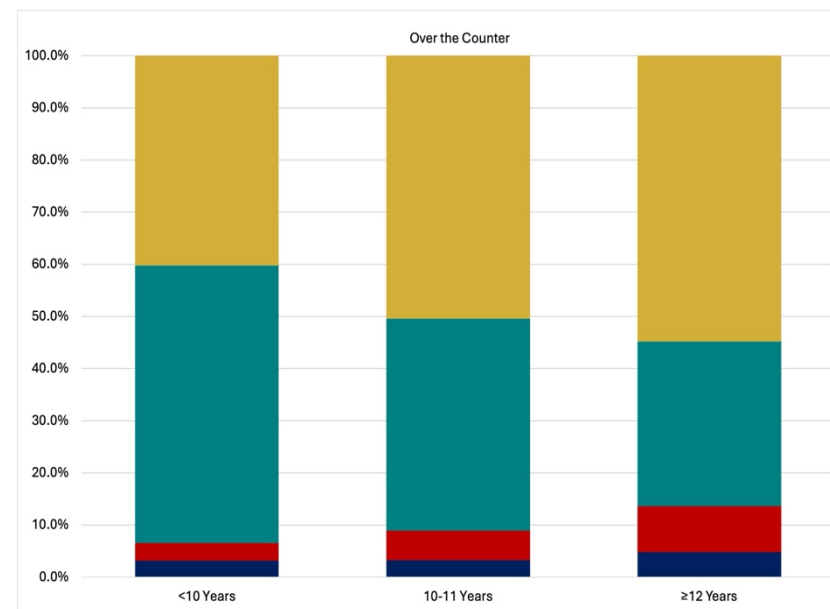
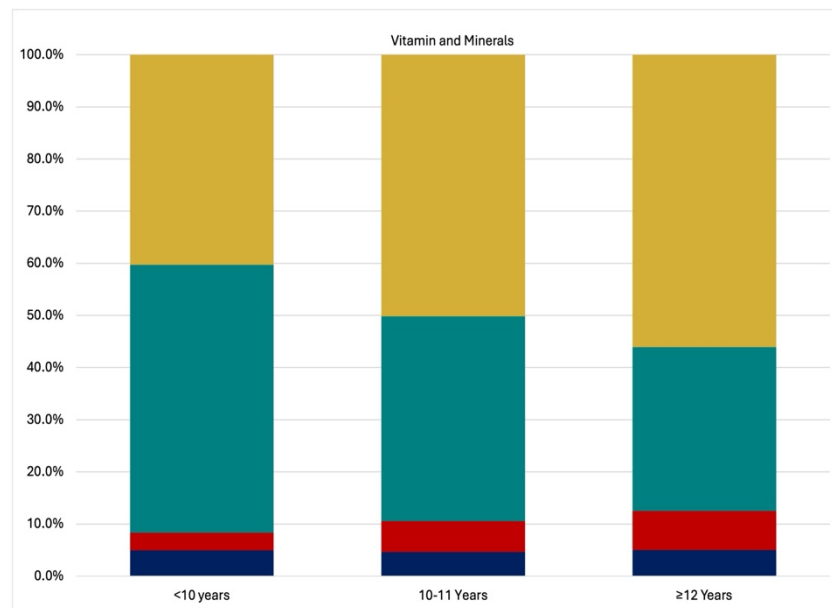












5.4 Analytical epidemiology

5.4.1 Introduction

Logistic regression modelling was developed to identify associations between polypharmacy and SES across each medication group, with and without adjustments for confounders. Again, similar to the justification provided in Chapter 4, Section 4.3.2 this regression was appropriate given that the outcome variable of interest was binary, the presence or absence of polypharmacy; multivariable models were then developed in order to help account for potential confounders. However, the logistic regression models developed isolated the group of individuals that were of particular interest, in order to provide a more nuanced understanding of the relationship between education and polypharmacy in respect to a given medication category – relevant to the given aim of this chapter. In order to allow for comparable associations to be made, logistic regressions between education and polypharmacy were carried out (similar to Chapter 4) but only on individuals that were using at least one medication. Finally, interaction models were created to further understand the education effect for people taking the medications. To prevent any repetition of methods, reference can be made to Chapter 4, Section 4.3 to understand the rationale for the methods of choice, however, discussion in relation to the creation of medication groups and the use of interaction models is provided in Chapter 5 Section 5.3.2 and Chapter 5 Section 5.4.4.

5.4.2 Relationship between education and polypharmacy across medication groups

Table 5.3 highlights the multivariable analysis for each medication category, showing the odds of being in receipt of polypharmacy, for individuals who are using at least one medication from the given category, and in respect to the number of years of education. The model compared individuals from a lower level of education (<10 years) and those of higher education (≥ 12 years) to the control group (10-11 years of education). Results are presented adjusting for age and sex and then additional adjustment for multimorbidity, despite its presence on the causal pathway, further discussed in Chapter 5 Section 5.5. In addition, a logistic regression model between education and polypharmacy was undertaken on this particular cohort of individuals, using at least one medication, in order to allow for comparison between the odds ratios.

On controlling for age and sex, individuals with lower education levels were more likely to be in receipt of polypharmacy than those of higher education levels. Results in Table 5.3 did not suffice many medication groups that deviated from this overall trend. However, taking the results in turn, education years showed a profound effect on cardiovascular medications. Those with <10 years had an increased odds of having polypharmacy - OR 1.28 (95% CI 0.98; 1.67)

and those with ≥ 12 years of education, a lower odds OR 0.81 (95% CI 0.63; 1.05). Similar trends were observed for hyperlipidaemia medications, whilst those with < 10 years of education demonstrated an OR 1.26 (95% CI 1.01; 1.56) and individuals with ≥ 12 years OR 0.73 (95% CI 0.60; 0.88).

There are, however, some groups whereby observations are less pronounced or deviated from the overall trend of lower education demonstrating an increased odds of having polypharmacy. For example, for the hypnotics/anxiolytics/benzodiazepines group, individuals with < 10 years of education had an OR 0.96 (95% CI 0.46; 2.01), whereas those with ≥ 12 years had OR 1.17 (95% CI 0.56; 2.47). However, it should also be noted, with the presence of such wide confidence intervals, the findings should be viewed with caution and suggestive that little influence of education on polypharmacy can be observed in this category.

The use of gastrointestinal medications revealed interesting findings, whereby little profound difference was present between the number of years of education and being in receipt of polypharmacy. Those with < 10 years of education showed an OR of 1.01 (95% CI 0.78; 1.32), close to 1.00 (referent, 10-11 years of education) suggesting little effect of education on individuals with gastrointestinal medication usage and being in receipt of polypharmacy. Similarly, those in the category with ≥ 12 years of education, showed a OR of 0.95 (95% CI 0.73; 1.23), whilst indicating a slightly lower likelihood of being in receipt of polypharmacy, being so close to 1.00 minimal practical difference can be implied.

In the second model, adjustments were carried out for the addition of multimorbidity. Overall, odds ratios for individuals with a lower level of education decreased or stayed consistent across most medication groups, implying an increased odds of being in receipt of polypharmacy remained from those with < 10 years of education. There were, however, some interesting observations; for example, cardiovascular medications where the addition of confounding for multimorbidity increased the odds ratio compared with the model only adjusting for age and sex. Despite an initial reduction in odds ratio when adjusting for age and sex (pertaining some of the apparent effect attribute to age and sex) an increased odds with the addition of confounding for multimorbidity suggests education may still have an independent effect on polypharmacy. Similar patterns were observed across the groups of endocrine, musculoskeletal and OTC groups. In contrast, there were some groups, such as those using a gastrointestinal medication, whereby less effect can be attributed to multimorbidity, individuals with < 10 years of education had an OR 0.95 (95% CI 0.72; 1.25) and ≥ 12 years of education OR 1.11 (95% CI 0.84; 1.46). Whilst the odds of being in receipt of polypharmacy for those with < 10 years

decreased when adjusting for multimorbidity, individuals with ≥ 12 years the odds of using a gastrointestinal medication and having polypharmacy increased. This observation highlights that factors beyond multimorbidity may contribute to the observed patterns of an increased likelihood of polypharmacy, given the presence of a gastrointestinal medication.

Table 5. 3: Multivariable analysis of medication groups and polypharmacy in CFAS II at wave 1.

Medication groups of interest include number of individuals in each category (n). Model 1 adjusted for age and sex, Model 2 adjusted for age, sex and multimorbidity. Having no polypharmacy was measured as 1-4 medication, polypharmacy ≥ 5 .

Medication Groups (n)	<10 years		≥ 12 years					
	Adjusted for age and sex		Adjusted for age, sex and multimorbidity		Adjusted for age and sex		Adjusted for age, sex and multimorbidity	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Logistic Regression	1.18	(1.03; 1.35)	1.14	(0.99; 1.32)	0.75	(0.67; 0.86)	0.82	(0.71; 0.94)
Gastrointestinal (2375)	1.01	(0.78; 1.32)	0.95	(0.72; 1.25)	0.95	(0.73; 1.23)	1.11	(0.84; 1.46)
Cardiovascular (2515)	1.28	(0.98; 1.67)	1.32	(1.01; 1.74)	0.81	(0.63; 1.05)	0.88	(0.68; 1.14)
Antihypertensives (3808)	1.13	(0.93; 1.37)	1.14	(0.93; 1.38)	0.75	(0.63; 0.90)	0.81	(0.67; 0.98)
Antiplatelet (2471)	1.22	0.94; 1.58)	1.15	(0.88; 1.51)	0.70	(0.55; 0.88)	0.75	(0.59; 0.97)
Hyperlipidaemia (3448)	1.26	(1.01; 1.56)	1.24	(0.99; 1.56)	0.73	(0.60; 0.88)	0.83	(0.68; 1.01)
Respiratory (910)	1.31	(0.80; 2.15)	1.32	(0.79; 2.22)	0.65	0.42; 1.01)	0.63	(0.39; 1.02)
Nervous System (912)	1.25	(0.77; 2.02)	1.22	(0.73; 2.02)	0.68	(0.46; 1.00)	0.66	(0.43; 1.01)
Hypnotics/Anxiolytics/ Benzodiazepines (282)	0.96	(0.46; 2.01)	0.84	(0.39; 1.83)	1.17	(0.56; 2.47)	1.30	(0.56; 3.00)
Antidepressants (836)	1.05	(0.66; 1.67)	1.05	(0.64; 1.71)	0.64	(0.42; 0.98)	0.75	(0.48; 1.19)
Opioids (1110)	1.09	(0.71; 1.67)	1.16	(0.73; 1.85)	0.67	(0.46; 1.01)	0.73	(0.47; 1.12)
Analgesic (non-opioid) (1802)	1.12	(0.83; 1.49)	1.07	(0.78; 1.47)	0.84	(0.64; 1.12)	0.85	(0.63; 1.15)
Infections (508)	2.65	(1.30; 5.41)	2.41	(1.13; 5.16)	1.02	(0.58; 1.80)	1.10	(0.60; 2.02)
Endocrine (959)	1.52	(1.03; 2.25)	1.55	(1.04; 2.31)	0.89	0.60; 1.31)	0.94	(0.62; 1.41)
Antidiabetic (765)	1.08	(0.62; 1.86)	1.07	(0.61; 1.90)	0.86	(0.51; 1.44)	0.89	(0.51; 1.56)
Genitourinary (701)	1.25	(0.76; 2.05)	1.31	(0.78; 2.20)	0.81	(0.53; 1.23)	0.78	(0.49; 1.22)
Blood and Nutrition (1168)	1.38	(0.96; 2.01)	1.35	(0.92; 1.97)	0.74	(0.52; 1.06)	0.90	(0.61; 1.32)
Immune and Malignant (217)	1.84	(0.76; 4.49)	3.81	(1.37; 10.58)	0.81	(0.38; 1.71)	0.72	(0.31; 1.67)
Musculoskeletal (842)	1.26	(0.80; 1.99)	1.33	(0.83; 2.15)	0.68	(0.45; 1.03)	0.76	(0.48; 1.21)
Vitamin and Minerals (775)	1.52	(0.99; 2.34)	1.27	(0.80; 2.03)	0.85	(0.60; 1.21)	0.93	(0.63; 1.37)
Over the Counter (695)	1.08	(0.67; 1.75)	1.11	(0.66; 1.85)	0.87	(0.61; 1.25)	0.93	(0.63; 1.36)

5.4.3 Linear trend analysis

A test was carried out, conducting a linear trend analysis and thereby treating the education groups as continuous, to understand if a linear trend across the groups was present. The results reflect observations discussed above and that were described in Chapter 4. Among the majority of the medication groups, for every step increase (moving from <10 years, 10-11 year to ≥ 12 years) there was an overall decrease in odds of being in receipt of polypharmacy (Table 5.4); the findings demonstrated the protective effect of education remained. This dose response effect was stronger for certain medication groups, such as cardiovascular, antihypertensives, hyperlipidaemia and musculoskeletal medications, even after adjustment for age, sex and multimorbidity. This is of particular interest as the findings suggest education retains a protective effect from polypharmacy, particularly in medication groups whereby individuals present with complex LTCs, which usually require treatment with multiple medications. In contrast, there are some groups in which such observed relationships are not as strong and diminish particularly after adjusting for multimorbidity; for example, genitourinary, and infections indicating the possibility of relationships being mediated by factors like chronic disease and age opposed to education alone. In groups such as OTC medications, and hypnotics/anxiolytics/benzodiazepines there was no evidence of a difference in the prevalence of polypharmacy by education group. In addition, for hypnotics/anxiolytics/benzodiazepines the estimate was reversed, though with low confidence due to small numbers.

Table 5. 4: Linear trend analysis of medication groups and polypharmacy in CFAS II at wave 1.
Medication groups of interest include number of individuals in each category (n). Model 1 adjusted for age and sex, Model 2 adjusted for age, sex and multimorbidity.

Medication groups (n)	Adjusted for Age and Sex		P _{trend}	Adjusted for Age, Sex and Multimorbidity		P _{trend}
	OR (95% CI)			OR (95% CI)		
Gastrointestinal (2375)	0.97	(0.83; 1.13)	0.681	1.08	(0.92; 1.27)	0.360
Cardiovascular (2515)	0.80	(0.69; 0.92)	0.003	0.82	(0.70; 0.95)	0.007
Antihypertensives (3808)	0.82	(0.73; 0.91)	<0.001	0.84	(0.76; 0.94)	0.003
Antiplatelet (2471)	0.76	(0.66; 0.87)	<0.001	0.81	(0.70; 0.94)	0.004
Hyperlipidaemia (3448)	0.76	(0.67; 0.85)	<0.001	0.82	(0.72; 0.93)	0.002
Respiratory (910)	0.70	(0.54; 0.92)	0.010	0.72	(0.54; 0.92)	0.010
Nervous System (912)	0.73	(0.57; 0.94)	0.016	0.73	(0.56; 0.96)	0.024
Hypnotics/Anxiolytics/ Benzodiazepines (282)	1.11	(0.72; 1.70)	0.648	1.24	(0.78; 1.98)	0.366
Antidepressants (836)	0.78	(0.60; 1.01)	0.060	0.84	(0.63; 1.13)	0.254
Opioids (1110)	0.79	(0.61; 1.02)	0.066	0.79	(0.60; 1.04)	0.096
Analgesic (non-opioid) (1802)	0.87	(0.74; 1.03)	0.104	0.89	(0.74; 1.07)	0.223
Infections (508)	0.65	(0.47; 0.91)	0.011	0.71	(0.49; 1.02)	0.060
Endocrine (959)	0.76	(0.61; 0.95)	0.016	0.77	(0.61; 0.98)	0.036
Antidiabetic (765)	0.89	(0.65; 1.22)	0.480	0.92	(0.65; 1.28)	0.591
Genitourinary (701)	0.81	(0.62; 1.04)	0.094	0.77	(0.59; 1.02)	0.064
Blood and Nutrition (1168)	0.73	(0.60; 0.90)	0.003	0.81	(0.65; 1.01)	0.061
Immune and Malignant (217)	0.67	(0.43; 1.06)	0.085	0.47	(0.29; 0.76)	0.002
Musculoskeletal (842)	0.73	(0.58; 0.94)	0.013	0.75	(0.58; 0.98)	0.036
Vitamin and Minerals (775)	0.76	(0.60; 0.96)	0.022	0.86	(0.67; 1.11)	0.251
Over the Counter (695)	0.89	(0.70; 1.13)	0.342	0.92	(0.71; 1.18)	0.491

5.4.4 Interaction model

An interaction model (Table 5.5 and 5.6) was developed in order to help capture the complex intertwined relationship between polypharmacy, education and the influence of a specific medication category. The model was constructed to first examine the main effects of education (categorised, but treated as a continuous variable) on polypharmacy, and the independent effect of using a given medication category on polypharmacy. The interaction then explored how all three variables may change when considered together. While the model initially builds on the foundation of the logistic model carried out in this chapter, its significance lies in its ability to add complexity by taking into consideration interactions that reflect real-world dynamics.

In contrast, the logistic regression model focusses on the independent effects of each variable. With the interaction model being able to identify if an observed relationship between education and polypharmacy may either be moderated or amplified in the presence of a specific medication category, such insights can help guide health policies and help clinicians be more vigilant in monitoring medication use with particular medication groups, particularly in understanding their use in the increased risk of developing polypharmacy. Interaction models are also useful in understanding potential synergistic or antagonist effects between the variables, for example, if the protective effect of education in being receipt of a polypharmacy is more pronounced in the presence of a given medication category (synergistic) or conversely, the beneficial effect of education is diminished (antagonistic), both of which can help influence clinical decision making.

Table 5. 5: Interaction model showing the odds ratio of the main effect of education and polypharmacy on each medication group using and not using a medicine, and the odd ratio of the interaction term. Model Adjusted for age and sex, education categories treated as continuous variable.

Medication Group	Education Effect in Each Medication Group						Risk of Polypharmacy in Each Medication Category		Interaction
	Not Using a Medication from the Given Group			Using a Medication from the Given Group					
	OR (95% CI)	P Value		OR (95% CI)	P Value		OR (95% CI)	P Value	P Value
Gastrointestinal	0.74 (0.67;0.81)	P<0.001		0.94 (0.81;1.08)	0.370		4.34 (3.08; 6.10)	<0.001	0.005
Cardiovascular	0.76 (0.69;0.84)	P<0.001		0.82 (0.71;0.95)	0.008		7.07 (4.98;10.02)	<0.001	0.411
Antihypertensives	0.74 (0.66;0.83)	P<0.001		0.86 (0.76;0.96)	0.007		4.15 (3.03; 5.69)	<0.001	0.045
Antiplatelet	0.76 (0.69;0.83)	P<0.001		0.80 (0.69;0.92)	0.001		5.33 (3.80; 7.50)	<0.001	0.532
Hyperlipidaemia	0.80 (0.71;0.89)	P<0.001		0.79 (0.70;0.89)	<0.001		7.31 (5.28;10.13)	<0.001	0.900
Respiratory	0.80 (0.74;0.87)	P<0.001		0.80 (0.61;1.05)	0.107		5.64 (3.14;10.15)	<0.001	0.981
Nervous System	0.78 (0.72;0.84)	P<0.001		0.80 (0.63;1.02)	0.074		4.06 (2.38; 6.92)	<0.001	0.829
Hypnotics/ Anxiolytics/ Benzodiazepines	0.77 (0.71;0.83)	P<0.001		1.01 (0.70;1.45)	0.978		2.31 (1.07; 4.98)	0.033	0.155
Antidepressants	0.78 (0.72;0.84)	P<0.001		0.81 (0.62;1.04)	0.102		4.83 (2.78; 8.43)	<0.001	0.796
Opioids	0.81 (0.75;0.88)	P<0.001		0.79 (0.62;1.00)	0.046		6.01 (3.67;10.08)	<0.001	0.795
Analgesic (non-opioid)	0.79 (0.73;0.87)	P<0.001		0.87 (0.74;1.02)	0.083		3.49 (2.44; 5.00)	<0.001	0.324
Infections	0.79 (0.73;0.85)	P<0.001		0.64 (0.47;0.87)	0.004		8.96 (4.54; 7.69)	<0.001	0.180
Endocrine	0.79 (0.73;0.85)	P<0.001		0.74 (0.60;0.91)	0.005		3.34 (2.13; 5.25)	<0.001	0.614

	Education Effect in Each Medication Group						Risk of Polypharmacy in Each Medication Category		Interaction	
	Not Using a Medication from the Given Group			Using a Medication from the Given Group						
	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value	P Value
Antidiabetic	0.79	(0.73;0.85)	P<0.001	0.94	(0.69;1.29)	0.704	5.93	(3.04;11.56)	<0.001	0.274
Genitourinary	0.76	(0.71;0.82)	P<0.001	0.82	(0.65;1.04)	0.099	2.93	(1.73; 4.97)	<0.001	0.571
Blood and Nutrition	0.78	(0.72;0.85)	P<0.001	0.72	(0.59;0.87)	0.001	5.18	(3.35; 8.02)	<0.001	0.432
Immune and Malignant	0.78	(0.72;0.84)	P<0.001	0.81	(0.53;1.26)	0.352	2.22	(0.88; 5.59)	0.092	0.833
Musculoskeletal	0.78	(0.72;0.84)	P<0.001	0.72	(0.57;0.91)	0.006	5.17	(3.06; 8.73)	<0.001	0.518
Vitamin and Minerals	0.78	(0.72;0.84)	P<0.001	0.76	(0.61;0.95)	0.015	1.18	0.72; 1.91)	0.509	0.875
OTC	0.77	(0.72;0.83)	P<0.001	0.88	(0.70;1.11)	0.289	0.60	(0.35; 1.01)	0.056	0.262

Table 5. 6: Interaction model showing the odds ratio of the main effect of education and polypharmacy on each medication group using and not using a medicine, and the odd ratio of the interaction term. Model Adjusted for age, sex and multimorbidity education categories treated as continuous variable.

