Multimorbidity and Polypharmacy:

A Health Informatics Approach

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Abstract

Introduction: Multimorbidity is increasing in prevalence, and is more common in older age groups. All bodily systems can be affected by multimorbidity (or multiple long-term conditions), and this is associated with increased healthcare utilisation and increased mortality. Additionally, people living with multiple long-term conditions are often on many drugs, which has been termed polypharmacy. This puts them at risk of adverse drug reactions, drug-drug interactions and poor adherence, all of which can increase healthcare costs. In this thesis, I have focused on cardiovascular and gastrointestinal drugs in order to understand the changes which have occurred in the usage of these drugs over the last two decades.

Objective: The thesis aims to describe the changing patterns of medication prescription practice over the last two decades in older people with cardiovascular and/or gastrointestinal diseases using the Clinical Practice Research Datalink (CPRD).

Methods: We extracted one million patient records from CPRD. Among these patients, we have included cardiovascular (CV) and gastrointestinal (GI) patients with two or more years of follow-up. These patients were then filtered further based on the second chronic condition and the patient's age (whether they were 50 years and above). After adjusting for the range between the years 2001 and 2020, the number of eligible patients for this study was reduced further (used for the first group analysis). An association rule mining was applied to investigate the prescription pattern between 2001 and 2020. When this is filtered to those who had 20 years of follow-up appointments, it reduced the number and was analysed accordingly for the second group analysis to examine the change in the prescription patterns by applying specifically the Apriori algorithm Association Rules Mining.

Results: For the first analysis, the extracted eligible CV and GI patients were 228,376 and 111,355, respectively. The eligible patients for the second analysis with continuous and constant 20 years follow-up were 17,075 and 3,110, respectively. In cardiovascular disease, the most commonly prescribed drug classes were statins followed by calcium channel blockers. The study also showed that there was a statistically significant increase (P-value <0.0001) in the mean number of total cardiovascular drugs prescribed in 2020 in comparison to 2001 (mean 2.201-1.581, standard deviation 1.153-0.860 respectively). In gastrointestinal disease, the most commonly prescribed drug classes were proton pump inhibitors followed by corticosteroids. In the same study period, there was a statistically significant increase (P-value <0.0001) in the mean number of total gastrointestinal drugs prescribed (mean 1.284-1.152, standard deviation 0.586-0.424 respectively). Evaluation of the 20 year follow-up data allowed association rule mining to be applied and the top 10 rules were identified.

Conclusions: There was a statistically significant difference in prescription patterns during the study period. In particular, the total number of drugs increased significantly in 2020 when compared to 2001. A limitation of the studies is that only drugs associated with CV and GI diseases were evaluated, and further studies on all systems are needed. Researchers and clinicians need to better understand drug prescribing patterns overall in patients with multiple long-term conditions to develop strategies to overcome the possible adverse consequences of polypharmacy.

Declaration

This thesis is entirely my own work. No portion of the thesis has been submitted either partially or otherwise in support of any other degree or qualification at this or any other institution.

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List of Tables and Figures

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
AHA	American Heart Association
ANNs	Artificial neural networks
ARBs	Angiotensin Receptor Blockers
ARM	Association Rule Mining
AR	Association Rule
ARs	Association Rules
BHF	British Heart Foundation
BNF	British National Formulary
CCB	Calcium Channel Blockers
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CKD	Chronic kidney disease
COVID-19	Coronavirus disease
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CVD	Cardiovascular disease
DT	Decision tree
EHR	Electronic health record
EMIS	Egton Medical Information Systems
ESC/ESH	European Society of Cardiology and European Society of Hypertension guidelines
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal

GIS	Gastrointestinal system
GPRD	General Practice Research Database
GP	General practitioner
GPs	General practitioners
HOPE	Heart Outcomes Prevention Evaluation
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IHD	Ischemic heart disease
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare Regulatory Agency
MI	Myocardial infarction
NIA	National Institute on Aging
NICE	National Institute for Health and Care Excellence guideline
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over the counter
PIM	Potentially inappropriate medication
PPIs	Proton-pump inhibitors
PUD	Peptic ulcer disease
RA	Rheumatoid arthritis
RF	Random forest
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SSRIs	Serotonin reuptake inhibitors
SVM	Support vector machine
US	United States
WHO	World Health Organization

Chapter 1

Introduction

1.1 Introduction

There has been a considerable increase in the number of patients suffering from multimorbidity, a condition where more than one disease is present. This causes various medical, financial, and social issues. Many studies shown that older persons are the most likely to consume five or more medications, termed polypharmacy (Hosseini et al., 2018). Also, suffer from more long-term diseases. Older people usually have at least one chronic condition such as a respiratory illness, cardiovascular disease, gastrointestinal disease, diabetes, and so on. Unfortunately, other, often relatively significant health issues, remain undetected. This includes depression, hearing and vision issues, overactive bladder, cognitive disorder, and nutritional deficiency (Chippa & Roy,2022). Nowadays, physicians become more capable of the early detection of disease. In fact, they are diagnosing more conditions earlier through asymptomatic screening and the positive consequence of that is that it delays or prevents some fatal conditions such as heart attacks and strokes. People, therefore, live longer but the inevitable consequence of age is that these conditions will eventually occur at some point leading to an older persons multimorbid population. With aging, older persons could be suffering from undetected disease for a prolonged period. This can cause a burden not only on the patient themselves, but also on the health care system. In many cases, these undetected conditions may arise from side effects and drug-drug interactions due to polypharmacy. Thus, it is highly recommended and extremely beneficial to review all the medications that the patient is taking, and to consider the side effects associated with each drug to identify any additional illness possibly caused by the drug itself.

As persons get older, the multimorbidity increases and becomes more complicated, which leads to an associated increase in polypharmacy too. With time, adverse effects and drug interactions caused by multidrug use become more complex. Along with this, the pharmacokinetics of drug absorption, metabolism, elimination, excretion, and distribution will change together with the increase of the patient's age (Hutchison & Brien,2007).

The percentage of older patients in the United Kingdom (UK) is quite similar to that in different high-income countries. The percentage of older persons in the UK aged 65 years old or over is increasing and is expected to reach 17 million by 2044, representing around 25% of the UK population (Stockdale, 2011). The most common chronic condition in older persons

is cardiovascular disease, which causes the majority of fatalities, with hypertension the most common form of the disease in this group (Jaul & Barron, 2017). Other chronic diseases are also common for example: osteoporosis, cancer, osteoarthritis, and diabetes mellitus. In 2010, the most medicated disease group in Scottish primary care was cardiovascular, followed by central nervous and gastrointestinal systems at 27%, 26%, and 18% respectively (Payne, 2016).

Medications are developed continuously leading to endless opportunities for using more drugs, in an attempt to find a new medication that could assist in treating certain diseases more efficiently. This can cause more problems for older persons because of both drug-to-drug interactions, as well as a drug to disease interactions, where one disease can get worse in the process of treating a different illness. Nowadays, treating older people with long-term diseases has become more challenging than ever. However, multimorbidity and polypharmacy are getting worse as the patients grow older.

Many studies have focused on multimorbidity and polypharmacy in different countries as shown in Table 1.1 below. The current study explores multimorbidity and polypharmacy in the UK with a specific focus on cardiovascular and gastrointestinal diseases utilising machine learning. The data was extracted from the Clinical Practice Research Datalink (CPRD) for patients aged 50 years old and over and concentrated on the period between 2001 to 2020.