Medication Group	Education Effect in Each Medication Group						Risk of Polypharmacy in Each Medication Category			Interaction
	Not Using a Medication from the Given Group			Using a Medication from the Given Group						
	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value	P Value
Gastrointestinal	0.79	(0.71;0.87)	P<0.001	1.00	(0.86;1.17)	0.965	1.27	(1.07;1.50)	0.005	0.009
Cardiovascular	0.83	(0.75;0.92)	P=0.001	0.84	(0.72;0.98)	0.023	6.60	(4.56;9.57)	<0.001	0.973
Antihypertensives	0.80	(0.71;0.91)	P<0.001	0.89	(0.79;0.99)	0.038	3.35	(2.41;4.66)	<0.001	0.217
Antiplatelet	0.81	(0.73;0.90)	P<0.001	0.85	(0.73;0.99)	0.032	4.70	(3.24;6.73)	<0.001	0.625
Hyperlipidaemia	0.85	(0.76;0.95)	P=0.005	0.84	(0.74;0.95)	0.007	6.10	(4.33;8.61)	<0.001	0.883
Respiratory	0.86	(0.79;0.94)	P<0.001	0.78	(0.59;1.04)	0.090	5.15	(2.80;9.50)	0.524	0.524
Nervous System	0.84	(0.77;0.92)	P<0.001	0.78	(0.60;1.01)	0.060	4.67	(2.66;8.20)	<0.001	0.567
Hypnotics/ Anxiolytics/ Benzodiazepines	0.82	(0.76;0.89)	P=0.056	1.07	(0.71;1.62)	0.732	2.28	(0.98;5.33)	0.056	0.210
Antidepressants	0.84	(0.77;0.91)	P<0.001	0.86	(0.65;1.14)	0.302	4.81	(2.61;8.87)	<0.001	0.855
Opioids	0.88	(0.81;0.96)	P=0.004	0.76	(0.60;0.98)	0.032	6.32	(3.73;10.72)	<0.001	0.282
Analgesic (non-opioids)	0.87	(0.79;0.95)	P=0.002	0.86	(0.73;1.02)	0.077	3.60	(2.45;5.28)	<0.001	0.947
Infections	0.85	(0.78;0.92)	P<0.001	0.67	(0.47;0.95)	0.025	8.45	(3.99;17.91)	<0.001	0.199
Endocrine	0.85	(0.78;0.92)	P<0.001	0.75	(0.59;0.95)	0.015	2.89	(1.76;4.77)	<0.001	0.322
Antidiabetic	0.84	(0.77;0.91)	P<0.001	0.93	(0.67;1.30)	0.686	4.69	(2.34;9.42)	<0.001	0.540

	Education Effect in Each Medication Group						Risk of Polypharmacy in Each Medication Category			Interaction
	Not Using a Medication from the Given Group			Using a Medication from the Given Group						
	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value	P Value
Genitourinary	0.83	(0.76;0.90)	P <0.001	0.76	(0.58;1.00)	0.047	4.19	(2.32;7.57)	<0.001	0.563
Blood and Nutrition	0.84	(0.77;0.92)	P <0.001	0.79	(0.63;0.98)	0.029	5.38	(3.34;8.68)	<0.001	0.574
Immune and Malignant	0.84	(0.77;0.91)	P <0.001	0.68	(0.46;1.01)	0.059	3.03	(1.31;7.04)	0.010	0.313
Musculoskeletal	0.85	(0.78;0.92)	P <0.001	0.71	(0.56;0.92)	0.009	6.56	(3.78;11.40)	<0.001	0.210
Vitamin and Minerals	0.83	(0.76;0.90)	P <0.001	0.85	(0.67;1.07)	0.161	1.26	(0.75;2.12)	0.377	0.873
OTC	0.83	(0.77;0.91)	P <0.001	0.91	(0.70;1.17)	0.455	0.67	(0.37;1.19)	0.171	0.526

Table 5. 7: Interaction model showing whether the relationship between education level and polypharmacy differs based on the use or non-use of medication from the gastrointestinal group.

Number of Years of Education	Using a Gastrointestinal Medication	OR	(95% CI)	P Value
< 10 years	No	1.16	(0.98; 1.37)	0.087
10-11 years	No	1.00	(ref)	(ref)
≥ 12 years	No	0.71	(0.60; 0.85)	<0.001
< 10 years	Yes	6.21	(4.92; 7.83)	<0.001
10-11 years	Yes	5.65	(4.80; 6.66)	<0.001
≥ 12 years	Yes	6.49	(5.02; 8.39)	<0.001

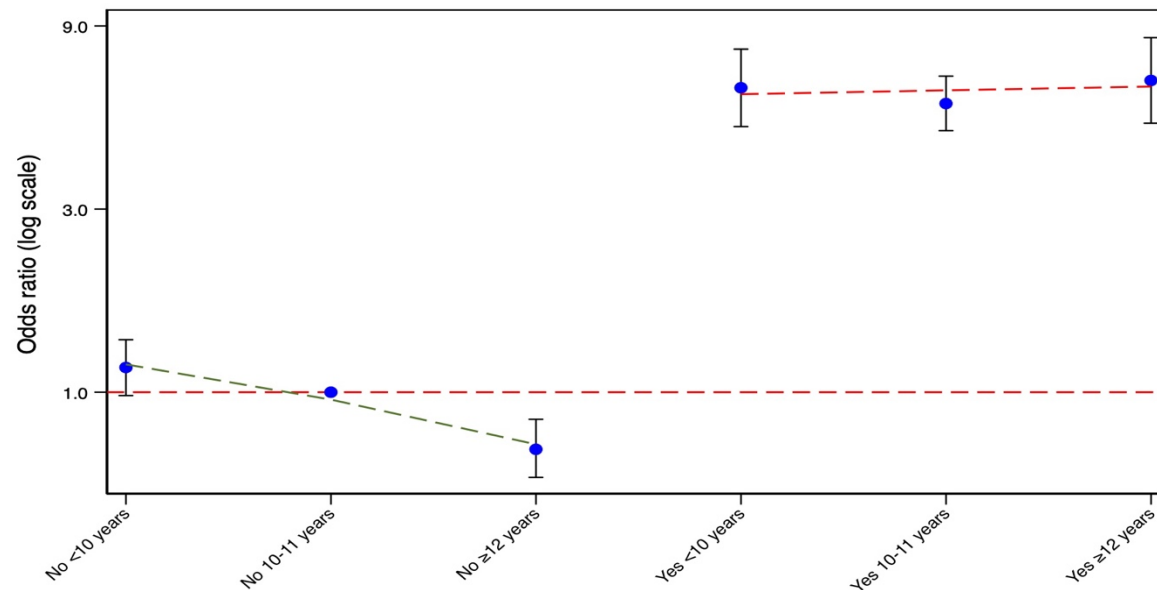


Figure 5. 4: Forest plot illustrating the interaction model, showing variations in the association between education level and polypharmacy dependent on the use or non-use of medication from the gastrointestinal group.

Table 5. 8: Interaction model showing whether the relationship between education level and polypharmacy differs based on the use or non-use of medication from the antihypertensive group.

Number of Years of Education	Using an Antihypertensive Medication	OR	(95% CI)	P Value
< 10 years	No	1.27	(1.03; 1.55)	0.022
10-11 years	No	1.00	(ref)	(ref)
≥ 12 years	No	0.82	(0.67; 1.02)	0.076
< 10 years	Yes	4.48	(3.68; 5.45)	<0.001
10-11 years	Yes	4.34	(3.72; 5.06)	<0.001
≥ 12 years	Yes	3.49	(2.86; 4.25)	<0.001

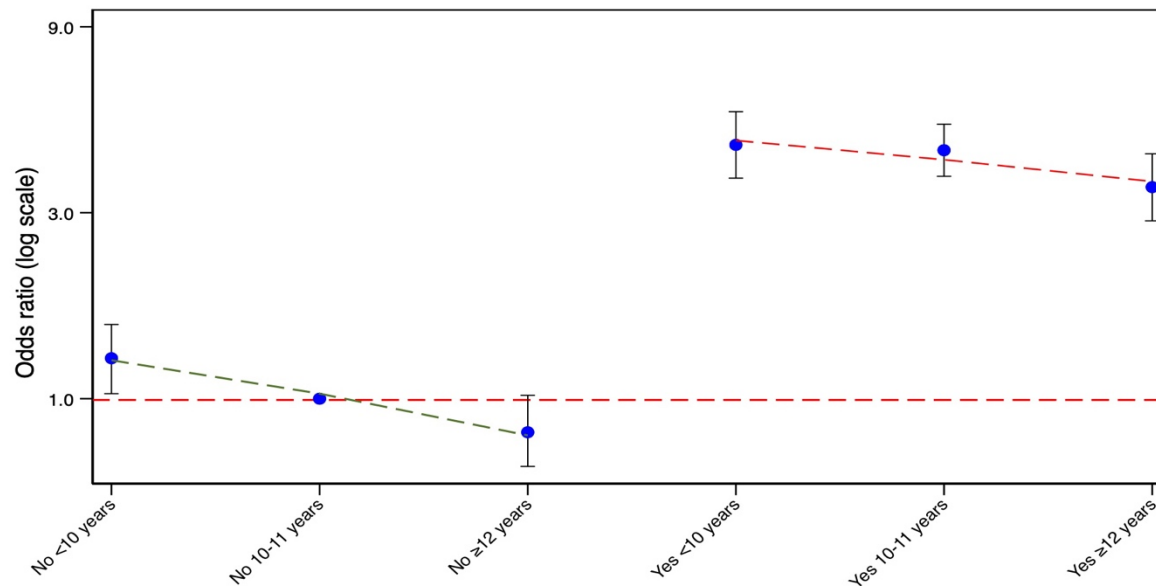


Figure 5. 5: Forest plot illustrating the interaction model, showing variations in the association between education level and polypharmacy dependent on the use or non-use of medication from the antihypertensive group.

Table 5. 9: Interaction model showing whether the relationship between education level and polypharmacy differs based on the use or non-use of medication from the hypnotic/anxiolytics/benzodiazepines group.

Number of Years of Education	Using a Hypnotic/Anxiolytics/Benzodiazepine Medication	OR	(95 % CI)	P Value
0< 10 years	No	1.12	(0.97; 1.30)	0.111
10-11 years	No	1.00	(ref)	(ref)
≥ 12 years	No	0.76	(0.66; 0.87)	<0.001
< 10 years	Yes	3.78	(2.17; 6.58)	<0.001
10-11 years	Yes	3.30	(2.18; 4.98)	<0.001
≥ 12 years	Yes	4.61	(2.33; 9.12)	<0.001

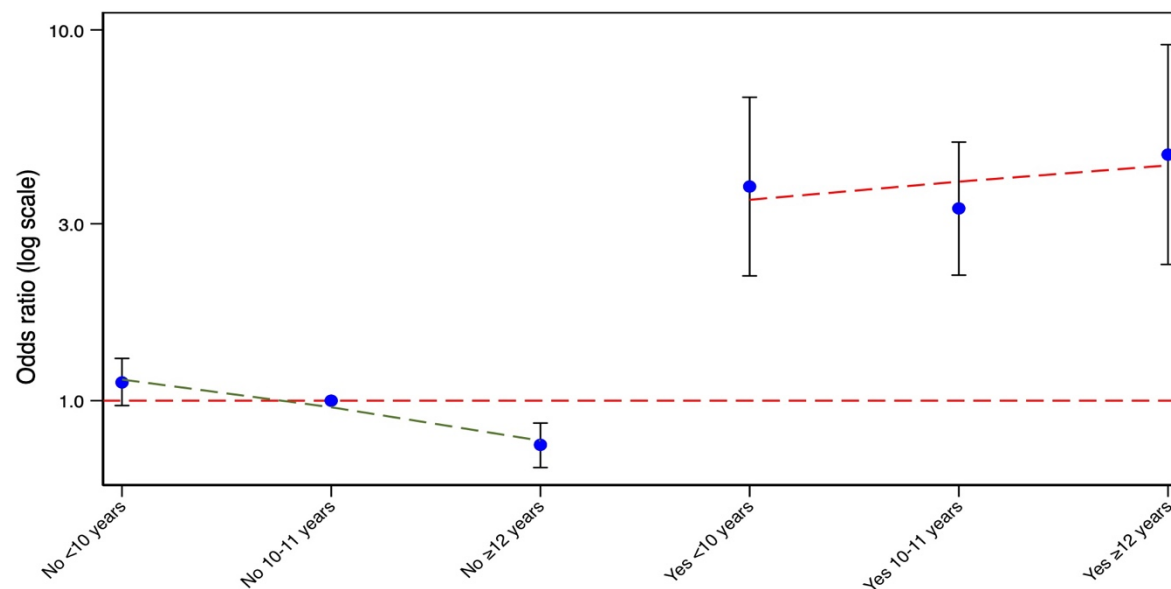


Figure 5. 6: Forest plot illustrating the interaction model, showing variations in the association between education level and polypharmacy dependent on the use or non-use of medication from the hypnotic/anxiolytics/benzodiazepine group.

The primary objective of the interaction model was to understand how the effect of education on being in receipt of polypharmacy differed according to whether an individual using a certain medication, for example, the use of an opioid or cardiovascular medication. This allowed for an understanding on how the given variables act both independently and in combination with each other. The overall results (Table 5.5 and 5.6) showed little evidence of differences across most medication groups, thereby suggesting that the overall protective effect of education on reducing the likelihood of being in receipt of polypharmacy remained consistent and did not vary substantially on the type of medication used.

The overall direction, when focusing on the education affect alone, reflected results that of Chapter 4, highlighting a lower odds ratio of being in receipt of polypharmacy from the given groups moving continuously from one education category to the next. In relation to the main effect of polypharmacy, higher odds were observed across most of the medication groups, as expected. For example, individuals using opioids were six times more likely to be in receipt of polypharmacy, and similar trends were observed when the model was adjusted for multimorbidity (Table 5.6). Those with cardiovascular medication also demonstrated higher odds of being in receipt of polypharmacy; however, results in part could be explained by the increased likelihood of such individuals often requiring multiple medications to manage complex health conditions. This being said, trends remained when multimorbidity was accounted for in the model. Nevertheless, observing the main effects of education or polypharmacy in the results reinstate two key points: i) an overall education effect present across the medication groups, often consistent with users and non-users of medication; ii) increased odds of polypharmacy in some medication groups more than others, even after accounting for multimorbidity. I will use the group of cardiovascular medications to illustrate this further as follows:

- i) In the model adjusted for age and sex, the education effect of polypharmacy for those not using a cardiovascular medication, OR 0.76 (95% CI 0.69; 0.84) and using a cardiovascular medication OR 0.82 (95% CI 0.71; 0.95), is similar suggesting education has similar effect on user and non-users.
- ii) Isolating the main effect of polypharmacy, individuals using a cardiovascular medicine are seven times more likely to be in receipt of polypharmacy, which can be expected given the complex health needs of such individuals and multiple medications to manage such conditions. However, whilst some effect is accounted for with the adjustment of multimorbidity (Table 5.6), the odds still remain high.

- iii) The interaction showed no difference between the variables, thereby the effect of education on polypharmacy appears to be consistent for those taking cardiovascular medication and those who are not.

Such results were found across most medication groups, however, there were some medication groups that did present significant interactions, thereby suggesting that the effect of education can change. Such groups were further explored and presented in Tables 5.7, 5.8, 5.9 And Figures 5.4, 5.5 and 5.6. Both the gastrointestinal group and antihypertensive demonstrated a significant interaction and thereby I wanted to explore this further and carried out an additional test focussing on the interaction model, in order to understand how and if education drives the outcome. The results demonstrated across all education categories individuals using gastrointestinal medications have significantly higher odds of having polypharmacy. Results suggest that the protective effect of education is diminished, and the presence of a gastrointestinal medication can substantially increase the overall likelihood of being in receipt of polypharmacy (Figure 5.4). Results from antihypertensive group of medication however demonstrated a present protective effect of education that was observed across the medication groups, therefore in line with previous observations. The final group of medications that was explored further was the hypnotics/benzodiazepines/anxiolytics, which demonstrated for individuals not using a medication, a protective effect of education. However, for individuals that were using a medication from this group, the estimate was reversed.

5.5 Interpretation of findings

The findings of this chapter indicate that the overall protective effect of education remained consistent among most medication groups. Some medication groups showed a diminished protective effect of education in being receipt of polypharmacy, therefore suggestive that other factors may be involved in mediating relationships, such as health seeking behaviours and or access to health care resources. The use of gastrointestinal medication particularly deviated from the overall observed trends, and the protective effect of education was less pronounced, a more complex relationship was evident.

Possible explanations to the results observed for the gastrointestinal group can be attributed to multiple reasoning such as: underlying health conditions, the intertwined relationship between polypharmacy and multimorbidity, prescribing cascades, ageing, patient expectations and behaviours. Firstly, medicines that fall into this group, are often used to provide symptomatic relief or treat conditions such as gastro-oesophageal reflux disease (GORD), inflammatory bowel disease (IBD) or peptic ulcers. Such conditions are unlikely to exist in isolation, and thereby concurrent with other MLTCs such as arthritis and diabetes.^{440,441} Therefore, the observations highlighted from the results may in actual fact be as a result of multiple medications being required to manage multiple conditions, irrespective of the education level, and feed into the concept of the intertwining relationship between polypharmacy and multimorbidity.

While the literature has highlighted that the use of gastrointestinal medications, in particular proton pump inhibitors (PPIs), are frequently used among individuals of a lower SES.⁴⁴² PPIs are often prescribed to help reduce stomach acid production, which can be exacerbated by lifestyle factors, such as increased stress or poor diet, this has also shown to disproportionately affect those from a lower socioeconomic background. For example, individuals with lower SES are often more likely to face higher stress levels and unhealthy diets, possibly due to financial burden and social pressures that they are exposed to.⁴⁴² A recent study investigating polypharmacy among individuals with, and without, GORD⁴⁴³ found polypharmacy was more prevalent among GORD patients. However, whilst not the primary objective of this work, the study also identified little socioeconomic differences in patients with polypharmacy experiencing GORD and thereby further supporting that a more complex relationship may be present.

Secondly, the observed results for gastrointestinal medications can be attributed to the prescribing cascade, discussed in depth in Chapter 1, whereby additional medications are

prescribed to treat a side effect of current medication, opposed to a LTC. This can therefore be an initial condition treated by a gastrointestinal medication, such as proton pump inhibitor, which can cause nutrient deficiencies or increased risk of both infections and fractures. Therefore, such patients can often require further treatment with medication. In such instances education may have little effect on outcomes, as the issues are as a result of adverse effects from the primary medication.

Thirdly, conditions such as GORD and peptic ulcers are increasingly more common and severe in older adults, primarily due to the natural ageing process.⁴⁴⁴ Therefore, whilst symptoms develop, and often present severe discomfort individuals are likely to switch focus on quick management with medication for symptom relief. Therefore, this urgency overrides wider considerations such as health literacy and broader implementation of lifestyle strategies. Therefore, education has little effect on reducing polypharmacy in such groups of medications.

The results for the anxiolytics/benzodiazepines/hypnotics group, showed a distinctive trend in comparison to the other groups of medications. For individuals that were not taking the medication, the protective effect of education against polypharmacy was prominent, however, this soon diminished when a medication from the given category was used, and polypharmacy was shown to be consistently high across all medication categories. Surprisingly, those with ≥ 12 years of education (highest education) showed much higher odds of being in receipt of polypharmacy, therefore suggesting that other factors have the potential to drive this effect, and education alone does not mitigate odds. This could be down to factors such as the use of these medications are often attributed to conditions such as anxiety and insomnia, which can affect people from all education levels. Whilst such conditions have been shown to be more likely in those of lower SES^{445,446} they can occur in all individuals. In addition, an increase in multimorbidity and mental health problems can lead to an increase in both the use of anxiolytics and hypnotics medications.⁴⁴⁷ For example, one study has highlighted 85% of individuals with multimorbidity were prescribed an anxiolytics/hypnotic. Furthermore, these challenges have resulted in prescribing practices that often lead multiple medication being prescribed,⁴⁴⁸ inevitably predisposing such individuals to an increased risk of polypharmacy, irrespective of SES. Therefore, whilst higher SES may attribute to some protection, for example, through better health literacy, the complexities behind treatment of mental health problems and prescribing practices can contribute to the observed trends.

Observations across other medication groups, such as opioids, did not show a strong protective effect. As reported in the literature, the use of opioids is often higher among individuals from a

lower SES background,⁴¹⁰ for several reasons. Firstly, a higher prevalence of chronic pain amongst such groups has been identified^{449,450} and therefore to reflect treatment needs, increased opioids are prescribed. Other factors, such as reduced access to non-pharmacological management strategies, and complex psychological needs, including higher dependency on opioids, have been shown to effect prescribing patterns amongst those with lower SES.^{411,435} Such complex healthcare needs may also lead to multiple pharmacological treatments, which thereby increases polypharmacy in such individuals. Whilst the logistic regression models aligned with broader observed trends, results from the interaction models demonstrated a diminished educational effect. Therefore, overall results can potentially suggest while the use of opioids has the ability to potentiate polypharmacy, the role of education may be more limited than expected, due to the need for effective pain management, however, further work will be required to unravel the intricates of this potential relationship.

Similar findings were observed for individuals using central nervous system medications and antidepressants, whereby the results did not reach significance in the interaction models. Such medications are most commonly used in the pharmacological treatment of mental health conditions, such as depression, anxiety and schizophrenia. Mental health challenges are often more prevalent among individuals from a lower SES^{411,451} and can be attributed to factors such as financial hardship, stress, and the burden associated with multiple chronic health conditions. The work of Kivimäki⁴⁵² has shown that mental health conditions, such as mood disorders and psychotic disorders, are more prevalent among individuals from a lower SES, and therefore can attribute to an increase in medication usage. While the interactions models did not significantly highlight the protective effect of education in being in receipt of polypharmacy, more intricate dynamics such as the severe nature of mental health conditions, *i.e.* complex treatment regimens and the high risk of relapse, thereby treatment needs may outweigh potential protective effects of education.

Understanding risk of polypharmacy in the main effect model demonstrated consistently higher odds of being in receipt of polypharmacy across the medication groups, with some medication groups showing a much higher odds ratio of having polypharmacy, for instance cardiovascular, hyperlipidaemia and infections. This may be partially attributed to complex medication regimens or complex health needs; for example, an individual taking a statin for high cholesterol will most likely be at risk of developing cardiovascular disease (CVD) and thereby administering long term medication to manage such conditions. Similarly, the management of hypertension often requires the use of two or three medications (*e.g.* calcium channel blocker, ACE inhibitor, or diuretic), and thereby highlights the significance that such results may be

attributed to complex chronic conditions. On the contrary, such relations may also be as a result of inappropriate medication management whereby often those with complex health needs are more likely to receive care from multiple healthcare professionals across different healthcare settings. Therefore, such increased odds of being in receipt of polypharmacy may be an indirect relationship between other issues such as fragmented care, or poor prescribing practices as a result of over reliance on treatment (as opposed to the use of non-pharmacological management), or inappropriate additions without adequate clinical review. In addition, challenges with medication adherence have been well noted, particularly across medications used to manage cardiovascular disease, whereby lifelong treatment inevitably results suboptimal adherence, and thereby opposed to the actual medication not being affective, add on therapy is provided.^{453,454}

Similarly, individuals with medications for infections were more than eight times more likely to have polypharmacy (Table 5.5 and 5.6) than individuals without medications for infections, possible justification for the observed trends can be explained as follows. Firstly, the presence of poor prescribing practices can lead to antibiotic resistance, therefore multiple therapies can be required by individuals to treat the condition present.⁴⁵⁵ Secondly, such individuals using medication from the infection group may be predisposed to polypharmacy as a result of multiple chronic health conditions. Inevitably multiple chronic conditions have shown to increase the risk of an infections, as a result of a compromised immune system; for example, individuals with diabetes or chronic kidney disease.⁴⁵⁶ Such individuals are also more likely to visit healthcare settings and/or be hospitalised, which thereby increases exposure to severe infections such as *Clostridium difficile*.⁴⁵⁷ They are also more likely to experience invasive procedures, such as the use of a catheter, leading to increased risk of being predisposed to an infection and requiring treatment. Thirdly, through the use of multiple medications, there is an increased risk of adverse drug reactions and, as a result, have the potential to reduce white blood cells, resulting in an increased risk of an infection. Furthermore, commonly used medications, such as NSAIDs, can predispose individuals to increased risk of infection through the effect upon mucosal barriers.⁴⁵⁸

The relationship between multiple medication usage and MLTCs is well established across the literature, but the exact involvement in the causal pathway of polypharmacy is complicated. While I adjusted for multimorbidity through my analysis, as an additional model, the relationship is intertwined, some of the complexities of which I will discuss. The diagram below, Figure 5.7, is adapted from the concept of a mediation model by Baron and Kerry.^{459,460} It demonstrates how socioeconomic inequalities influences polypharmacy, both directly, and

indirectly through, for example, multimorbidity. SES, through many of the underlying pathways of the social determinants of health, can contribute to healthcare outcomes, and therefore specifically to medication use and, in the focus of this thesis, polypharmacy (outcome). The mediator in this model is multimorbidity, showcasing the indirect affects that SES has on polypharmacy, with an increase in MLTCs resulting in a driver of medication usage. The diagram showcases three possible explanations for the increases in medication usage. Firstly, Path A, showcases the direct effect of SES on multimorbidity, with inequalities in social positioning significantly involved in the development and progression of MLTCs. Discussed in much greater depth in Chapter 6, individuals of lower SES are exposed to many of the fundamental wider determinants of health such as poorer housing, poorer nutritional food and limited health literacy. Poorer lifestyle factors such as smoking, limited physical activity and increased stress levels further potentiate poorer health outcomes. Such factors, which accumulate and over time, further increase the likelihood of the development and progression of MLTCs, such as diabetes, cardiovascular disease and respiratory disease. This increases the need for using multiple medications, whether to treat each different conditions or manage adverse effects associated with increased medication usage.

LTCs, such as diabetes, may require management with antidiabetic medication; for example, the biguanide, metformin. However, individuals with diabetes are twice as likely to experience hypertension, necessitating additional medications; for example, a calcium channel blocker. This highlights how the need to address MLTCs can lead to an accumulation of medicines thereby, increasing the likelihood of polypharmacy. The effect of multimorbidity on polypharmacy is shown with Pathway B. The final direct pathway, SES on polypharmacy is shown *via* Pathway C. SES results in a direct effect on polypharmacy, independent of MLTCs. Therefore, as shown and explained in the work of my systematic review, lower SES can increase the likelihood of polypharmacy for multiple reasons. Often individuals are at risk of poorer access to healthcare services, poorer communication with healthcare professionals and poorer health literacy, all predisposing a risk to inappropriate prescribing practices. Therefore, the mediator model is demonstrating in order to address some of the challenges of socioeconomic inequalities, both indirect (pathway A and B) and direct (Pathway C) effects should be considered.

There are, however, challenges in understanding both the direct and indirect effects of multimorbidity which are reflected in the complexities of building accurate models to capture these dynamics. For example, different chronic conditions can have varying impact on health outcomes and, therefore, medication usage. Such severity and complexity in treatment

management presents issues in accounting for them in the statistical model, and therefore having a binary cut off for multimorbidity may be an oversimplification (*e.g.* some conditions require more treatment than others). For example, an individual with heart failure will be using more medications than an individual with irritable bowel syndrome – thereby showcasing the difficulty in adjusting with a binary cut off in any model. There are however indices that have been created, such as the Charlson Comorbidity Index⁴⁶¹ and the Cumulative Illness Rating Scale⁴⁶² to help quantify multimorbidity; however, these indices also struggle to fully capture the complexities of multimorbidity and thereby have the potential to influence the strength and or direction of effect. Other issues in accounting for multimorbidity within the model can pertain to collinearity with variable such as age can also arise complexity. Age is not only strongly associated with multiple chronic conditions, it also associated with polypharmacy and, therefore, the effects between age and multimorbidity can be difficult to separate. While multimorbidity is an important factor, particularly in the causal pathway of polypharmacy, capturing its adjustment in the model persist.

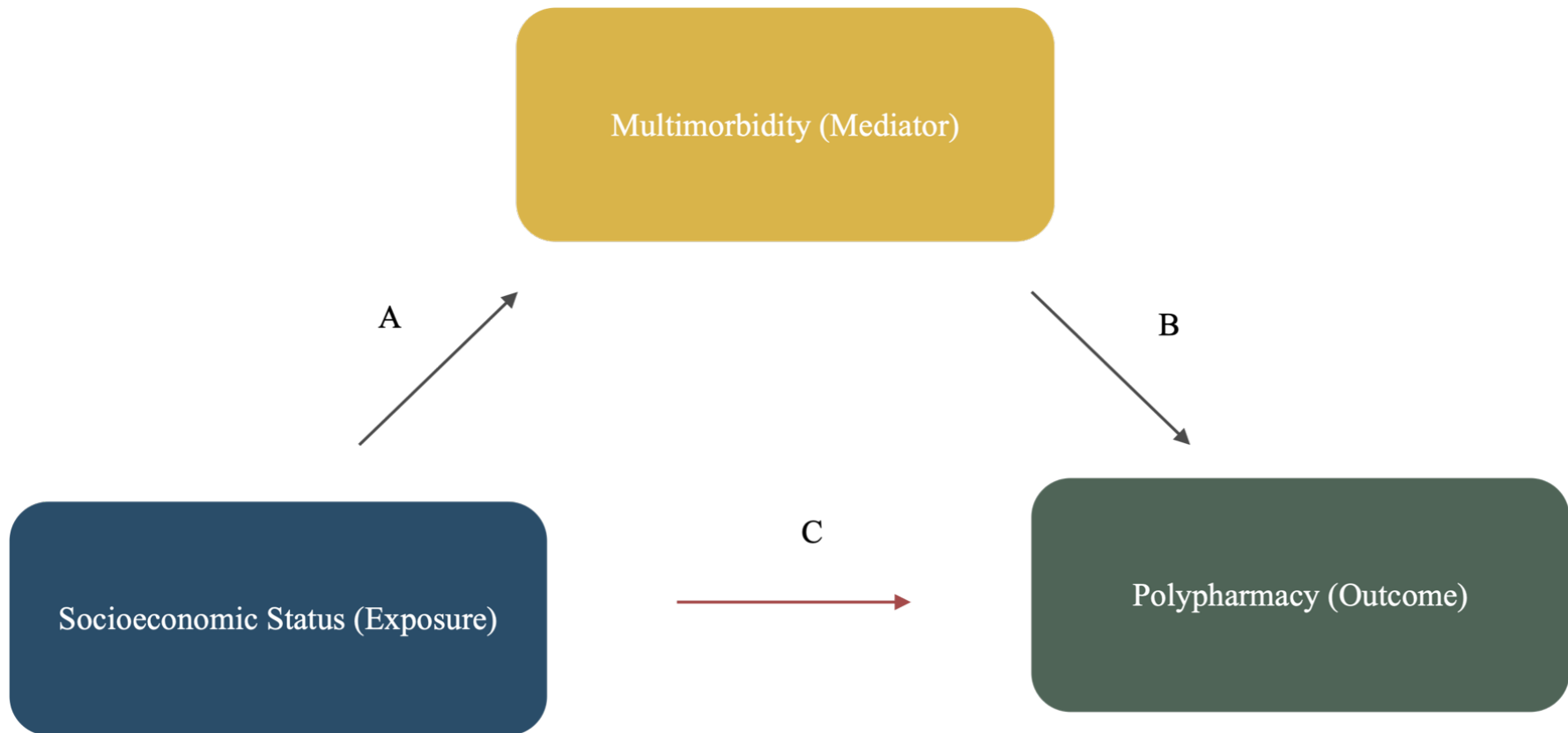


Figure 5. 7: Showing the mediation model for multimorbidity, socioeconomic status and polypharmacy adapted from⁴⁵⁹

5.6 Strengths and limitations

The work of this chapter used the data from CFAS, a multicentre population-based cohort study, including participants from varying sociodemographic backgrounds. The study design reduced the potential of bias, and the large number of participants included in the study allowed for a good representation for analysis. The study included information on participants medication usage, allowing me to use my clinical expertise and knowledge of the literature to explore different medication groupings. Using this method, twenty-two medication categories were created, ensuring all medications were grouped appropriately. As previously referred to in Chapter 4, using education as a proxy for SES allowed for deprivation to be measured at an individual level, as opposed to using a geographical measure such as area level, allowing for conclusions to be drawn at an individual level. There are, however, some methodological limitations, as discussed below.

Firstly, the use of an arbitrary cut off for multimorbidity (2 or more chronic conditions) is reflective of current guidelines^{31,32} however, does not capture the complexities in some health conditions, and thereby has the potential to be an oversimplification; similarly not all health conditions have the same effect on polypharmacy (*i.e.* the number of medications that can be prescribed or required to help manage a condition). Therefore, accounting for such confounders in the model can inevitably affect model accuracy. Secondly, acknowledging that factors, such as multimorbidity, age and sex are valid confounders for the model building, there are also other factors than can indirectly or directly influence polypharmacy that this analysis was unable to capture (*e.g.* healthcare access or inappropriate prescribing practices). Thirdly, while the sample size of CFAS includes a breadth of participants, the subsamples that are included for the subgroups can result in a reduction of statistical power. This inevitably makes it more challenging to identify significant associations and increasing the risk of both type I and II errors, false negative/positive. Therefore, the findings for some of the subgroups may require larger sample sizes to identify a true affect. However, this is a reasoning as to why multiple tests were carried out, with varying model building to help understand the nuances of some of the findings. Lastly, a further limitation in relation to the small sample sizes in subgroups resulted in individuals being categorised as having polypharmacy in a given medication category, if taking at least one medication from the category. Therefore, whilst parts of the analysis suggest that the drug groups can directly contribute to polypharmacy, in reality such observations are a result of one or two medications within the group. As a result, such assumptions can lead to the potential of over estimation of some of the effects of a given drug category.

5.7 Conclusion

Using data from across CFAS, results demonstrate people with increased levels of education are less likely to be in receipt of polypharmacy. Whilst the protective effect of education was more profound in some medication groups than others. Further analysis is warranted on larger populations to understand the intricacies of the observed relationships. Given polypharmacy still remains a persistent and growing public health issue, it is important to explore why such inequalities are present, so appropriate recommendations for policy can be suggested. The goal in a publicly funded healthcare system should ensure that all individuals receive fair and equitable treatment.

Chapter 6. Discussion And Conclusion

6.1 Introduction

Chapter 5 showcased the concluding analysis of this thesis, by investigating how the relationship observed between education and polypharmacy (results described in Chapter 4) differed across specific medication categories. The results highlighted that the overall protective effect of education remained consistent across the majority of the medication categories, although such an effect was not always as pronounced when observing the effect of education on polypharmacy. This chapter aims to bring together the entirety of the work from this thesis by discussing the findings in relation to the research question as previously outlined in Chapter 1.

The aims of this chapter are to:

- I. Provide a summary of the work of this thesis, in the context of the initial thesis aims.
- II. Discuss the significance of the findings, in the context of wider literature.
- III. Discuss the implications of the work for policy and practice.
- IV. Evaluate the strengths and limitations of the work.
- V. Suggest future research directions.

I will first provide a summary of the findings of each chapter. Individual discussions have been included in the respective chapters; however, here I present an overall discussion in relation to the wider literature reflective of the whole thesis. I will then outline the strengths and limitations of this work and, finally, I will provide a discussion in relation to the significance of the findings for both policy and practice. This will provide further reflection on unanswered questions and thereby suggestions for future research direction(s).

6.2 Chapter summaries

This thesis set out to establish whether there is a relationship, and, if so, to what extent, between an individual's socioeconomic status (SES) and being in receipt of polypharmacy. This was met through three main analyses, results of which are provided in the summary sections below.

6.2.1 A systematic review and meta-analysis

Chapter 2 set out to meet the first objective of my thesis: i) systematically review and appraise the literature identifying and exploring the associations between SES and polypharmacy, amongst older people. This chapter was important foundation work for this thesis, by providing

an overview of the literature surrounding the topic and allowing to help identify research gaps to direct further analyses. The chapter identified and concluded with the following:

- Most of the included studies used an arbitrary cut off for defining polypharmacy, the use of five or more medications.
- SES was measured using a variety of ways; for example, income and occupation; however, the most commonly used measure was education. This was a rationale for using education as a SES measure with CFAS data going forward.
- Overall trends demonstrated that individuals with lower SES were more likely to be in receipt of polypharmacy, across a variety of markers.
- Individuals with lower educational attainment had 21% increased odds of being in receipt of polypharmacy when compared to those with a higher education level; OR 1.21 (95% CI 1.15, 1.28; $I^2 = 94\%$).
- Included studies originated from a range of countries, both with publicly and private funded healthcare systems.

6.2.2 Education effect on polypharmacy across CFAS

Chapter 3 introduced data for my primary analyses. This chapter provided rationale for selecting CFAS (*e.g.* due to the longitudinal study design and the detailed medication records provided). The chapter outlined the study aims for my thesis, as well as the sampling and recruitment for CFAS. CFAS was conducted in three geographical locations across the UK – Newcastle upon Tyne, Nottinghamshire and Cambridgeshire, areas with high and low levels of deprivation.

Chapter 4 set out to address the following objectives: i) to determine the association between SES (measured as the number of years of education) and polypharmacy in England; ii) explore longitudinal associations; iii) understand wider public health implications of the work. The following were identified:

- Over the observed 20-year time period, there was a four-fold increase in polypharmacy, with the median number of medications amongst CFAS participants increasing from two to four.
- A higher odds ratio of being in receipt of polypharmacy was identified in individuals with <10 years of education, CFAS I: OR 1.03 (95% CI 0.84, 1.27), CFAS II: OR 1.61 (95% CI 1.44, 1.80).
- After adjusting for confounders, including age, sex and multimorbidity, the effect of education on being in receipt of polypharmacy was still pronounced: individuals with higher education were less likely to be in receipt of polypharmacy.

- PAF was calculated to estimate the proportion of polypharmacy attributed to modifiable (education) and non-modifiable (age and sex) risk factors. Results suggested the effect of education over time had a more pronounced effect on polypharmacy, with a larger proportion of polypharmacy being attributed to education category 2 (10-11 years) in CFAS II compared to CFAS I. As showcased in CFAS I, 12.5% of people with polypharmacy were attributed to education category 1 (<10 years) and 2.7% attributed to education category 2 (10-11 years). In CFAS II, however, 7.2% of polypharmacy cases were attributed to having less than 10 years of education, and 8.9% to having 10-11 years of education

6.2.3 Association between education and polypharmacy across medication categories

Chapter 5 set out to address the objective: i) to identify changes and patterns of the findings between SES and polypharmacy across medication groups, in order to inform policy decisions. This chapter highlighted:

- Some groups of medication were associated with an increased likelihood of polypharmacy compared to other groups of medication. For example, opioids and cardiovascular groups.
- Overall trends demonstrated protective effects of education towards polypharmacy; however, this was more pronounced in some medication groups than others.
- Some of the medication groups demonstrated no protective effect of education (*e.g.* gastrointestinal medication), suggesting other external factors account for these relationships.