Table 1.1 Summary of various global multimorbidity and polypharmacy studies

Authors / Study design	Country	Purpose	Summary of findings
Aoki, Tet al. (2018) / (Observational cross-sectional study)	Japan	The purpose of this study was to determine multimorbidity patterns in a Japanese population and determine if they had different effects on polypharmacy and dosage frequency.	Malignant/digestive/urologic and cardiovascular/renal/metabolic patterns were found to have the strongest relations with excessive polypharmacy and the number of concurrent OTC medications. The effects of multimorbidity on excessive polypharmacy and dosage frequency vary. Malignant/digestive/urologic patterns may be more vulnerable to medication safety issues and increased treatment burden than other patterns (Aoki et al., 2018).
Sakib, M.Net al. (2019) / (Observational cross-sectional study)	Canada	The aims of the research consisted of investigating the prevalence of multimorbidity among middle-aged Canadians; and investigating the relationship between lifestyle factors (smoking, alcohol consumption, physical activity) and multimorbidity in this age group.	Multimorbidity is not limited to the older persons; it is also common among middle-aged people. To better understand the temporal relationship between lifestyle factors and multimorbidity, longitudinal research is required (Sakib et al., 2019).
Schneider et al., (2021) / (A cross-sectional study)	Germany	The aim is to assess the level of polypharmacy, multimorbidity, and potential medicine-related issues in older persons receiving home care for chronic pain.	Multimorbidity and polypharmacy are common in older outpatients receiving home care for chronic pain. Drug-related issues that may risk the safety of medication treatment in this group of people stem from potentially relevant drug interactions, overprescribing, and misuse (Schneider et al., 2021).

Rozsnyai et al., (2020) / (Observational cross-sectional study)	Swiss	The purpose of this study was to determine deprescribing barriers and enablers as reported by older individuals with polypharmacy and multimorbidity.	The majority of polypharmacy-affected older persons are willing to deprescribe. By building trust with their patients and communicating evidence about the risks of taking drugs, GPs may be able to increase deprescribing (Rozsnyai et al., 2020).

1.2 Multimorbidity

Multimorbidity has become a major concern in global public health and is a massive burden on the healthcare system. Multimorbidity is defined as the occurrence of two or more chronic diseases, or "the existence of multiple medical conditions in a single individual" (Afshar et al., 2015; Calderón-Larrañaga et al., 2016; The Academy of Medical Sciences, 2023). Old age and social deprivation are known to have a substantial correlation with multimorbidity (Barnett et al., 2012).

The prevalence of multimorbidity grows rapidly as people age, rising from 29.7% in the 45–49 year age group to 52% in people aged 60–64 years (Sakib et al., 2019). However, the majority (21 out of 25) of studies that explore gender differences found that females at 28.4 % had a higher prevalence of multimorbidity than males at 25.9% (Nguyen et al., 2019).

Multimorbidity is expected to increase with age. In England, more than 14 million adults, which is around one in four of the entire country's population, have two or more medical disorders (Stafford et al., 2018). Around 15 million people in England had a long-term illness in 2012; of which 58% were older than 60 years, 25% of those indicated they had two or more long-term illnesses (Department of Health, 2012). The Clinical Practice Research Datalink (CPRD), which represents 6.9% of the UK population, was utilised by Cassell et al. to describe the epidemiology of multimorbidity among 403,985 adults in England. According to their findings, multimorbidity rose dramatically with age, reaching its greatest level (83.2%) in those who were in the oldest group (85 years old). In addition, more than 50% of clinic appointments, 56.1% of hospital admissions and most prescriptions were linked to individuals with

multimorbidity (Cassell et al., 2018). There are a number of predisposing factors related to multimorbidity. In 2011, Marengoni et al conducted a systematic review that comprised of 41 papers, to summarise the existing scientific research on the occurrence, causes, and effects of multimorbidity in older individuals. They and others showed that female gender, older age, and low income status were all factors directly related to multimorbidity (Agur et al., 2016; Marengoni et al., 2011; Violan et al., 2014).

Multiple long-term conditions are an inevitable consequence of aging. It is expected and the current norm. The challenge facing this issue is actually in the way that the health care service is set up. The current healthcare system might not be perfectly designed to manage complex older people with multiple long-term conditions. It might be more beneficial to move to an approach that is more multi-disciplinary and holistic. In order to do that, it could be important to define what conditions co-localise with each other in order to be able to re-design the way that care is delivered in order to meet the needs of multimorbid people. it is highly important to manage diseases such as high blood pressure, obesity, diabetes, and high cholesterol properly, in order to prevent subsequent more disabling conditions.