6.2.4. Overall findings and reflection on hypotheses

- Polypharmacy has increased over the last 20 years.
- Lower SES is associated with an increased likelihood of being in receipt of polypharmacy.
- Inequalities in polypharmacy appear to be widening over time.
- Some groups of medications may be more problematic in respect to polypharmacy inequalities than others.
- H1: The hypothesis that lower SES is associated with a higher likelihood of polypharmacy was confirmed across both CFAS I and CFAS II, with individuals with fewer years of education exhibiting higher odds of polypharmacy, even after adjustment for confounding variables such as age, sex, and multimorbidity.

- H2: The hypothesis that inequalities in polypharmacy have widened over time was also supported. The effect sizes observed in CFAS II were larger compared to CFAS I, suggesting a strengthening association between SES and polypharmacy over the 20-year period.
- H3: The hypothesis that inequalities would vary by medication group was partially supported. Stronger SES gradients were found in some classes, particularly cardiovascular medications, where conditions are more common among those with lower SES. However, in other groups (*e.g.* gastrointestinal medications), the associations were weaker or non-significant, suggesting a more complex pattern of inequality.

6.3 Findings and implications

The work of this thesis has built upon findings in relation to increased medication usage for individuals with low SES^{196,230,250,251,294} and has also added to the wider issues surrounding health inequalities in the UK.^{4,5} The UK operates a publicly funded healthcare system, which provides free universal coverage at the point of entry,³ yet the findings from my thesis have demonstrated that individuals of lower SES are more likely to be in receipt of polypharmacy, and such inequalities have widened over time. This thesis first presented such inequalities, through the work of Chapter 2, clearly showcasing the implication of social inequalities for medication usage. My analyses went on to show how such relationships are present in the UK and that inequality gaps are widening. Whilst there are some limitations to this work, discussed in each chapter and further below in Section 6.5, this thesis raises important questions focused around how does low SES increase an individual's likelihood of being in receipt of polypharmacy?

There is extensive literature showing that socioeconomic inequalities are persistent in both access to healthcare and health outcomes,^{158,159,163} with people of higher SES often living longer and in better health.^{4,5,312} Chapter 1 of this thesis discussed the multifactorial nature of SES. Therefore, whilst education alone was used as a measure in the work of this thesis, people of lower SES are most likely to face multiple challenges that may contribute to the findings of this work. Individuals from lower SES are often perceived as less able to adopt a healthy lifestyle,^{463,464} live or work in better physical environments.^{465,466} There are also more likely to have precarious employment.^{158,467} Whilst, on the surface it may appear that such individuals are *choosing* to adopt poorer behaviour and practises, these attributes are often driven by the social determinants of health, the conditions in which individuals born, grow, live and work.⁴⁶⁸

Lower SES has been associated with an increased risk of ageing more rapidly, another factor that can have a contributing effect to disease profile and medication usage.⁴⁶⁹ A study conducted by Crimmins *et al*,⁴⁷⁰ investigated biological risk (*i.e.* factors that can lead to disease) in respect of age patterns and found individuals of lower SES, in their forties, have a biological risk factor level similar to that of an individual of higher SES in their sixties. With the presence of increased biological risk factors, such individuals are more prone to developing MLTCs health conditions and thereby inevitably an increased usage of medication, discussed in greater depth in Chapter 5. Essentially, both MLTCs and polypharmacy have intertwining relationships whereby one has the potential to affect the other. For instance, multimorbidity may increase the likelihood of polypharmacy, through the accumulation of chronic conditions which are managed with multiple medications.^{471,472} An individual with multiple, or complicated health conditions can be under the supervision of a variety of medical specialities and therefore can be affected by *fragmented care*, a concept discussed in Chapter 1. Fragmented care is often associated with increased risk of inappropriate prescribing and poor prescribing practices.⁴⁷³ In addition to the multimorbidity burden, an increase in taking more medications, can lead to an increased likelihood of adverse drug reactions, non-adherence, and poorer quality of life through poorer health outcomes; the overall effect of these issues is the worsening or further development of chronic conditions and thus increasing multimorbidity.⁴⁷¹ As represented in Chapter 5, acknowledging this relationship, where possible and within the scope of this PhD, models accounting for this confounding relationship were constructed. However, as previously outlined, such adjustments are not without challenges. This is important when adjusting for a variable that sits on the causal pathway; for example, multimorbidity can act as both a driver and mediator of polypharmacy and, as such, careful consideration of this is required in any interpretation of findings.

Unhealthy lifestyle factors, such as poor-quality diet, in particular the increased likelihood of consuming less nutritious food,^{463,464} are also more commonly observed in individuals of lower SES. These differences are not only observed in the UK, but are also reflected worldwide – even in countries where policies have reduced socioeconomic inequality, (*e.g.* the Scandinavian countries).⁴⁷⁴ Again, such differences can be attributed to, and driven by, the wider determinants of health; for example, limited educational knowledge on the importance of nutritional food resulting in it being difficult to understand the important health implications of a balanced diet.^{475,476} In addition, healthier food options are often attributed to increased cost, thereby individuals of lower SES (who are likely to have lower incomes) can often not afford to purchase nutritional food.^{158,477,478} People of lower SES are also more likely to work multiple

jobs and have longer working hours, which can leave little time to prepare nutritional meals.⁴⁷⁹ Other adverse lifestyle factors that may be common amongst individuals of lower SES include an increased likelihood of smoking,^{468,480,481} excessive drinking⁴⁸² and substance misuse⁴⁸³ – all of which can attribute to poorer health outcomes. Such behaviours, again, are often as a result of wider determinants, such as use smoking and alcohol as a coping mechanism to stress related issues, where this may be linked to financial insecurity, housing instability and precarious employment.^{468,484} Evidence has also showed that marketing and general availability of such products, in particular tobacco, have been targeted toward people living in more deprived neighbourhoods, thereby helping to target sales.^{484,485} This has led to public health initiatives by the WHO, to reduce the accessibility of these products – particularly in more deprived neighbourhoods.⁴⁸⁶ All of the aforementioned lifestyle factors have been strongly attributed to an increased burden of disease, increased medication usage, and thereby increased likelihood of polypharmacy. Such worsening health outcomes have been well documented in individuals with lower SES, whereby often, a combination of multimorbidity and polypharmacy can lead to more rapid deterioration in health (*e.g.* through the lack of coordinated care, or the development of adverse drug reactions).⁶¹ Not only do these issues have the scope to result in poorer health outcomes, they can also impact the socioeconomic position of an individual, (*i.e.* poor health increases the likelihood of unemployment and so forth). A so-called *domino effect* that can present across multimorbidity, polypharmacy and socioeconomic position^{212,418} is the reason consideration was given when adjusting for confounders, as discussed in Chapter 5.

Education has been shown to play a fundamental role in the development and life of an individual; for example, childhood education is critical for cognitive development, and for developing fundamental skills, such as critical thinking and problem solving.^{487–489} Education is also vital in a child's social, emotional and physical development. Such education foundations in the early years also have importance in later life. Education has also been shown to be an important determinant of health literacy, defined as an “individual [having] the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions.”^{490,491} This concept has been discussed throughout this thesis – the importance of health literacy to effectively self-manage conditions,⁴¹⁸ and the close relationship between low education and an individual having reduced health literacy. As explored in more detail in Chapter 4, individuals with higher SES tend to better understand the implications of medication usage and the treatment options that they have available to them. Often, as a result, individuals with higher SES are more likely to have meaningful discussions with healthcare professionals and potentially try non-pharmacological treatment

approaches^{492,493} (e.g. physiotherapy for osteoarthritis rather than using analgesics). Furthermore, adherence to treatment, no doubt improves treatment outcomes, which reduces need of additional medications. Often people of lower SES have reduced adherence to medication, as a result of not necessarily having the same level of health literacy than someone of higher SES. For instance, if we focus on an example of being diagnosed with type 2 diabetes: individuals with slightly raised blood sugar (clinically referred to as *pre-diabetes*) can implement lifestyle changes to reduce blood sugar levels and, thus, reduce the potential of developing of type 2 diabetes. Similarly, increased complexity of disease(s) is more commonly observed amongst individuals with lower SES, (e.g. diabetes requiring more complex treatment). This can – at least in part - be attributed to people of higher SES having better health literacy, enabling them to understand the complications associated with different conditions. For example, with diabetes an increased likelihood of developing microvascular and macrovascular complications such as nephropathy, retinopathy and cardiovascular disease.^{494,495}

In the UK, there are provisions in place to support and overcome the financial barriers to medication use. It is important, however, to acknowledge the other challenges that exist. For example, financial barriers to attending medical appointments (e.g. transportation costs, time off work, childcare responsibilities) can remain significant challenges - particularly for people of lower SES.^{496,497} Looking beyond the example of diabetes, other conditions, such as depression⁴⁹⁸ and hypertension,^{499–501} are often more likely to occur in people of lower SES. The reasons for this are complex but it has been attributed to greater exposure to stress, poor living environments, and reduced access to healthcare resources, creating a viscous cycle.^{498–501} People of lower SES not only have MLTCs, but the conditions are also often more complex to manage, which can result in worse health outcomes.¹⁵⁸

Overall, as stated above, it is important to consider the fact that whilst, such behaviours discussed above are often framed as *choices* such events occur as a result of structural inequalities. It is important to appreciate and acknowledge that the influence of the social determinants extend beyond an individual's behaviour and includes wider elements such as access to healthcare services, education opportunities, health resources that all coerce to support healthier behaviours. Therefore, such health behaviours should not be viewed and evaluated in isolation from the realms of both social and economic elements in which people live, as they have a strong influence on shaping both the opportunities and limitations in peoples' lives.¹⁵⁸

Addressing health inequalities should target broader elements beyond behaviour and include the systems and policies that are in place to access resources related to health and healthcare.

6.4 Significance of findings

The work outlined in this thesis provides further understanding of the complexity surrounding polypharmacy inequalities and has several novel findings. Firstly, this thesis has presented the first systematic review and meta-analysis that examined the association between SES and polypharmacy in a global ageing population. My results are the first of their kind to quantify polypharmacy in the presence of a range of socioeconomic factors. In addition, the thesis has presented analysis of data from a longitudinal cohort study, investigating specifically the relationship between education and polypharmacy, the first of its kind in an English setting. Findings further presented the association between SES and specific medication groups, allowing for policy direction. Overall outputs from this work can be beneficial to both members of the public, policy makers and direct for future research, as summarised below.

Understanding the presence of inequalities in polypharmacy can primarily guide healthcare professionals to undertake more tailored interventions, particularly for those at risk of polypharmacy. Highlighting inequalities in medication usage or across specific medication categories can help guide practice and reduce potential exposure to adverse drug events. In addition, addressing the concerns of medication burden in socially economically disadvantaged populations can help inform policies that enable patients' better access to care.

It is acknowledged that inequalities in healthcare are currently present across the NHS, despite the founding principles of free universal coverage at the point of contact. My research has the potential to influence changes to policy and practice, focused on reducing inequalities in healthcare and with the potential to direct resources more efficiently. Therefore, the findings can provide such individuals with support and potentially reduce negative outcomes associated with polypharmacy (*e.g.* hospitalisations and inappropriate medication use). The findings from this work can also play a wider significance in closely aligned issues, such as multimorbidity. Being able to understand the relationship between polypharmacy and SES can, no doubt, have the potential to reduce multimorbidity, through addressing social determinants of health much earlier in an individual's life. Overall, this may reduce unnecessary burdens on a system that is already under significant pressure.

6.5 Implications of findings for policy and practice

The findings of this thesis highlight the challenges of inequalities in polypharmacy amongst older people and demonstrate the importance of having a plan in place to address these

inequalities. The results have demonstrated that both policymakers and healthcare professionals should be made aware of the polypharmacy inequalities to shape the delivery of future services; for example, through more targeted interventions in ensuring equitable distribution of healthcare services.

A current strategy, under Health Innovation Network,⁵⁰² has set out to support local systems and primary care to focus on problematic polypharmacy within local areas. The programme has three distinct pillars of work, which will be discussed in turn. Firstly, pillar 1 focuses on population health management, by identifying patients at greatest risks of harm from polypharmacy, which then allows for prioritisation of a Structured Medication Review (SMRs). Pillar 2 focuses on education and training, through upscaling healthcare professionals in advocating shared decision making. Through this process, healthcare professionals are then able to work with the patient to assess the potential risks and benefits of treatment to agree appropriate actions regarding each medication. The final pillar aims to work around empowering patients to discuss and share issues and concerns in relation to their medicines. It aims to move away from the perception of “pill for every ill,” the concept of overreliance on medication as a first resort.^{502,503} People likely to be at risk medication-related harm are often identified through the use of specific high-risk medications (*e.g.* anticoagulants) or the location of the patient (*e.g.* a care home). Currently, the socioeconomic status of an individual patient is not considered in this approach, whereas the results from my work suggest that future policies should consider this, going forward.

In addition, as introduced in Chapter 1, SMRs were developed and implemented as part of the NHS Long Term Plan 2019 and aimed to address some of the issues surrounding polypharmacy, medication safety and decision-making.⁵⁵ The introduction of SMRs had the objectives of providing a systematic evidence-based process to ensure regular review and optimisation of medications, and thereby ensured an individual’s medication regimen was safe, effective and appropriate.^{55,504,505} Whilst formally adopted in the UK, similar processes exist in other countries, such as Home Medication Reviews (HMRs) in Australia⁵⁰⁶ whereby medication reviews were introduced to reduce medication-related harm in older people. SMRs are implemented through targeting specific groups of people; for example, individuals in care homes, complex problematic polypharmacy (specifically using 10 or more medications), medication most commonly associated with errors (*e.g.* co-prescribing of anticoagulants and NSAIDs; the use of long-term benzodiazepines; use of opioids without laxatives), people living with severe frailty and or in isolated homes, and those using potentially addictive pain management medications.⁵⁰⁵ The evidence^{504,505} has suggested individuals with LTCs using

multiple medications have better clinical outcomes and show overall improvement of quality of life following a SMR. SMRs have also been shown to reduce hospital admission for those at risk of problematic polypharmacy, reduce the number of overprescribed medications,^{505,507} as well as reducing the overall risk of an adverse drug reaction. SMRs have the potential to reduce waste and improve environmental sustainability by working in partnership with patients to choosing appropriate treatment; for example, to reduce the prescribing of metered dose inhalers.^{505,507} In addition potential cost savings have also been shown for the NHS through the reduction of inappropriate prescribing of medications.^{508–510} Whilst the NHS broader initiatives acknowledge health inequalities, such as through the NHS Long Term Plan, SMRs specifically do not directly target people from lower SES. The results from my thesis – particularly that inequalities in polypharmacy appear to be widening – suggest that policy underpinning the provision of SMRs should consider the SES of a patient when deciding who should be prioritised for a medication review.

Evidence from the literature suggests that interventions to address health inequalities can follow three approaches:^{4,511–513} (i) disadvantage gap, (ii) gradient, (iii) proportionate universalism (a combination of the previous two approaches). The disadvantage gap approach focusses on improving health outcomes for individuals or groups from the most deprived groups of society, to reduce the gap between the most and least affluent individuals. In the context of SMRs as a healthcare intervention, using the disadvantaged gap approach will allow for medication reviews to be targeted at those *worse off*, directing resources to them, with the aim of reducing problematic polypharmacy. However, this approach risks neglecting others along the socioeconomic gradient. Furthermore, using such an approach to direct resources and target SMRs may require the use of different area-level indicators, such as IMD. Such indicators may help to identify people that should be targeted, but as discussed earlier and throughout this thesis, using area level measures presents challenges of ecological fallacy.³³⁷ A gradient approach, on the other hand, recognises the presence of inequalities across the entire socioeconomic gradient,⁵¹³ and thereby sets to improve health outcomes across all levels; however, this will require substantial time and resources to showcase a measurable impact. The last, and potentially most suited approach to address health inequalities through an intervention would that be of proportional universalism.⁴ In the context of SMRs, they are available to all of society (or those who qualify under the current guidance), but additional resource should be directed for healthcare practitioners located in the most deprived areas. This approach has been suggested⁴ to reduce the steepness of the social gradient, essentially reducing inequalities without impacting on other groups of society. In order to implement proportional universalism

approaches in the provision of SMRs, both a strategic and multifaceted approach is required. Firstly, targeted additional funding across GP practices in deprived neighbourhoods (through using areal level indicators such as IMD) could be implemented. Generally, such practices face higher workloads, challenges in recruiting staff and therefore overall limited resources^{514–516} that could potentially hinder the delivery of SMRs. Increased funding for these practices could support the recruitment of healthcare professional, such as pharmacists, that have the competence to undertake SMRs. Further funding could support staff in receiving appropriate training to identify targeted population groups. Furthermore, community pharmacies could potentially play a role in delivering SMRs, given community pharmacies still arguably have good accessibility in deprived neighbourhoods.^{517,518} Providing financial incentives to general practices, as well as community pharmacies could allow for an increased uptake of SMRs for people living in the most deprived neighbourhoods. Lastly, work around outreach in the local community to raise awareness of SMRs and the potential benefits, is crucial in order to address barriers that have been discussed within this thesis, such as health literacy.^{502,512}

6.6 Strengths and limitations

Within each chapter of this thesis, I have discussed the strengths and limitations relevant to the methods used for the analyses, this section therefore provides discussion in relation to my overall thesis.

The work has primarily focused on a British cohort, and to highlight the extent of the issues of health inequalities and polypharmacy, the systematic review and meta-analysis was fundamental in providing a strong foundation for the direction of this research. The work carried out in the review, was invaluable and distinctive, quantifying the relationship between SES and polypharmacy globally. Ensuring the systematic review included international literature, allowed for the inclusion of studies from public, private and state funded healthcare systems. Another strength of the systematic review was the broad inclusion criteria, which were carefully considered to reflect the complexity of different SES measures. Furthermore, the meta-analysis allowed for an extension of the findings of the review, by providing context through numerical weighting showcasing the extent of inequalities in polypharmacy amongst older people.

Analysing relationships over time, enabled me to showcase the widening inequalities that are being witnessed. In my thesis I was fortunate to access data across a 20-year time period, which included significant structural changes across Britain, such as the continuous shift between Labour and Conservative governments, involving many social reforms and notoriously an overall negative impact on health inequalities.⁵¹⁹ Whilst not all the data from CFAS was utilised

in this thesis, the availability of in-depth medication records, such as doses, duration and strengths, allowed me to use my expert knowledge and characterise polypharmacy in ways that I believed were most appropriate. It further allowed me to address some of the unanswered questions emerging from the analysis of Chapter 4, whereby I was able to characterise medication to appropriate categories. Work in this area has always focused on single medication categories, or patient groups, whereas my work was able to draw on multiple medication categories, to understand how the relationships deduced in Chapter 4 reflected across specific groups of medication. In addition, whilst not the sole focus of the work in this thesis, multimorbidity was accounted for through, again, having this information available in the CFAS dataset, allowing for appropriate accountability and reflective confounding relationships to be considered.

Despite multiple strengths of this PhD, there are, however, some limitations to acknowledge; specific methodological limitations have been discussed in each chapter. Firstly, my systematic review and meta-analysis was purposefully constructed to include international studies and did not solely focus on a British population. Whilst education was the most commonly used measure, the close relationship between different socioeconomic factors; for example, education and income, should not be downplayed.¹⁵⁸ Essentially, an individual who has spent more years in education, is often more likely to have an occupation that provides more income and thereby able to afford better healthcare.^{386,387,520–522} This is less likely to be an issue in the UK: despite individuals being able to afford private healthcare, approximately 90% of the population primarily use the NHS for healthcare.^{523,524}

Defining polypharmacy as an arbitrary value was a limitation across this thesis. While it was pragmatic to take a numerical cut off, particularly to help direct decisions, as previously discussed in earlier chapters, a numerical threshold would inevitably fail to differentiate between inappropriate and appropriate polypharmacy. As discussed in Chapter 1, polypharmacy may sometimes be appropriate and reflective of treatment needs; however, it can still present multiple challenges to an individual's life and increase the risk of adverse outcomes. For example, the use of multiple medications can predispose an individual to increased risk of developing an adverse drug reaction and possible hospitalisation.^{43,70} Such individuals may have a diminished quality of life,¹⁰⁵ particularly though the burden of treatment, which can also cause poor adherence. Reduced quality of life can also occur as a consequence of medication adverse effects, which inevitably worsens with the use of multiple medications. The so-called *prescribing cascade*^{525,526} is a phenomenon whereby additional medications are prescribed, not to treat a comorbidity, but, instead, to manage an adverse effect associated with

initial treatment, which further adds to treatment burden. One such example is the use of NSAIDs for pain: individuals can be predisposed to developing hypertension that would require the use of additional therapy to reduce blood pressure.⁵²⁷ Similarly, the use of medications with an anticholinergic burden⁵²⁸ can predispose an individual to develop multiple adverse effects; for example, developing constipation, which requires the use of a laxative. Furthermore, some medications can cause electrolyte imbalance, leaving people to experience symptoms such as fatigue, and muscle weakness.⁵²⁹ The use of multiple medications has also been associated with increased cognitive impairment; for example, additive drug-drug interactions between medication which cross the blood brain barrier causing drowsiness or confusion.⁵³⁰ There is also evidence associated with multiple medications increasing the risk of mortality,^{531–533} with increased risk from certain medications. However, on the contrary, if particular conditions are left untreated this can also result in detrimental outcomes for individual patients. Most recent work⁵³⁴ has also demonstrated the limited value an arbitrary cut off is to assess polypharmacy in prescribing practices, and thereby the future could potentially involve more resource efficient methods through data and artificial intelligence (AI) Incorporating ‘minimum data sets’⁵³⁴ whereby standardised data combines information such as demographics and patient outcomes could be far more clinically meaningful to assess polypharmacy. Future research could aim to move beyond the measurement debate of polypharmacy and aim to assessing appropriateness of medication, although this is challenging when using large data sources.

A further methodological limitation relates to the use of odds ratios to express associations between SES and polypharmacy. While logistic regression is appropriate for binary outcomes, ORs can give the impression of a stronger strength of association when the outcome is common which may lead to misinterpretation of the effect size. Alternative measures such as risk ratios or absolute risk differences offer more intuitive interpretations of relative and absolute risk, but were not used here due to model constraints and data availability. Therefore, interpretation of the ORs with this caveat in mind is important, particularly when comparing effect sizes across subgroups.

As mentioned above, the CFAS datasets are comprehensive and longitudinal, which, despite being primarily collected for dementia research, contained detailed medication data that was used to answer the research question posed in this thesis. However, with medication not being a primary focus of these datasets, there were some limitations directly to the collected data. Firstly, data cleaning was tasking with over 7,000 individuals in each study. Therefore, whilst doses, durations and strengths were provided, understanding the indication of the medication was less clear. Read codes (Chapter 3) were provided in the dataset and provided some direction

with the indication; however, in order to categorise the medication to a correct category; for example, whereby one medication is used for multiple indications (*e.g.* aspirin), this required careful examination, through reviewing the individuals' conditions, doses and duration to appropriately assign the medication to the correct medication category. Furthermore, all medication data, alongside multimorbidity, were self-reported and, therefore, whilst individuals should have knowledge regarding their own health, individuals being interviewed were older and interviewers were not healthcare professionals. Similarly, it was challenging to deduce if a medication was prescribed for prevention or for treatment, which would be a useful step to aid in understanding of medication appropriateness going forward. Whilst there was a good overall deduction on assigning medication, the data collected in CFAS I began as early as 1994, thereby current practice has most certainly changed since and thereby the indications of certain medications may have also changed. Data was also collected regarding the use of over-the-counter medication, which is a large strength for these datasets. However, after closer inspection I was limited in using this within the analysis as it was unclear whether the purchase of over-the-counter medications were aligned with my definition of medication, discussed in depth in Chapter 3; for example, the possibility of including wounds and dressing. In addition, whilst data was analysed using baseline waves of CFAS I and II and recruitment of sample size reflected each other closely, different cohorts were used at both sites.

6.7 Future research

There are many unanswered questions that have come as a result my research, and these will now be discussed in terms of possible future research directions.

Using additional data from CFAS. The analysis carried out used individual data from wave 1 across both CFAS I and CFAS II, to understand how inequalities in polypharmacy have changed overtime. However further longitudinal work could be carried out around using multiple waves of the same cohort, most likely CFAS II, given this study is more reflective of current prescribing practices. Additionally, other indicators of SES could be used, to understand if the same relationships are being observed; for example, through using the IMD, an area level measure of deprivation. Other possible analyses could also include individual measures, such as income and occupation, which were not used in this thesis. Being appreciative of other markers of SES can strengthen the findings of this thesis, despite no single domain being the most appropriate measure; each measure has strengths and limitations, as discussed in Chapter 1 and Chapter 2 of this thesis. In addition, the analysis carried out used 5 medications as an

arbitrary cut off for polypharmacy; using different medication cut off points could be done as sensitivity analyses to determine if there is still an association between SES and polypharmacy.

Further analyses. Future analyses could be considered to better understand the mechanisms underpinning the relationship between socioeconomic status and polypharmacy, through applying causal inference methods. While the current study highlights significant associations, it cannot establish causality due to its cross-sectional design. Techniques such as marginal structural models, instrumental variable approaches, or longitudinal mediation analyses could be employed in future research to examine causal pathways and better isolate the direct and indirect effects of SES on medication burden. These methods would be particularly valuable for identifying actionable targets for reducing inequalities in polypharmacy.

Using other datasets. Having access to additional data, could allow for a higher threshold for polypharmacy to be explored, given that a large majority of individuals in CFAS did not use five or medications – this was particularly evident for CFAS I (median 2). In addition, analysis from findings in Chapter 5 could be explored further, particularly as some medication groups had small number of individuals, making it difficult to draw firm conclusions from the data. In addition, the work of my thesis did not explore negative outcomes of polypharmacy; for example, hospitalisation or mortality – it would be prudent for future research to explore how this varies according to SES. Any further work should, however, include a dataset that could provide access to primary care medication records and therefore an appropriate choice for further work could be the Clinical Practice Research Datalink (CPRD).⁵³⁵

6.8 Concluding remarks

Overall, this PhD has explored the role of socioeconomic status in being in receipt of polypharmacy, through a systematic review and meta-analysis as well as further analysis carried out using a longitudinal data set. My research overall highlighted multiple findings firstly there was socioeconomic inequality present in individuals being in receipt of polypharmacy, overall, a lower educational status was found to be associated with being less likely in receipt of polypharmacy. Secondly, education was a very useful measure of socioeconomic status and was the most commonly used measure globally. Thirdly inequalities were present in polypharmacy whereby individuals of lower education status were more likely to have polypharmacy and over the 20-year time period that had been analysed, this has worsened. Fourthly observations in relation to specific medication categories showed an increased risk of polypharmacy was present amongst specific medication groups than others, further research in this area is required to truly understand the differences across using different types of

medication in order to address the health inequalities that we are experiencing in our health system

Chapter 7. Appendices

Appendix A: Full publication - How should a physician assess medication burden and polypharmacy?

EXPERT OPINION ON PHARMACOTHERAPY
2022, VOL. 23, NO. 1, 1–4
<https://doi.org/10.1080/14656566.2021.1978977>



EDITORIAL



How should a physician assess medication burden and polypharmacy?

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ARTICLE HISTORY Received 27 April 2021; Accepted 7 September 2021

1. Introduction

With the rise of multimorbidity and polypharmacy, people are using more medication than ever before. This has led to the consideration of 'treatment burden' and the impact medication can have on the lives of patients. Treatment burden, broadly defined as the 'workload' associated with healthcare and the impact on patient well-being, can cover many different aspects of treatment including administering medication, financial challenges, and the additional pressures placed upon family members. This editorial seeks to describe the way a physician can assess medication burden, polypharmacy as well as the prescribing of inappropriate medication. The following paragraphs provide a brief description into some of the common challenges that occur with both burdensome treatment and polypharmacy, with the expert opinion allowing us to explain how a physician may assess medication burden and polypharmacy within busy clinical practice, and what should be prioritized for future research.

2. Treatment burden

The rise of multimorbidity – the occurrence of two or more chronic conditions – has led to an increase in medication usage, particularly among older people, whereby polypharmacy is common. The prescribing of multiple medications and the complexities of such treatments have resulted in both practical challenges for patients and financial challenges for healthcare systems. The accumulation of such challenges suggest the issues surrounding multimorbidity have contributed directly to the concept of 'treatment burden.' Whilst there is no formal definition of treatment burden, some researchers have suggested that the 'workload' generated with treatment regimens (e.g. people taking a proactive role in understanding their condition, having an awareness of when to administer their medication, or understanding adverse effects associated with multiple medications) all contribute to the concept of treatment burden [1]. Other factors have been identified in contributing to treatment burden and include: managing medical appointments, enlisting support from families and friends, financial challenges and limitations placed on daily activities [1]. Researchers have previously taken a more systematic approach to defining burdensome treatment and identified a number of categories: *logistical* (organizing

appointments and visits), *technical* (modifying environments to accommodate treatment), *relational* (requiring support from family and friends) and *sense-making* (knowing when to seek help) [2]. Meanwhile, it has been suggested that treatment burden is often subjective and may change according to context. For example, whilst patients may be accommodating towards the use of multiple oral medications, challenges can arise – in terms of treatment burden – when the medications are self-administered through other routes [3]. In addition, treatment burden may not only be problematic for the patient, but also amongst those involved within their care, with many studies showing family carers have experienced deteriorating health, lack of support, self-neglect and, in some countries where healthcare systems are privatized, financial burden associated with treatment [3].

3. Assessing treatment burden

There are many tools available for physicians to use in order to evaluate appropriate treatment and assess the impact it has on patient's lives. For example, a widely available instrument in this regard is the Treatment Burden Questionnaire (TBQ) – a tool originally composed of 13 items on a Likert scale ranging from zero (not a problem) to 10 (a big problem) [4]. The TBQ was initially developed in French from a literature review and qualitative interviews, with a version then developed and validated for English-speaking countries [5]. However, some researchers have suggested the revised version is not particularly user-friendly for patients, given the complex phrasing of some of the questions [6]. The TBQ considers the direct burden associated with taking medication, such as the size of tablets, route of administration and frequency. It further assesses burden associated with broader aspects of healthcare such as laboratory testing, making arrangements for medical appointments, and self-monitoring (e.g. taking blood pressure). These factors can directly contribute to treatment burden, with evidence highlighting a strong relationship between the number of medications taken and increasing treatment burden [7]. Another tool used for assessing treatment burden is the Multimorbidity Treatment Burden Questionnaire (MTBQ), which focuses specifically on people with multimorbidity [6]. The MTBQ was originally developed through a series of qualitative interviews and focus groups and, similarly to the TBQ,

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focuses on potential burdensome factors related to using multiple medications (e.g. patients remembering to take their medication, collecting their prescriptions and attending appointments with healthcare professionals). However, the MTBQ showcases a more user-friendly interface and aims to be quick and concise in capturing the main aspects of treatment burden, making it potentially more transferable to clinical practice. This particular tool was developed and validated in a large multicentre, cluster randomized control trial, the 3D study [8], that aimed to improve the management of patients with multimorbidity within primary care. Another tool, the Patient Experience with Treatment and Self-management (PETS) [9], consists of 48 questions, covering a variety of factors contributing to burdensome treatment; for example, personal relationships and medical expenses. Whilst the aforementioned tools cater for people with different long-term conditions, there are also disease-specific tools that can be used to assess burden (e.g. the Diabetic Treatment Burden Questionnaire) [10]. Although such tools may be useful in helping to determine the treatment burden associated with a specific disease, it is important they are not used in isolation to determine treatment decisions. Tran *et al* have shown a negative correlation between treatment satisfaction and treatment burden [4], which furthers strengthens the argument that such tools should be used as a starting point to facilitate treatment discussions between a physician and their patient.

4. The challenges of polypharmacy

Along with the rise of multimorbidity, there has also been a significant increase in people taking multiple medications [11]. It has been suggested that taking multiple medications – or polypharmacy – is one specific aspect of treatment burden. Similarly, like treatment burden, there is no universal definition for polypharmacy [12], although the most commonly adopted definition is the use of five or more regular medications by a single patient at any one time [13]. In view of the high prevalence of polypharmacy in older populations, a further subcategory, hyper-polypharmacy – the use of 10 or more medications [12,14] – has also been proposed to reflect the increase in medication usage. The pervasiveness of this problem is worldwide, with many researchers commenting on the rise of polypharmacy over the years. The challenges associated with polypharmacy are expected to increase in the future given our aging population: a recent study showed around 50% of over 85 year olds took between

5 and 9 medications (with a median of 6) [15]. With respect to the UK, Guthrie *et al* further showcased the extent of polypharmacy, rising from 11.4% to 20.8% between 1995 and 2010 [16]. Similarly, in Australia, the number of older people experiencing polypharmacy increased by 52% from 2006 to 2017; from 543950 people to 828950 people [17]. Clearly, polypharmacy represents a growing public health concern and is thought to be a significant prescribing challenge faced by physicians, especially those working in primary care given the majority of medications are prescribed in this setting [18]. With an increasing trend of polypharmacy amongst older people, there have been many concerns highlighted; for example, the development of adverse drug reactions and drug–drug interactions [16]. Furthermore, Davies *et al* highlighted the potential harms that polypharmacy can bring for older people, including malnutrition, frailty, inappropriate prescribing and increased risk of hospitalization [19]. In some contexts, the increasing trend of prescribing medications and polypharmacy are appropriate – that is, when the medication is necessary to manage certain long-term conditions and when using the medication is in agreement with the best available clinical evidence. However, it is only possible to truly evaluate medication appropriateness by looking at individual patient circumstances and contexts [20]. It has previously been highlighted that older people, in particular, have increasing levels of polypharmacy, which can result in poorer patient outcomes [21]. Furthermore, Wallace *et al* showed that inappropriate prescribing can have potential negative health outcomes for patients including: an increase in adverse drug reactions, poorer quality of life and increase likelihood to attend the A&E department [22]. Physicians, therefore, have an important role to play when prescribing, as well as reviewing, medication in older people.

5. Assessing polypharmacy and inappropriate prescribing

Whilst there is no agreed consensus on the best approach to evaluate polypharmacy and medication appropriateness, there are a number of explicit and implicit tools developed that identify medications posing a higher risk in certain patient groups. Examples of explicit tools include the STOPP/START criteria [23] and the AGM Beers Criteria® [24]. The AGM Beers Criteria® for potentially inappropriate medication use highlights a number of medications that should be avoided in older people, and in specific circumstances (Table 1). The criteria also provides information on medications to

Table 1. The different lists included in the AGM Beers Criteria®, with specific medication examples [24].

Context of medication use	Examples of specific medications
Medication that should be avoided by the majority of older people	Anticholinergics (e.g. chlorpheniramine, diphenhydramine)
Medication that should be avoided by older people with certain long-term conditions	NSAIDs/COX-2 inhibitors in older people with symptomatic heart failure
Medication that should be avoided in combination with other medications owing to the increased risk of drug interactions	Avoid using opioids with gabapentin or pregabalin owing to increased risk of severe sedation-related adverse effects
Medication that should be used with caution in older people because there is potential for harmful adverse effects	Aspirin for primary prevention of cardiovascular disease owing to increase risk of bleeding
Medication that should be dose reduced or completely avoided in older people with impaired renal function	Ciprofloxacin owing to increase risk of CNS adverse effects (e.g. seizures)

potentially avoid in renal impairment, as well as addressing concurrent medications that could result in toxicity through the development of severe drug–drug interactions. Similarly, the STOPP/START criteria, originally developed by experts in Ireland, provides a list of medications that may be potentially inappropriate to use in older people and, conversely, when it is appropriate to commence certain treatments (e.g. stopping an ACE inhibitor in hyperkalemia; starting an ACE inhibitor in congestive heart failure) [23]. Both tools provide a good foundation for physicians when assessing medication appropriateness. However, with explicit tools being derived from literature, expert opinions, and consensus techniques [25], trying to use a defined set of standards to assess prescribing appropriateness can be challenging. A ‘one size fits all’ approach in this regard can often downplay the complexities of real-world clinical practice and therefore such tools should not replace clinical judgment of the physician. It is also important to consider the interplay between multimorbidity and polypharmacy and whether medications are representative of a patient’s condition. In order to assess the real-life burden that polypharmacy may have on a patient, it is important to consider the use of implicit tools; one example of an implicit tool in this context is the Medication Appropriateness Index [26]. Such tools allow physicians to evaluate the appropriateness of treatment through a patient centered approach and require the use of professional judgment. However, they are often time-consuming and have low reliability and reproducibility [25]; thus, their use can often be limited, particularly with the practical constraints faced in busy clinical practice.

6. Expert opinion

Although there are a range of tools available that can be used to assess polypharmacy, inappropriate prescribing or treatment burden, there is not one specific instrument that assesses all three aspects. When considering treatment burden, tools measure a range of factors; however, they cannot cover all possible elements that contribute to burden, as this is subjective to each patient. Whilst polypharmacy may contribute to an aspect of burden, the role that tools, such as the STOPP/START criteria, the Beers criteria and the Medication Appropriateness Index, have are useful in assessing medication appropriateness. However, just because a prescribed medication is clinically appropriate does not necessarily mean that it is free of burden; similarly, a medication that is considered clinically inappropriate might not necessarily be burdensome. Future work is required to evaluate the relationship between polypharmacy, inappropriate prescribing and burdensome treatment, and whether burden itself should be considered when a physician assesses inappropriate prescribing and polypharmacy. The relationship between a physician and a patient is important to support joint working to assess if a medication is burdensome. Developing one single integrated tool – assessing polypharmacy, inappropriate prescribing and treatment burden – may on the surface appear beneficial. However, it would not necessarily capture the individual contexts and the complex challenges faced by patients or be necessarily appropriate for implementing into busy clinical practice. The practical utility of an integrated tool may therefore be of limited value. In conclusion, while there are

many tools available to a physician to assess treatment burden, polypharmacy and inappropriate prescribing, there is no universal instrument covering all aspects that has been adopted and embedded into clinical practice. To improve the holistic care of patients, it is important that the tools described in this work should only be used as a mechanism to enhance existing medication-related conversations and consultations between physicians and their patients, and not necessarily replace them.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This work is supported by a grant from the National Institute of Health Research (NIHR) Applied Research Collaboration (ARC) for the North East and North Cumbria (NENC).

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Appendix B: Full publication – Are there socioeconomic inequalities in polypharmacy among older people? A systemic review and meta-analysis.

Iqbal et al. *BMC Geriatrics* (2023) 23:149
<https://doi.org/10.1186/s12877-023-03835-z>

BMC Geriatrics

RESEARCH

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Are there socioeconomic inequalities in polypharmacy among older people? A systematic review and meta-analysis



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Abstract

Background Socioeconomic status (SES) may influence prescribing, concordance and adherence to medication regimens. This review set out to investigate the association between polypharmacy and an individual's socioeconomic status.

Methods A systematic review and meta-analyses of observational studies was conducted across four databases. Older people (≥ 55 years) from any healthcare setting and residing location were included. The search was conducted across four databases: Medline (OVID), Web of Science, Embase (OVID) and CINAHL. Observational studies from 1990 that reported polypharmacy according to SES were included. A random-effects model was undertaken comparing those with polypharmacy (≥ 5 medication usage) with no polypharmacy. Unadjusted odds ratios (ORs), 95% confidence intervals (CIs) and standard errors (SE) were calculated for each study.

Results Fifty-four articles from 13,412 hits screened met the inclusion criteria. The measure of SES used were education (50 studies), income (18 studies), wealth (6 studies), occupation (4 studies), employment (7 studies), social class (5 studies), SES categories (2 studies) and deprivation (1 study). Thirteen studies were excluded from the meta-analysis. Lower SES was associated with higher polypharmacy usage: individuals of lower educational backgrounds displayed 21% higher odds to be in receipt of polypharmacy when compared to those of higher education backgrounds. Similar findings were shown for occupation, income, social class, and socioeconomic categories.

Conclusions There are socioeconomic inequalities in polypharmacy among older people, with people of lower SES significantly having higher odds of polypharmacy. Future work could examine the reasons for these inequalities and explore the interplay between polypharmacy and multimorbidity.

Keywords Medication Usage, Socioeconomic Status, Health Inequalities, Polypharmacy, Ageing, Meta-analysis

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Introduction

The burgeoning impact of polypharmacy, often defined as the use of five or more medications [1], has become an increasing challenge for healthcare professionals. With the growing usage of medication, the term hyper/excessive polypharmacy has also been used, which refers to people typically using ≥ 10 medication at any one time [2]. The increased use of multiple medications has raised some concerns, particularly across older people, as this population is more likely to develop adverse drug events, including drug-drug interactions, non-adherence and falls [3, 4].

Increasing numbers of people are experiencing polypharmacy and this challenge has become a global public health concern. In the United Kingdom (UK), for example, the number of people experiencing polypharmacy has quadrupled over a 20-year period [5], while an Australian based study [6] highlighted a 52% increase in polypharmacy between 2006–2017.