Eventually, there is no fundamental solution for multimorbidity and polypharmacy in older persons. Therefore, it would be essential to understand the way that drugs and diseases co-localise and overlap to understand shared mechanisms between co-localising diseases and design better drugs that target multiple targets across different diseases. In addition, there is a critical need to re-design the healthcare system to better meet the needs of multimorbid people.

1.2.1 Problems Associated with Multimorbidity

Multimorbidity is a common problem which is increasing every year. Multimorbidity patients requiring comprehensive care, usually needing frequent GP consultations. There is also an increase in the cost of treatment due to a high rate of unplanned hospitalizations and recurrent consultations (Moffat & Mercer, 2015). Soley-Bori et al., conducted a literature review that included 17 papers, observing the costs and consumption of healthcare of multimorbidity in the UK (Soley-Bori et al., 2021). Multimorbidity appears to be associated with higher medical costs and consumption, including overall costs, hospital costs, healthcare transition costs,

primary care use, and hospital admissions. Multimorbidity has the greatest impact on unexpected, potentially avoidable hospitalizations, with 14.38 times greater risk for people with four or more diseases in an age independent manner (Soley-Bori et al., 2021).

Also, multimorbidity was linked to an increased in the all-cause mortality rate. Older people with five or more comorbidities had double the risk of mortality as opposed to those with none and are in good health condition. There are several diseases associated with the increased mortality rate, including diabetes, cancer, chronic obstructive pulmonary, and coronary heart diseases. In general, cardiac-related diseases are the most common cause and play a major role in increasing the mortality rate among adults (Gallacher et al., 2018). In addition, the treatment burden is increased in multimorbidity patients, this term refers to the amount of demand that the healthcare system places on patients and their careers. These multimorbidity patients commonly have to manage an increasingly stressful medical lifestyle, where they must work through multiple appointments and complex drug regimens. This can influence patient adherence to both clinical appointments and medication consumption (Moffat & Mercer, 2015).

Therefore, any drug or therapy with poor or reduced benefits should be discontinued or diminished. This is to ensure that the prescribed treatment plan maximises drug benefits while minimising polypharmacy and negative drug effects.

1.3 Polypharmacy

Recently, polypharmacy has attracted increasing attention. There has been a wide range of definitions utilised within the literature. The most common refers to five or more unique medicines to be taken by an individual, and was used in 46.4% (n = 51) of studies (Masnoon et al., 2017). Six or more drugs was the second most common term for polypharmacy, with ten papers adopting this definition. However, one paper described the polypharmacy as a patient's use of numerous drug classes (Masnoon et al., 2017)**.** The prevalence of polypharmacy is increasing in multimorbidity patients and older people in general (Payne, Avery, et al., 2014). Other risk factors include female gender, having many clinicians at once, and where medications are dispensed from a number of different pharmacies. Globally, polypharmacy is

growing in the general population, with more than half of people over 65 in the United Kingdom consuming three or more prescription drugs. In a large-scale Scottish cohort study, the percentage of adults who were prescribed five or more drugs increased from 11.4 to 20.8% between 1995 and 2010 (Rawle et al., 2018). In this same study, people received 5–9, 10–14, or 15 or more drugs 16.3%, 4.7%, and 1.1% of the population, respectively (Payne, 2016).

In England, it has been illustrated that 8.4 million people were receiving five or more medications via the primary care system, and 3.8 million were receiving eight or more different medications in the period between October and December 2019 (Department of Health and Social Care, 2021). Whereas most Brazilian people over 60 years of age received only four or more medicines, and that 11% of the Swedish population and 6% of the rural Chinese people have five or more medicines (Payne, 2016). The summary of these studies is shown in the following Table 1.2.

Table 1.2 Different polypharmacy values across different countries

Country	Number of drugs consumption
United Kingdom	It has been reported that there are three or more drug prescriptions per patient (Rawle et al., 2018).
Scotland	The percentage of adults who were prescribed five or more drugs increased from 11.4 to 20.8% (Rawle et al., 2018).
England	There are 8.4 million people receiving five or more medications via the primary care system, and 3.8 million receiving eight or more drugs (Department of Health and Social Care, 2021).
Brazil	Patients over sixty years old receive four or more drugs (Payne, 2016).
Sweden	11% of the Swedish population have received five or more drugs (Payne, 2016).
China	A total of 6% of rural Chinese people have received five or more drugs (Payne, 2016).