In some contexts, the increasing trend of prescribing medication and the resulting polypharmacy is appropriate and necessary; multiple medications are often required to manage long-term conditions. As such, with rising multimorbidity and increasing life expectancy, polypharmacy may be clinically appropriate and thus reflective of treatment needs [7, 8]. However, there are situations where polypharmacy may be inappropriate and problematic; it is only possible to evaluate medication appropriateness by looking at individual patient preferences, circumstances, and contexts [9].

While previous studies have shown that certain patient-based factors, such as age, are associated with increased levels of polypharmacy, the role of socioeconomic factors such as education, income and occupation, is less clear. The literature suggests that such socioeconomic factors could play an important role in polypharmacy, with studies highlighting factors such as income [10–14] and employment [15–17] as possible contributors to the prevalence of polypharmacy. For example, a Swedish study [18] investigated the relationship between polypharmacy, socioeconomic status (SES) and inappropriate medication usage. The results showed that lower levels of education were associated with increased levels of polypharmacy and potential drug-drug interactions. Further to this, some authors have highlighted the rising concerns of low SES on the adverse impact on life expectancy, access to healthcare and multimorbidity. One study [19] has showed that low SES was associated with 2.1-year reduction in life expectancy for men and women aged 40–85 years. Such an impact is important given there is potential that those of lower SES being exposed to higher levels of polypharmacy and thus the associated harms.

Whilst there is significant academic interest on this topic, there is no single review and meta-analysis which

draws together the current literature around polypharmacy and how prevalence may differ according to SES. Therefore, this systematic review and meta-analysis aimed to investigate the association between socioeconomic status and the prevalence of polypharmacy, in older people.

Methods

This review was registered with accordance to The International Prospective Register of Systematic Reviews PROSPERO (CRD42021285455) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data sources

A literature search was conducted across the following databases: Medline (OVID), Web of Science, Embase (OVID) and CINAHL, from inception to July 2021. The search was developed around three key terms: 'polypharmacy' 'socioeconomic status' and 'ageing' which captured the literature surrounding the key purpose of this review. The full search strategy can be found in Supplementary 1. Additional articles were identified through hand searching reference lists and forward citations of eligible articles.

Study selection

Studies included in this review met the following criteria:

- Population: older people. In line with previous reviews [20] older people were defined as people aged ≥ 55 years. Studies required at least 50% of participants to be over ≥ 55 years.
- Exposure: lower socioeconomic status
- Comparison: higher socioeconomic status
- Outcome: receipt of polypharmacy
- Setting: all settings were considered, irrespective of country, private or public healthcare systems.
- Study type: all observational study types including cohort and cross sectional.

To be eligible for inclusion, articles were required to be available as full text and published in English. After discussion with the review team, prescribing practices before 1990 were considered to be less relevant to address the review question, and hence articles published before 1990 were not eligible for inclusion.

Selection criteria and screening

Records were uploaded to End Note and duplicates were removed. Rayyan QCRI was used for screening of titles

and abstracts, which was conducted by one reviewer (AI). Two reviewers (CR,ZI) independently reviewed 25% of extracted articles. Full text screening was conducted by one reviewer (AI) and checked by another reviewer (CR,ZI); any discrepancies were resolved through discussion and consensus (AT). The level of agreement between the review team was determined by a Kappa score – 0.85 showing excellent agreement.

Data extraction and quality appraisal

The following information was extracted using a pre-populated data extraction form: first author, year, study data, participant characteristics, socioeconomic measure, main data extraction in relation to SES and polypharmacy. Data extraction was conducted by one reviewer (AI) and checked by the review team (CR,ZI); any discrepancies were resolved through discussion and consensus (AT). For the quality appraisal, one reviewer (AI) used the relevant critical appraisal tool from the Joanna Briggs Institute (JBI), which was checked (CR,ZI); any discrepancies were resolved through discussion and consensus (AT).

Statistical methods

Random effects meta-analysis was performed to assess the association between a given socioeconomic factor and polypharmacy. Eligibility criteria for studies to be

included in the meta-analysis were as follows: i) unadjusted raw data reporting polypharmacy rates for an individual socioeconomic factor ii) total participants/information to identify total number of participants displaying polypharmacy and no polypharmacy for the socioeconomic factor being investigated. Unadjusted odds ratios, confidence intervals and standard errors were then calculated independently by two reviewers (AI, FM). I^2 was calculated to determine the degree of heterogeneity amongst the studies. Odd ratios were calculated by comparing the bottom 25% of each study population to the remainder participants for each given socio-economic factor. Log odd ratios and SE were then entered into Revman 5.4 to generate forest plots.

Results

Literature search

Searches retrieved 20,064 citations. After de-duplication, 13,412 articles were screened for eligibility based on title and abstract. A further 187 articles were progressed to full text screening, which resulted in 54 articles meeting the inclusion criteria (Fig. 1); 13 articles were excluded from the meta-analysis.

Study characteristics

The 54 included studies used a range of measures to assess SES factors. Fifty studies focussed on education [16, 18,

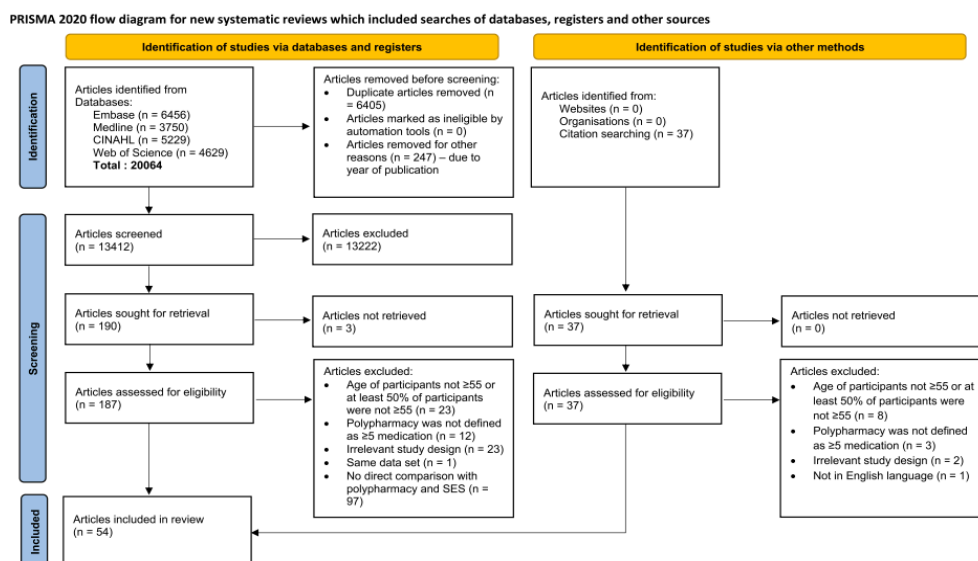


Fig. 1 Study selection and exclusion according to the PRISMA flow diagram

20–67], 18 studies on income [16, 23, 30, 32–34, 37, 41, 46–48, 50, 53, 61, 63, 64, 66, 68], 6 on wealth [22, 27, 45, 57, 67, 69], 4 studies on occupation [23, 44, 48, 57], 7 studies on employment [16, 17, 49, 58, 60, 63, 66], 5 studies on social class [17, 25, 36, 38, 60], 2 used SES categories [31, 70] and 1 used area-level deprivation [20]. Studies were conducted across a range of countries as follow: India [60, 66], Jordan [21], Netherlands [70], Sweden [18, 23, 39, 52], Spain [25], Belgium [26, 30], Pakistan [29, 68], UK [17, 20, 36, 38, 69], China [33, 44, 59, 65], Japan [46, 67], Singapore [40], Kuwait [42], Malaysia [43, 58], Poland [45], Togo [47], Saudi Arabia [55, 61], Taiwan [56], Vietnam [57]. Most studies were conducted within Brazil [28, 31, 32, 37, 41, 48, 50, 51, 53, 62, 63] and the US [16, 24, 27, 34, 35, 49, 54, 64]. One study included participants from across Europe and Israel [22]. Studies ranged in size from 59 [24] to 1,742,336 [52] participants. Full study characteristics can be found in Supplementary 2.

Quality appraisal

The included 54 studies scored in the range 6–8, out of a possible 8 (S2). Articles often scored poorly on

identifying and reporting confounders. The majority scored well on displaying inclusion criteria, using appropriate statistical analysis, and describing subjects and setting.

Association between education and polypharmacy

Fifty studies [16, 18, 20–67] investigated the association between education and polypharmacy, 38 studies [18, 21–31, 33, 35, 37, 40–42, 44, 46–48, 50–55, 57–61, 63–67] were eligible for meta-analysis giving a pooled OR of 1.21 (95% CI 1.15–1.28; $I^2=94\%$) for receipt of polypharmacy in those of lower education when compared to higher education (Fig. 2).

Association between income and polypharmacy

Eighteen studies [16, 23, 30, 32–34, 37, 41, 46–48, 50, 53, 61, 63, 64, 66, 68] investigated the association between income and polypharmacy, 12 studies [23, 30, 33, 37, 41, 46, 47, 50, 53, 61, 64, 66] were eligible for meta-analysis giving a pooled OR of 1.10 (95% CI 0.98–1.23; $I^2=46\%$) for receipt of polypharmacy in those of a low compared to high income (Fig. 3).

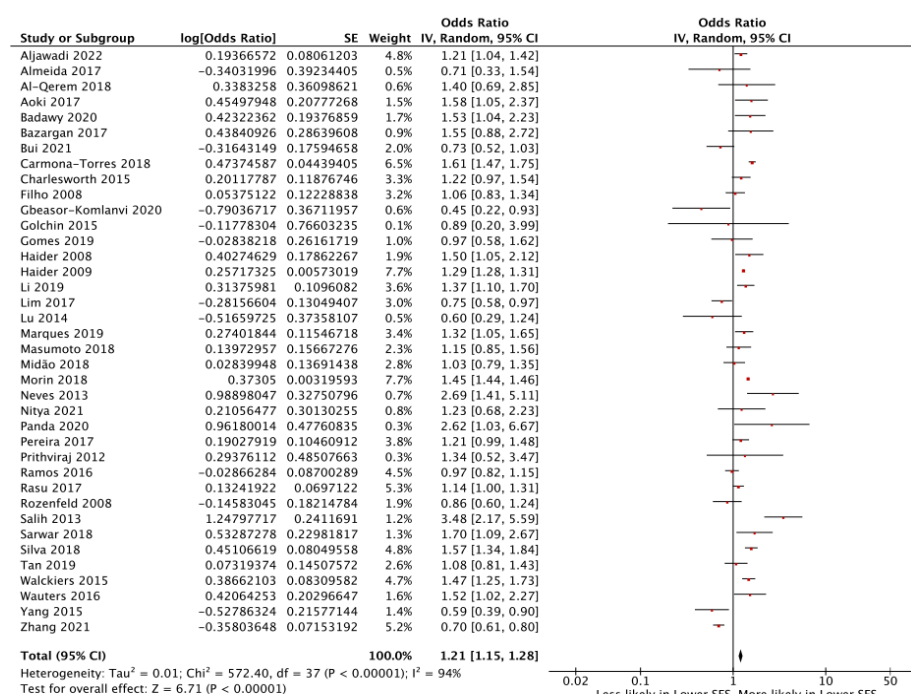


Fig. 2 Forest plot showing the likelihood of polypharmacy according to education

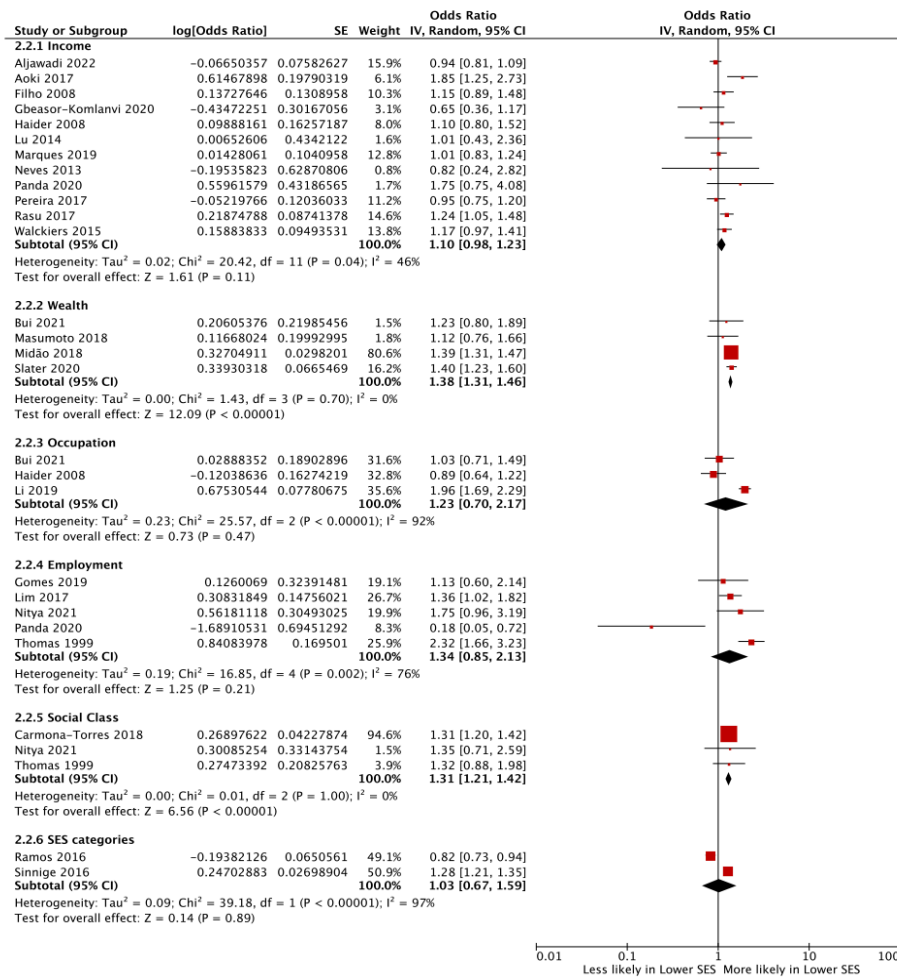


Fig. 3 Forest plot showing the likelihood of polypharmacy according to income, wealth, occupation, employment, social class and SES categories

Association between wealth and polypharmacy

Six studies [22, 27, 45, 57, 67, 69] investigated the association between wealth and polypharmacy, 4 studies [22, 57, 67, 69] were eligible for meta-analysis, giving a pooled OR of 1.38 (95% CI 1.31–1.46; $I^2 = 0\%$) for receipt of polypharmacy in those of less wealthier backgrounds (Fig. 3).

Association between occupation, employment, and polypharmacy

Four studies [23, 44, 48, 57] reported the association between occupation and polypharmacy, and 7 [16, 17, 49, 58, 60, 63, 66] reported the association between employment and polypharmacy. Three studies [23, 44, 57] assessing occupation and 5 studies [17, 58, 60, 63, 66]

assessing employment were eligible for meta-analysis (Fig. 3). A pooled OR of 1.23 (95% CI 0.70 - 2.17; $I^2=92\%$) was calculated for those in receipt of polypharmacy from lower occupations. Similarly, the pooled OR was 1.34 (95% CI 0.85–2.13; $I^2=76\%$) for receipt of polypharmacy in unemployed, compared to employed, individuals.

Association between social class, SES and polypharmacy

Five studies [17, 25, 36, 38, 60] reported the association between social class and polypharmacy, and 2 studies [31, 70] focused on SES and polypharmacy. Three studies [17, 25, 60] assessing social class were eligible for meta-analysis and the pooled OR was 1.31 (95% CI 1.21–1.42; $I^2=0\%$) for receipt of polypharmacy in those of lower social class compared to higher social class. Two studies [31, 70] assessing SES were eligible for meta-analysis and the pooled OR was 1.03 (95% CI 0.67–1.59; $I^2=97\%$) for receipt of polypharmacy for those of lower, compared to higher, SES.

Discussion

Main finding

This systematic review and meta-analysis found that, overall, polypharmacy is associated with lower socioeconomic status. In particular, pooled estimates revealed a significant association when using education as a marker of SES: those of lower educational backgrounds had 21% higher odds to be in receipt of polypharmacy when compared to those of higher education. Significant associations were also observed when wealth and social class were used as SES measures. Similar trends were observed for income, occupation, employment and SES categories, although the results did not reach statistical significance. The majority of the studies included in this review used education as a marker of socioeconomic status, while fewer studies used socioeconomic measures such as occupation, income and social class.

Comparison with other reviews

To the best of our knowledge this is the first systematic review and meta-analysis that has been carried out exploring the relationship between polypharmacy and socioeconomic status; focusing on an ageing population irrespective of co-morbidities or drug class. A previous review revealed that there were significant associations between socioeconomic factors, such as education and deprivation, and multimorbidity whereby people of lower socioeconomic status have a higher risk of multimorbidity [71]. This work, unlike our review, did not focus on polypharmacy or older people, but can be used as a possible justification of our findings. Given, older people with multimorbidity are more likely to use more medications, and people of lower SES have higher

risk of developing multimorbidity, may help explain – at least in part – some of our findings. However, the interplay between multimorbidity and polypharmacy is likely to be complex and should be the subject of further investigation. For example, those of higher SES may still have high levels of multimorbidity but their social status has the potential influence to ensure that they can better manage their conditions, have access to better healthcare services, reduced waiting time to see healthcare professionals, all factors of which have the potential to influence medication usage. Some of the literature has touched on the aspect of healthcare access [72] and the so called ‘wealth health’ gradient, showcasing that socioeconomic status has a direct influence on healthy ageing. Others have also revealed the potential influence that patients have on the medication that is prescribed to them [73, 74]. Those of higher SES are often better at navigating healthcare systems (both public and private) and are potentially more able to obtain multiple clinical opinions for their concerns resulting in an increased likelihood of being prescribed the medications they want or believe they need. Prosser et al. [75] showcases prescribing of medication is often patient mediated, and thus more costly, beneficial treatment may be prescribed to those that are more proactive in their health, often those of higher SES.

Other reviews that have been conducted which investigate treatment adherence and subsequent factors have all revealed that socioeconomic status plays an integral role [76–79]. Whilst these reviews are not primarily focused on polypharmacy or the ageing population, they provide important information on medication usage: treatment adherence. The reviews have shown statistical significance whereby socioeconomic factors, such as lower income, unemployment, and lower education, are associated with medication non-adherence. It can therefore be suggested that non-adherence to medication could play an important role in deteriorating health and has a subsequent effect in the rise of multimorbidity and polypharmacy. It is also worth noting that, although we calculated unadjusted odds ratios for the meta-analysis, many of the studies included in this review did adjust for multimorbidity in their analysis and still yielded statistical significant results—with a higher odds of polypharmacy in older people of lower socioeconomic status.

Individual socioeconomic factor results

To conceptualise socioeconomic status, this systematic review included studies employing different methods to assess socioeconomic status, including education, income, and employment.

With respect to education status, the overall findings of the review revealed that older people with lower educational backgrounds are of greater odds of polypharmacy.

The literature suggests there are several reasons as to why this may be the case. Firstly, individuals with lower levels of education can be viewed as playing a less proactive role in preventive measures to improve/maintain their health, and thus are of greater risks of developing conditions that would likely result in them taking multiple medications [80, 81]. Secondly, some have suggested those of lower education are less likely to challenge healthcare professionals and be less involved with shared decision making [82, 83]. This, therefore, may have the potential for people to take additional medication without requiring a detailed explanation from their healthcare professional [84, 85]. Such patients are also seen to be less concerned in asking key questions regarding their medical care [86], thus it can be questioned whether they are truly aware of the potential additional harm that may be associated with taking multiple medications. However, other researchers have argued that people with lower levels of education may be less likely to approach healthcare professionals for medication and thus inevitably display lower levels of medication usage [87].

Previous work has shown that people entitled to free medications were more likely to display higher levels of polypharmacy [88]. In most instances, unemployed individuals, or individuals with lower income would be entitled to free prescription coverage and as there is no direct cost to the patient, they would be more likely to show higher medication usage. These findings can be used to support our results when assessing employment or income as a marker of socioeconomic status—that is unemployment or low income is associated with more polypharmacy. Out of pocket cost of medication, has a clear influence on the likelihood of individuals not wanting to take more medication. However, this can also be influenced by education attainment, and often people with higher income are more likely to have higher education attainment. As previously discussed, people with higher education attainment maybe more proactive in making decisions about their health and also be aware of the risks associated with polypharmacy.