The literature shows that males and females have different incidences of polypharmacy, with numerous studies indicating females having the higher rate (Feng et al., 2018a; Knopf & Grams, 2013; Slater et al., 2018; N. Zhang et al., 2020). However, there are a limited number of papers that conflict with this, indicating that males had a higher rate of polypharmacy (Badawy et al., 2020; Jyrkkä et al., 2009). This difference between men and women has been correlated to variations in medical prescribing patterns, educational factors, and socioeconomic levels (Hofer-Dückelmann, 2013; Ong et al., 2018).

In addition, there are substantial gender variations with men and women requiring different diagnoses and therapy approaches, which affects the type and quantity of medications recommended. The differences in the management of drug therapy and the use of healthcare services means women more frequently obtain preventative medical care than men leading to more drug prescriptions (Orlando et al., 2020). Furthermore, gender-related morbidity also affects the prevalence of polypharmacy between men and women. It should be highlighted that polypharmacy is not always dangerous, and in fact can be important for successful treatment. It is always important to take into consideration the therapeutic reasons for taking several drugs.

1.3.1 Benefit of Polypharmacy

There are potential benefits to administrating multiple medications for the treatment of chronic illnesses. Notably, the used drugs are provided with the correct and most appropriate combinations to avoid the possibility of having the side effect and expected drug interaction, this is known as appropriate polypharmacy. This term is used for prescribing multiple drugs for complicated or numerous conditions. The aims of the prescribed multiple medications should be to provide a good quality of life and to reduce drug-related harm (Cadogan et al., 2016).

The lifestyle could be improved by using proper polypharmacy, enhancing disease-specific clinical outcomes (e.g. blood pressure), and decreasing the relevant negatively associated outcomes such as hospital admissions and cardiovascular problems. Treating multiple diseases is different than treating mutable conditions, the harms and benefits might vary depending on the patient's clinical characteristics. As a result, it could be challenging to anticipate the harms,

benefits, and effects of polypharmacy for patients with complicated or multiple conditions, such as chronic obstructive pulmonary disease, the combination of diabetes, and heart failure, but doing so is extremely important to ensure that they receive the best medical care available. In this case, treatment should consist of a variety of drugs and polypharmacy becomes an important factor to provide the greatest benefits and improvements in quality of life.

The management of polypharmacy in older persons and multimorbid patients is challenging. According to the findings of the Delphi questionnaire, first-line drugs that are endorsed in clinical recommendations for a single ailment are also thought to be beneficial for older multimorbid individuals (Sirois et al., 2020). However, a sizable proportion of drugs were rated as being high or very high risk and negative or very negative benefit by the panel. These findings show how challenging it is to strike an appropriate balance between benefits, dangers, and quality-of-life effects when the number of prescribed drugs rises. Only a limited selection of treatments would be deemed suitable polypharmacy based on these criteria. Thus, it is crucial to customise care according to the needs of each patient.

Evidence-based medicine as well as making decisions based on the most current medical knowledge of the most recent clinical guidelines could be extremely beneficial in the management of multimorbidity (Sirois et al., 2020). It has been confirmed that polypharmacy has been utilised to treat millions of patients successfully. However, a number of facts should be taken into consideration to achieve this goal.

1.3.2 Issues Related to Polypharmacy

Polypharmacy is becoming more common, especially among aging people. This acknowledges that polypharmacy can be beneficial for certain individuals, but it can also be dangerous if improperly managed. Problems related to polypharmacy centre on the improper prescribing of many drugs or when the medications intended benefit is not achieved, meaning that it is potentially related to a variety of negative consequences. It could be harmful to some patients by increasing the risk of adverse drug reactions, drug-drug interactions and affecting medication adherence (Payne, Abel, et al., 2014).