Strengths and limitations

This systematic review and meta-analysis showcased comprehensive findings in relation to the association of socioeconomic status on polypharmacy in older people. Whilst our approach was comprehensive and the methodology robust, we do acknowledge that our work has limitations. Firstly, the definition we used to conceptualise older people (≥ 55 years) was arbitrary – the appropriateness of which can be debated. It is important to acknowledge that our approach was in keeping with previous reviews in the field of older people and polypharmacy. For example, the work of Davies et al. was used

to help establish our definition of older people; our initial scoping searches also supported using the ≥ 55 years definition, as this conservative approach enabled the inclusion of key literature, and ensured that articles were not excluded for being too broad in their inclusion criteria. Another advantage to this review was that included studies were from a variety of low, middle, and high-income countries. Whilst this is advantageous, it is important to acknowledge that studies undertaken in a variety of healthcare systems have been included, this also contributes to the large heterogeneity observed. In some cases, it was challenging to ascertain how studies assessed different socioeconomic factors; for example, the definition of 'high' education varied across studies. To account for these variations and differences, when conducting the meta-analysis, the decision was made to compare the lowest 25% of each population (in terms of SES factor) to the remainder of the population. This approach also ensured that all participants within the included studies were included and factored into the meta-analysis.

Future work

Whilst this review highlights that there are socioeconomic inequalities in polypharmacy – whereby people of lower SES are more likely to receive polypharmacy, the work does not explore the potential causes of this. It would be useful to understand how people of lower socioeconomic status engage with medication reviews, with such reviews having the potential to aid deprescribing decisions and possibly reduce polypharmacy. Previous work has shown that certain populations (e.g. ethnic minority communities), struggle to engage in medication review services [89, 90]. Whilst this review has demonstrated that there is socioeconomic inequalities in polypharmacy, it is important that policies be put in place to enable healthcare professionals to work towards reducing such inequalities and not exacerbate them further. At present, certain patient demographic (e.g. age) or medication-related factors (e.g. using a high risk medication) may trigger a medication review. Our work suggests that other factors, such as SES, could be used to trigger for medication related review services. Indeed, health inequalities have been at the forefront of healthcare policy formulation for many years, particularly in the UK, especially since the wide-spread appreciation of the existence of a 'postcode lottery' [91]. This concept suggests that healthcare standards and subsequently polypharmacy and medication utilisation can be influenced by an individual's geographic location. For example, people living in the North of England are more likely to use an opioid analgesic, compared to people living the South of England [92]. If factors such as education/poor healthcare literacy play a critical role in polypharmacy it is important

for healthcare professionals to understand the needs of their patients and factor these into consultations.

Conclusion and implications

There are significant socioeconomic inequalities in polypharmacy among older people, whereby people with lower SES have higher odds of being in receipt of polypharmacy. This association was found using a range of markers of SES including education, and social class. Future work could examine the reasons for these inequalities and explore the interplay between polypharmacy and multimorbidity.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-023-03835-z>.

Additional file 1.

Additional file 2.

Acknowledgements

Not applicable.

Authors' contributions

AI and AT were a major contributor in writing the manuscript and conducting the search. HK, BH contributed to the search strategy. ZI and CR contributed to reviewing included papers and data extraction. FM and AI both contributed to the meta-analysis. This article has been approved by all the co-authors, meets all conditions of the ICMJE and we can also confirm that there is no conflict of interest. The author(s) read and approved the final manuscript.

Authors information

Not applicable.

Funding

This research is funded by the National Institute for Health and Care Research (NIHR) [Applied Research Collaboration North East and North Cumbria (NIHR200173)].

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 10 September 2022 Accepted: 20 February 2023
Published online: 18 March 2023

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Appendix C: PRISMA checklist



PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

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You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Section/Topic	Item No.	Checklist item	Reported on Page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	35
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	36-37
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	39-41
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	37-46
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	37-47
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	182-187
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	38-41, 187
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	42-61
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	37-41
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	45-46

Section/Topic	Item No.	Checklist item	Reported on Page No.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	43-44
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	45-46
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	45-46
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	45-46
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	47
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	48-57
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	65, 194-199
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	63-66
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	63-66
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	194-199
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	194-199
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	66-67
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	70-72
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	67-70
FUNDING			

Section/Topic	Item No.	Checklist item	Reported on Page No.
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Once you have completed this checklist, please save a copy and upload it as part of your submission. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Appendix D: Search strategies used for systemic review and meta-analysis across all databases.

Embase (OVID)

1. exp Socioeconomic Factors/ or socioeconomic*.mp.
2. social class.mp.
3. *social class/ or *social factors/ or *sociology, medical/
4. socioeconomic factor*.mp.
5. socioeconomic statu*.mp.
6. income.mp. or *Income/
7. (income adj6 category).mp.
8. household income.mp.
9. employment status.mp.
10. Unemploy*.mp.
11. Employment characteristic*.mp.
12. ((Education or Employ* or Unemploy*) adj6 (demographic or variable)).mp.
13. education.mp.
14. Education level.mp.
15. index of multiple deprivation.mp.
16. socioeconomic position.mp.
17. Carstairs index.mp.
18. townsend index.mp.
19. area level deprivation.mp.
20. wealth.mp.
21. occupation*.mp. or *Occupations/
22. poverty level.mp.
23. exp polypharmacy/
24. polypharmacy.mp.

25. hyperpolypharmacy.mp.
26. medic* usage.mp.
27. medic* utili*.mp.
28. ((number or multiple or more or total or prescrib* or many or several) adj2 (medicine* or medication* or drug*)).mp.
29. polypharmacotherapy.mp.
30. polymedic*.mp.
31. polydrug*.mp.
32. polytherapy.mp.
33. multimedico*.mp.
34. exp "Aged, 80 and over"/ or exp Aged/
35. exp Retirement/
36. exp Veterans/
37. Geriatrics/
38. exp Residential Facilities/
39. exp Nursing Homes/
40. ((residential or nursing or care) adj home*).mp.
41. exp Long-Term Care/
42. ((old* or elder*) adj2 (adult or person* or people* or age*)).mp.
43. "aged, over 55".mp.
44. *Poverty/ or poverty.mp.
45. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 44
46. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
47. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
48. 45 and 46 and 47

Medline (OVID)

1. exp Socioeconomic Factors/ or socioeconomic*.mp.
2. social class.mp.
3. *social class/ or *social factors/ or *sociology, medical/
4. socioeconomic factor*.mp.
5. socioeconomic statu*.mp.
6. income.mp. or *Income/
7. (income adj6 category).mp.
8. household income.mp.
9. employment status.mp.
10. Unemploy*.mp.
11. Employment characteristic*.mp.
12. ((Education or Employ* or Unemploy*) adj6 (demographic or variable)).mp.
13. education.mp.
14. Education level.mp.
15. index of multiple deprivation.mp.
16. socioeconomic position.mp.
17. Carstairs index.mp.
18. townsend index.mp.
19. area level deprivation.mp.
20. socioeconomic*.mp. or exp socioeconomics/
21. wealth.mp.
22. occupation*.mp. or *Occupations/
23. poverty level.mp.
24. poverty.mp.
25. exp polypharmacy/
26. polypharmacy.mp.

- 27. hyperpolypharmacy.mp.
- 28. medic* usage.mp.
- 29. medic* utili*.mp.
- 30. ((number or multiple or more or total or prescrib* or many or several) adj2 (medicine* or medication* or drug*)).mp.
- 31. polypharmacotherapy.mp.
- 32. polymedic*.mp.
- 33. polydrug*.mp.
- 34. polytherapy.mp.
- 35. multimedico*.mp.
- 36. exp "Aged, 80 and over"/ or exp Aged/
- 37. exp Retirement/
- 38. exp Veterans/
- 39. Geriatrics/
- 40. exp Residential Facilities/
- 41. exp Nursing Homes/
- 42. ((residential or nursing or care) adj home*).mp.
- 43. exp Long-Term Care/
- 44. ((old* or elder*) adj2 (adult or person* or people* or age*)).mp.
- 45. "aged, over 55".mp.

CINAHL

- S1 TX socioeconomic* OR "social class*" OR poverty OR wealth OR "socioeconomic factor*" OR "socioeconomic statu*" OR income OR "household income" OR "employment status" OR unemploy* OR "employment characteristics" OR occupation* OR education OR "education level" OR "index of multiple deprivation" OR "socioeconomic position" OR "Carstairs index" OR "townsend index" OR "area level deprivation" OR "poverty level" OR poverty
- S2 TX income N6 category
- S3 TX ((Education or Employ* or Unemploy*) N6 (demographic or variable))
- S4 TX ((number or multiple or more or total or prescrib* or many or several) N2 (medicine* or medication* or drug*))
- S5 TX polypharmacy OR hyperpolypharmacy OR "medic* usage" OR "medic* utili*" OR polypharmacotherapy OR polymedic* OR polydrug* OR polytherapy OR multimedic*)
- S6 TX "aged, over 80" OR retirement OR veteran OR geriatric* OR "residential home" OR "nursing home" OR "long term care" OR aged OR "age, over 55"
- S7 TX (residential or nursing or care) N home*)
- S8 S1 OR S2 OR S3
- S9 S4 OR S5
- S10 S6 OR S7
- S11 S8 AND S9 AND S10

Web of Science

1. TS=(socioeconomic* OR "social class*" OR poverty OR wealth OR "socioeconomic factor*" OR "socioeconomic statu*" OR income OR "household income" OR "employment status" OR unemploy* OR "employment characteristics" OR occupation* OR education OR "education level" OR "index of multiple deprivation" OR "socioeconomic position" OR "Carstairs index" OR "townsend index" OR "area level deprivation" OR "poverty level" OR poverty)
2. TS=((Education or Employ* or Unemploy*) NEAR/6 (demographic or variable))
3. TS=(polypharmacy OR hyperpolypharmacy OR "medic* usage" OR "medic* utili*" OR polypharmacotherapy OR polymedic* OR polydrug* OR polytherapy OR multimedic*)
4. TS=((number or multiple or more or total or prescrib* or many or several) NEAR/2 (medicine* or medication* or drug*))
5. TS=(income NEAR/6 category)
6. TS=("aged, over 80" OR retirement OR veteran OR geriatric* OR "residential home" OR "nursing home" OR "long term care" OR aged OR "age, over 55")
7. TS=((residential or nursing or care) NEAR home*)
8. #1 OR #2 OR #5
9. #3 OR #4
10. #6 OR #7
11. #8 AND #9 AND #10

Appendix E: Decision process used to aid prioritisation of included studies in systematic review and meta-analysis.



Appendix F: Critical appraisal tool used in systematic review and meta-analysis, JBI cross sectional studies.

Introduction

JBI is an international research organisation based in the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia. JBI develops and delivers unique evidence-based information, software, education and training designed to improve healthcare practice and health outcomes. With over 70 Collaborating Entities, servicing over 90 countries, JBI is a recognised global leader in evidence-based healthcare.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available literature (that is, evidence) and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. JBI takes a particular view on what counts as evidence and the methods utilised to synthesise those different types of evidence. In line with this broader view of evidence, JBI has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in healthcare. There now exists JBI guidance for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the [JBI Evidence Synthesis Manual](#).

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive

peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CAT), in journal clubs and as an educational tool.

JBI Critical Appraisal Checklist for analytical cross sectional studies

Reviewer_____

Date_____

Author_____Year_____

Record

Number_____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Explanation of analytical cross sectional studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *JBIManual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the criteria for inclusion in the sample clearly defined?

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Were the study subjects and the setting described in detail?

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at

the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

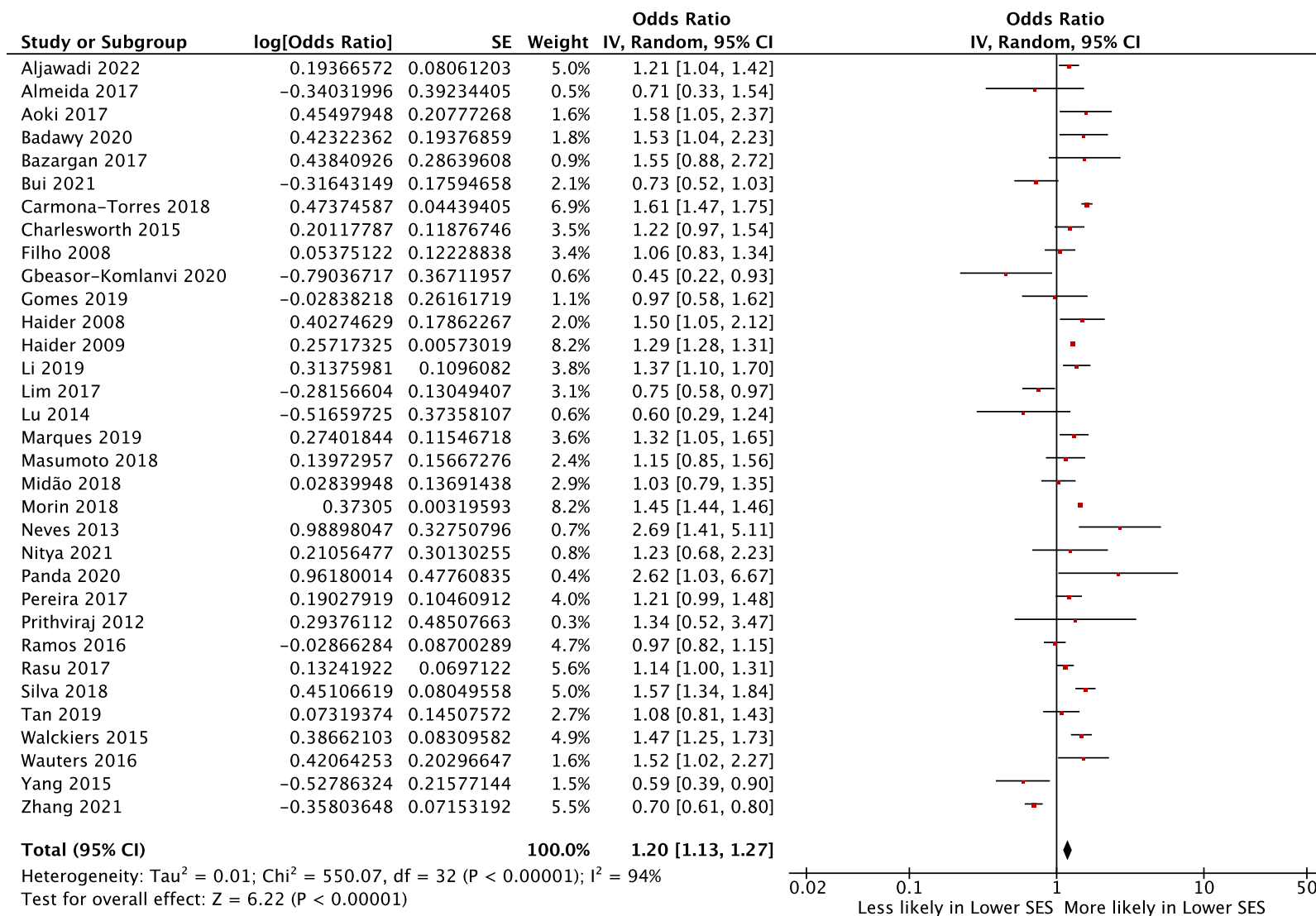
8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

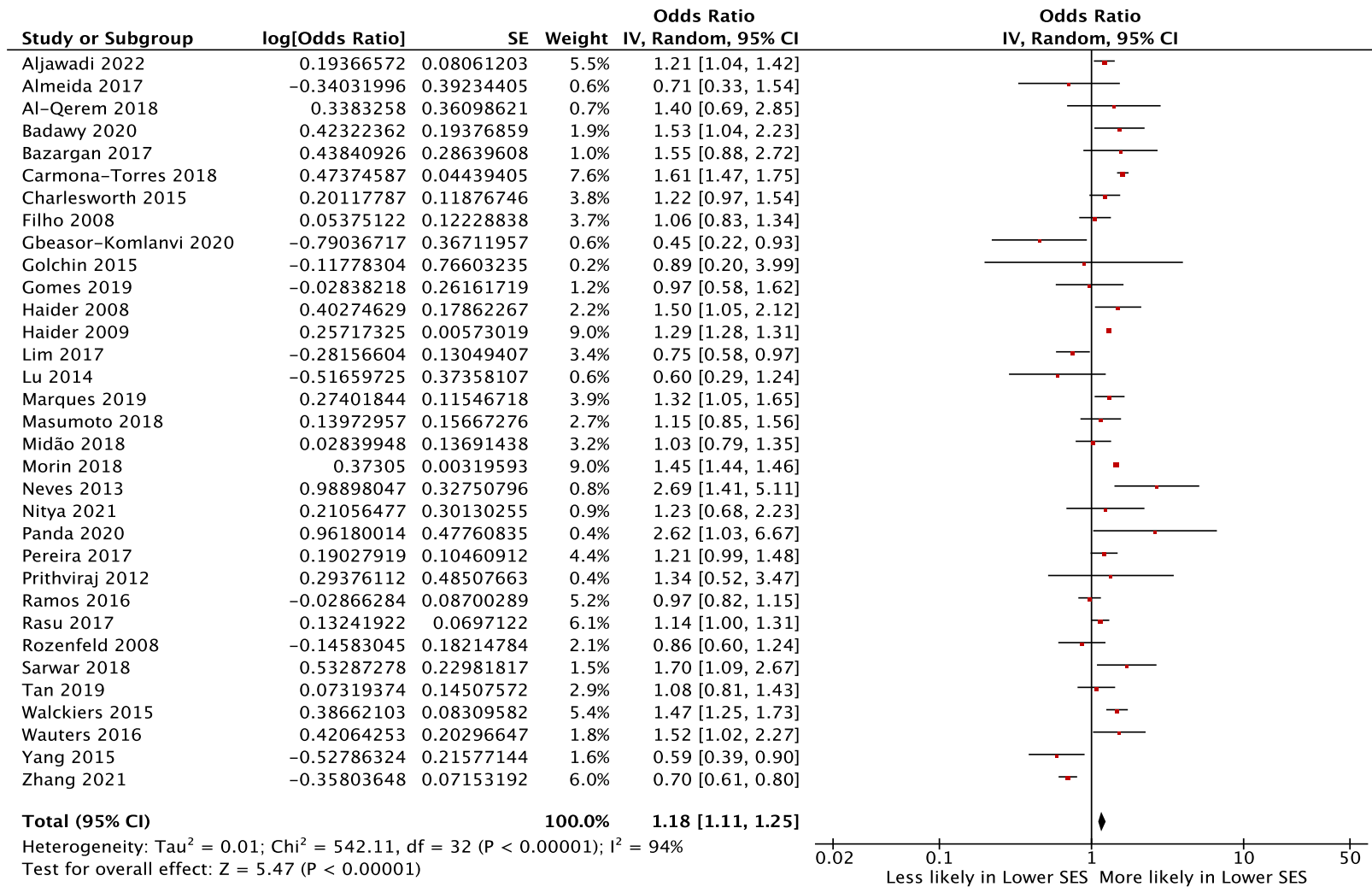
Appendix G: Sensitivity analysis excluding studies that did not meet $\geq 80\%$ on quality appraisal requirements when using education as SES measure.

Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance.