Previous studies have emphasized that polypharmacy and adverse drug reactions are certainly related. According to Dagli & Sharma, taking more than four drugs was associated with a higher risk of having an adverse drug reaction. The incidence of adverse reactions rises exponentially with the number of medications taken (Dagli & Sharma, 2014). Additionally, there are increasingly drug-drug interactions as more drugs are used. When the number of drugs reaches eight the chance of drug-drug interactions is close to 100 % (Santos-Díaz et al., 2020). Sometimes rash clinical decisions may result in a dosage increase or the addition of a supplementary medication to promote effectiveness, which increases the patient's risk of polypharmacy and drug-drug interactions. In addition, it has been found that 50% of people do not consume their drugs properly as advised (Brown & Bussell, 2011), and in some cases this may be due to forgetfulness and message misunderstanding.

Polypharmacy is also a major risk factor for hospital admissions in older patients as it is one of the main reasons for falls and death. In 2014, Payne et al showed that unplanned hospital admissions of patients taking 4 to 6 drugs were 10.3 %, whilst this rose to 24.8 % for patients taking 10 or more drugs (Payne, Abel, et al., 2014). It has been demonstrated that the number of medications is also the main determinant of hospitalisation for adverse drug effects (Mitchell et al., 2016). Adverse drug effects increase from 6.5% to 15% between 2004 to 2022 increasing hospital admissions, which caused by the inappropriate polypharmacy (Pirmohamed et al., 2004; Osanlou et al., 2022). Polypharmacy increases the incidence of hospitalisation due to a fall, with 7.9 % of falls occurring in people with polypharmacy (5 up to 9 medications). It has been found that the highest fall rate was 14.8 % for people with 10 or more medications who are considered as people with heightened polypharmacy (Zaninotto et al., 2020).

1.4 Multimorbidity and Polypharmacy Relationship

Multimorbidity is known to be associated with polypharmacy. As mentioned in the previous section the prevalence of polypharmacy is steadily increasing in older people, primarily due to the increased in multimorbidity. Also, specific chronic conditions have a stronger relation to polypharmacy in comparison to others (Vrettos et al., 2017). For instance, the therapeutic approach for cardiovascular disease is complicated and requires numerous drugs. This was investigated in research undertaken in Japanese individuals between 18 and 84 years old.

The study found that the strongest links were between excessive polypharmacy in cardiovascular drug patterns which increased the treatment burden on the patient (Aoki et al., 2018).

In 2018 Feng et al. conducted a cross-sectional study that included 38,329 participants with multimorbidity between the ages of 45 and 64 years old, and attempted to identify the relationship between polypharmacy and multimorbidity. The study found that hypertension and hyperlipidemia were the two most common coexisting chronic diseases, where 64.9 % of the study population, most of them female, were exposed to polypharmacy. Polypharmacy was also found to be extensively linked with multimorbidity and levels varied with various chronic diseases (Feng et al., 2018). The necessity for many medications to treat illnesses or serious unintended drug effects may lead to the identification of additional chronic conditions. For instance, long-term corticosteroid use may result in the diagnosis of diabetes mellitus (Hwang & Weiss, 2014). The main issues with multimorbidity and polypharmacy are the increased risk of adverse drug reactions, drug-drug interactions, and non-adherence to medication regimens.

Additionally, the complexity of managing multiple chronic conditions can lead to confusion and difficulty in understanding the treatment plan. This can lead to poor health outcomes and increased healthcare costs. Therefore, polypharmacy and multimorbidity issues need to be properly managed by physicians, who must be aware of the variety of issues it can cause and ensure the advantages of utilising numerous medications are properly weighed against the disadvantages, especially in older persons (Payne, 2016).

1.5 Older People

Ageing is described at the biological level. Cellular and molecular production deteriorates over time. As a result, physical and mental abilities gradually deteriorate, disease risk increases, and eventually, death occurs. These changes are neither linear nor constant, and are only indirectly related to an individual's age expressed in years (World Health Organization, 2022).

Older persons are individuals aged 65 and over. They often have unique health needs due to age-related alterations in their bodies, such as decreased mobility, increased risk of chronic diseases, and changes in cognitive abilities. It is important to provide older people with appropriate care and support to ensure their health and wellbeing (Yin et al., 2021).