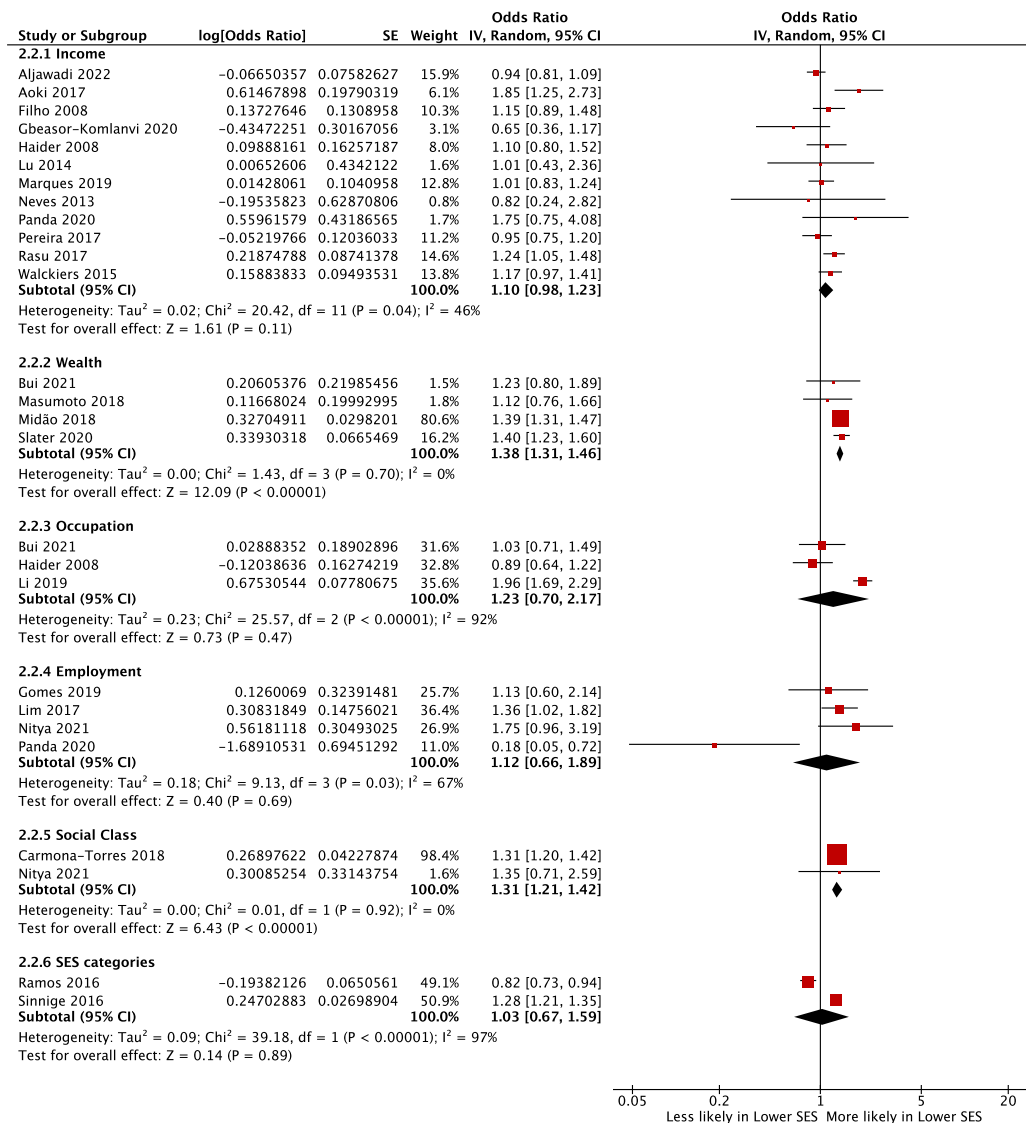
Appendix H: Sensitivity analysis excluding studies that did not have all participants ≥ 55 years old when using education as a measure of SES.

Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance.



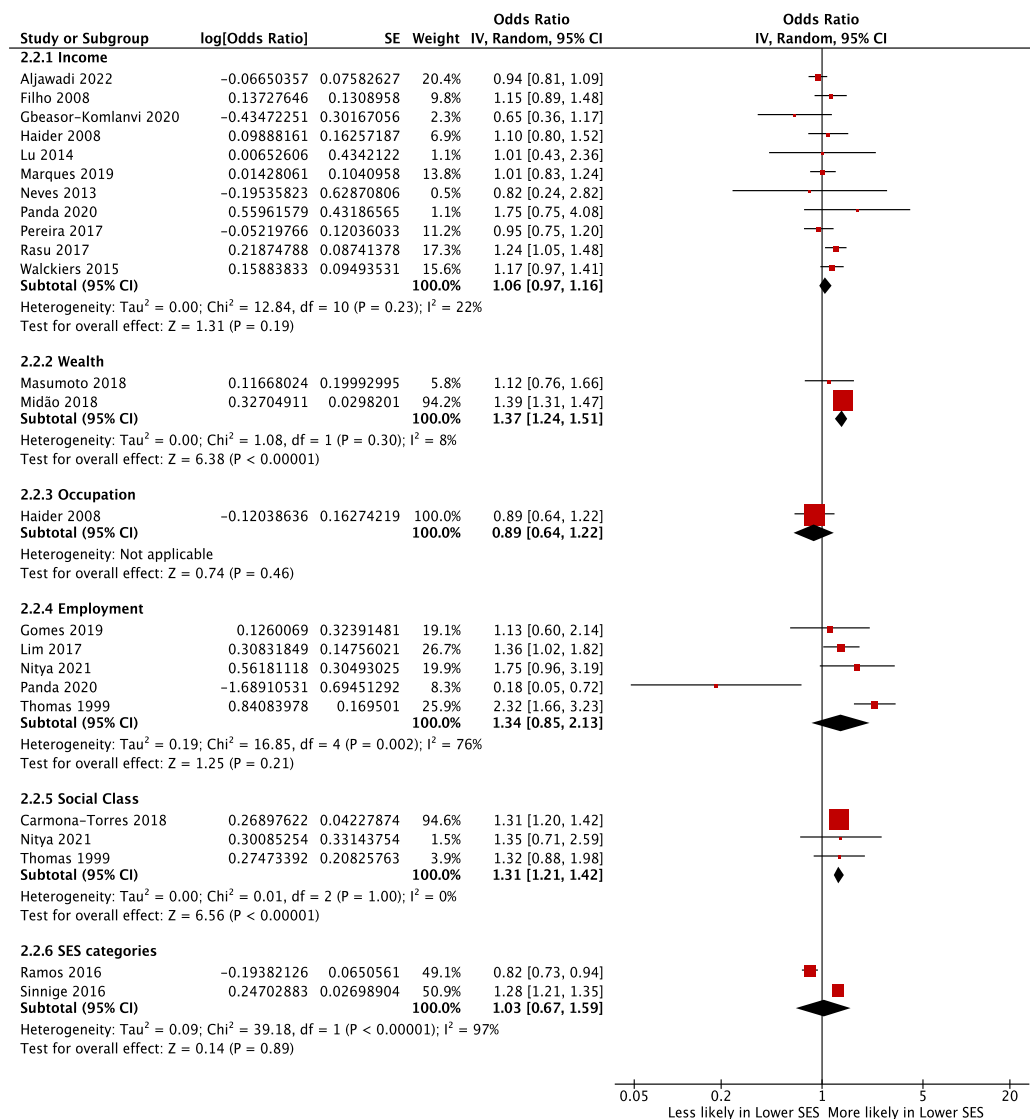
Appendix I: Sensitivity analysis excluding studies that did not meet $\geq 80\%$ on quality appraisal requirements when using income, wealth, occupation, employment, social class or SES as a measure of SES.

Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance

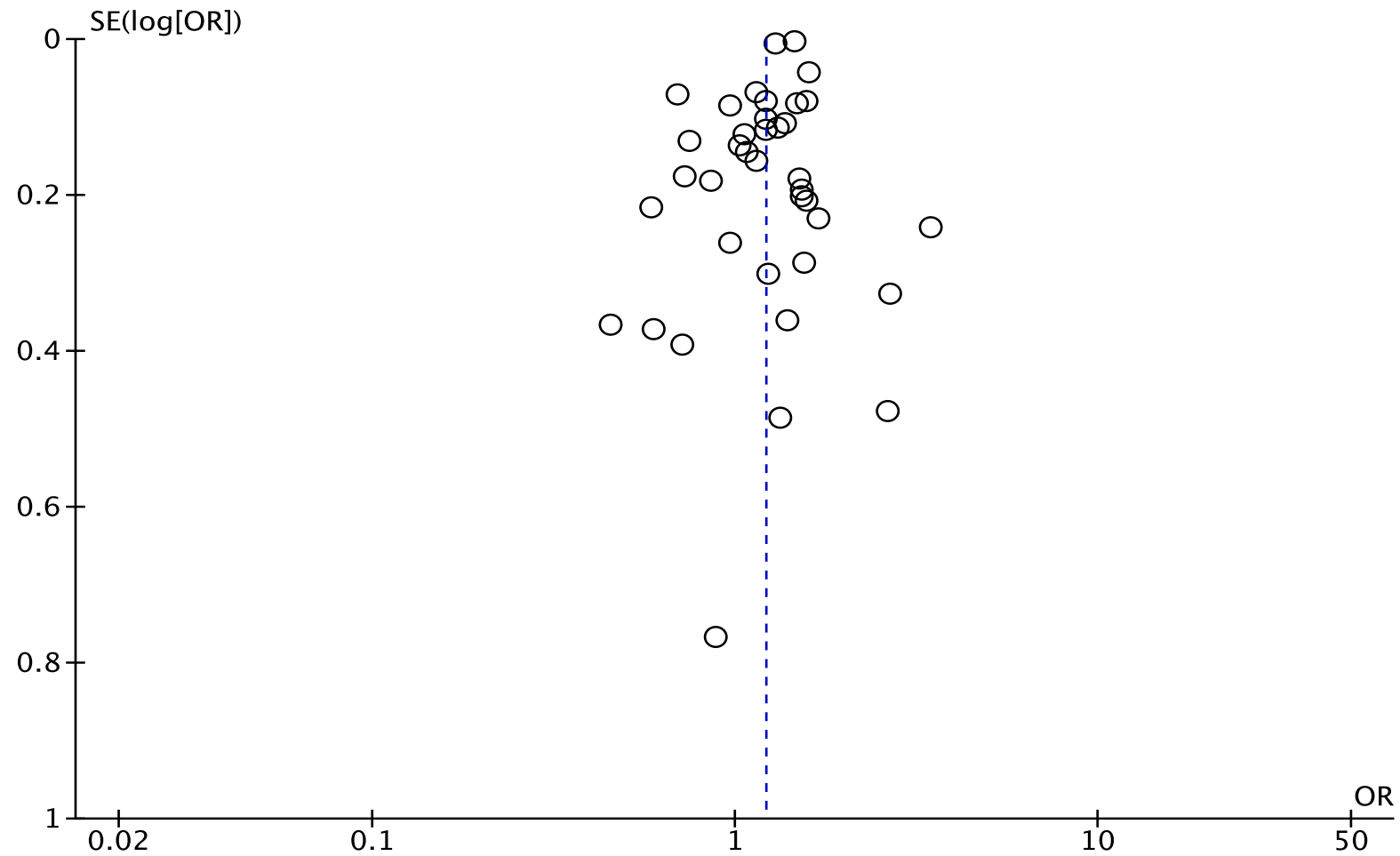


Appendix J: Sensitivity analysis excluding studies that did not have all participants ≥ 55 years old when using income, wealth, occupation, employment, social class or SES as a measure of SES.

Abbreviations: SES: Socioeconomic status; SE: Standard error; CI: Confidence interval; IV: Inverse variance.

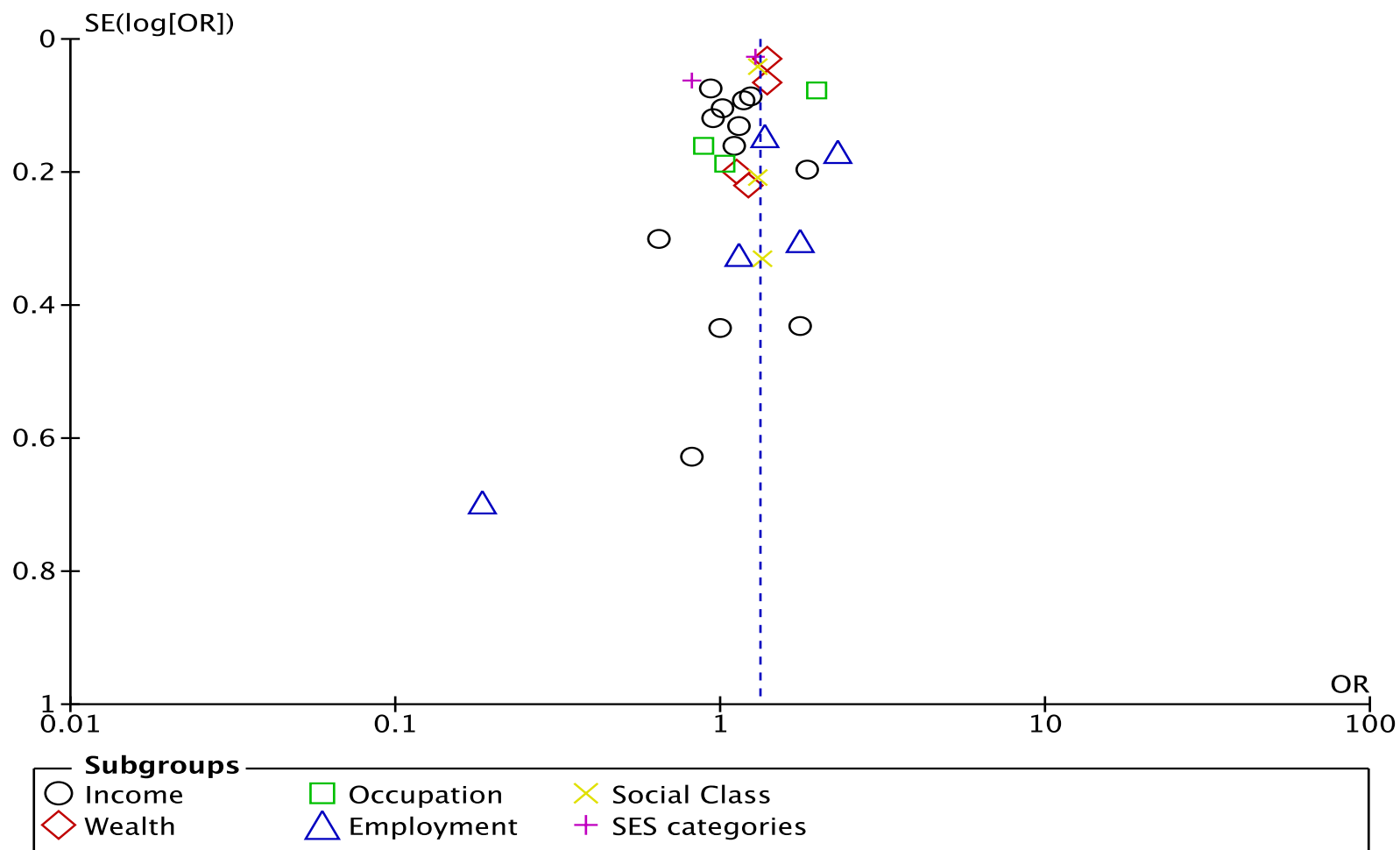


Appendix K: Funnel plot of included studies showing the likelihood of polypharmacy in relation to education.
Abbreviations: OR: Odds ratio.



Appendix L: Funnel plot of included studies showing the likelihood of polypharmacy in relation to income, occupation, social class, wealth, employment and SES categories.

Abbrevaiton Odds ratio; SES: Socioeconomic status.



Appendix M: MLTCs included across the studies to undertake the analysis in this thesis.

Angina
Arthritis
Asthma
Cancer
Chronic Bronchitis
Dementia
Depression
Diabetes
Epilepsy
Heart Attack
High Blood Pressure
Intermittent Claudication
Parkinson
Peptic Ulcer
Percutaneous Anaemia
Stroke
Thyroid

Appendix N: Medication groups that were created to undertake the analyses in this thesis.

Gastrointestinal	• Reflective of BNF 82 for example included Aminosalicylate and Antispasmodics.
Cardiovascular	• Placement of combination drugs such as Co-Triamterizide Other cardiovascular related medication reflective of BNF 82 for example: • Beta Blockers (Atenolol) • Potassium Channel Blockers (Amiodarone) • Sodium Channel Blockers (Flecainide) • Rate Limiting Calcium Channel Blockers (Verapamil and Diltiazem) • Cardiac Glycosides (Digoxin) • Nitrates (Isosorbide Mononitrate) • Anticoagulants (Warfarin) • Loop Diuretics (Furosemide) • Potassium Sparing diuretics (Spironolactone)
Antihypertensive	• Angiotensin Converting Enzyme Inhibitors (ACE) (Ramipril) • Angiotensin Receptor Blockers (ARB) (Irbesartan) • Calcium Channel Blockers (CCB) (Nifedipine) • Thiazide Diuretics (Indapamide) • Thiazide like diuretic (Bendroflumethiazide) • Alpha blockers (Doxazosin)

	• Combination medication with sole indication for hypertension (Co-Diovan) • Vasodilator (Hydralazine)
Antiplatelet	• Reflective of BNF 82 for example: Aspirin, Clopidogrel
Hyperlipidaemia	• Statins (Simvastatin) • Fibrates (Fenofibrate) • Cholesterol Absorption Inhibitor (Ezetimibe)
Respiratory	Reflective of BNF 82 for example: • Anticholinergics (Ipratropium) • Beta-2 Receptor Agonists (Salbutamol) • Inhaled Corticosteroids (Fluticasone)
Central Nervous System	Reflective of BNF 82 for example: • Anticonvulsants (Topiramate) • Antihistamine (Loratadine) • Dopamine Agonists (Bromocriptine)
Hypnotics, anxiolytics and benzodiazepines	Reflective of BNF 82 for example: • Benzodiazepines (Lorazepam) • Non-Benzodiazepines (Zopiclone)
Antidepressants	Reflective of BNF 82 for example: • Selective Serotonin Reuptake Inhibitors (SSRIs) (Fluoxetine) • Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (Venlafaxine) • Tricyclic Antidepressants (TCAs) (Amitriptyline) • Atypical Antidepressants (Mirtazapine)
Opioids	Reflective of BNF 82 for example: • Opioids (Codeine)

	• Opioids (Tramadol) • Opioids (Morphine)
Analgesic Non-Opioids	Reflective of BNF 82 for example: • Non-steroidal anti-inflammatory (NSAIDs) (Ibuprofen) • NSAIDs (Diclofenac) • Analgesic non-opioids (Paracetamol) • Antiplatelet (Aspirin)
Infection	Reflective of BNF 82 for example: • Penicillin (Amoxicillin) • Tetracycline (Doxycycline) • Antivirals (Acyclovir)
Endocrine	Reflective of BNF 82 for example: • Thyroid Hormones (Levothyroxine)
Antidiabetic	Reflective of BNF 82 for example: • Insulin (Insulin Glargine) • Biguanides (Metformin) • Sulphonylureas (Gliclazide) • Meglitinides (Repaglinide) • Thiazolidinediones (Pioglitazone) • Dipeptidyl peptidase-4 inhibitor (DDP4) (Sitagliptin) • Alpha glucoside inhibitors (Acarbose)
Genito-urinary	• Alpha Blocker (Tamsulosin) • Oestrogen (Oestradiol) • Phosphodiesterase Inhibitors (PDE) (Sildenafil) • 5-alpha reductase inhibitors (Finasteride)
Blood and nutrition	Reflective of BNF 82 for example:

	• Medication to treat anaemia, metabolic disorders, fluid and electrolyte imbalances • Vitamin deficiency (Calcium Carbonate)
Immune and malignant	• Aromatase Inhibitors (Anastrozole) • Anti-oestrogens Tamoxifen
Musculoskeletal	• Bisphosphates (Alendronic acid) • Xanthine Oxidase Inhibitor (Allopurinol) • Bone Resorption inhibitors (Strontium Ranelate)
Vitamin and Mineral	• Cod Liver Oil Capsules • Vitamin Complexes such as B or C • Multivitamins
Over the Counter	OTC products were pre-labelled as OTC in the data set however additional products such as Garlic Products and Starflower Oil were categorised to be included.

Appendix O— Total number of individuals using a medication from each medication category across the studies.

	CFAS I		CFAS II	
Total Population in Each Study	7639		7762	
Medication Groups				
Gastrointestinal	1264	(16.5)	2462	(31.7)
Cardiovascular	2104	(27.5)	2581	(33.3)
Antihypertensives	1172	(15.3)	3875	(49.9)
Antiplatelet	505	(6.6)	2544	(32.8)
Hyperlipidaemia	21	(0.3)	3520	(45.4)
Respiratory	613	(8.0)	938	(12.1)
Nervous System	555	(7.3)	980	(12.6)
Hypnotics/Anxiolytics/Benzodiazepines	677	(8.9)	299	(3.9)
Antidepressants	320	(4.2)	896	(11.5)
Opioids	1021	(13.4)	1138	(14.7)
Analgesic Non-Opioids	1741	(22.8)	1861	(24.0)
Infections	339	(4.4)	525	(6.8)
Endocrine	440	(5.8)	988	(12.7)
Antidiabetic	237	(3.1)	801	(10.3)
Genitourinary	54	(0.7)	713	(9.2)
Blood and Nutrition	317	(4.2)	1240	(16.0)
Immune and Malignant	69	(0.9)	222	(2.9)
Musculoskeletal	119	(1.6)	874	(11.3)
Vitamin and Minerals	593	(7.8)	786	(10.1)
Over the Counter	181	(2.4)	698	(9.0)

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