The development of contemporary preventative methods and medical therapies, alongside developments in the biomedical sciences and public health, have led to people living longer than they did in previous decades. This has resulted in a sharp rise in the total number and frequency of older individuals. Globally, there were 1 billion older persons aged 60 years or over in 2019. By 2030, there will be 1.4 billion, and by 2050 the number will increase to 2.1 billion. This rise is occurring at an unprecedented rate and will pick up speed in the upcoming decades, especially in developing nations (WHO, 2023).

In England, the percentage of older persons over the age of 65 has increased from 16 % to 18% of the total population over the last 20 years, and there are now also about 50 % more people over the age of 85. This pattern is anticipated to persist, with the number of individuals above the age of 85 expected to nearly double over the next 25 years, rising from approximately 1.3 million to 2.6 million (Raymond et al., 2021). This rapid expansion, particularly among those over 85 years old, will lead to many challenges to the welfare, public finances, and health services.

1.5.1 Older People and Healthcare Utilisation

Age is a factor in health expenditure and this cost pressure results from an aging population. That is, older people are more likely to have chronic illnesses with numerous morbidities, which are more expensive to treat including hospital and community health care, family health services, and pharmaceutical services, whose use rises with age (Ferguson & Belloni, 2019).

Older people often require more frequent and complex medical care due to age-related changes in their bodies. Additionally, older persons are more likely to suffer from chronic conditions such as hypertension, arthritis, heart disease, diabetes, and dementia, which can require long-

term management. The required efforts to deal with this situation would lead to an increase in both resources and the cost of healthcare (Jaul & Barron, 2017).

There is a strong association between the increased prevalence of multimorbidity, polypharmacy and older patients. In 2015, approximately 60.4 % of all prescribed medications in the United Kingdom were provided to older patients (Prescribing and Medicines Team, 2016). This percentage is expected to increase as people continue to live longer. The increase of the individual age is directly related to the possibility having long term disease as the age increase is considered a major cause of multimorbidity and polypharmacy (Marengoni et al., 2011). Long-term conditions and multimorbidity could have an impact on the amount of healthcare used, with long-term condition patients accounting for 50 % of all GP appointments, 64 % of outpatient appointments, and at least 70 % of inpatient bed days (The King's Fund, 2023). Additionally, there is a considerable amount of expenditure spent on health care for those suffering from long-term conditions. This association has an influence on the increased cost burden of older persons. In the UK, after the age of fifty, the average amount spent on healthcare per person experienced a sharp surge, with the estimated early healthcare cost for the older persons expected to almost double over the next two decades (Caley & Sidhu, 2011).

1.6 Health Informatics

Health informatics is considered one of the most rapidly developing specialties in medical fields. It is concentrated to improve the field of medicine and healthcare through the use of data and information technology (Imhoff, 2002). Health informatics is a broad term that covers numerous healthcare-related topics, such as medical data analytics, electronic health records, and electronic medical records. An electronic record is known as a digital form of a paper file in a physician's practice. It comprises the treatment and medical history of the patients in a single practice.

By utilising such an electronic approach, physicians can review the patient’s treatment plan along with concerning specific criteria, such as the readings of blood pressure. This process can facilitate monitoring and determining which patients require check-ups.

The electronic health record (EHR) makes it easier to deliver patient information to the physician, hospital, nurse, or send it to other cities or countries. The EHR is defined as a

digital form of a patient's paper file that is secure and promptly makes information accessible to the correct authorised users. In addition, an EHR includes the patient demographics, medical history, medications, diagnosis, allergies, radiology images, and laboratory results. The EHR has succeeded in having a positive role into healthcare. Digital technology has fundamentally changed the world and has the potential to contribute to advance methods of treatment (Heart et al., 2017). Health informatics demands intelligent machine learning of data and technology to improve patient care. Machine learning is most often associated with the field of computer science which itself has a big influence on ways of managing different health informatics approaches.

1.7 Machine Learning

Machine learning is concerned with processes, tools, and techniques that allow computers to "learn" to perform tasks by given examples, as opposed to being directly programmed to perform some task. The term machine learning first appeared in 1959 with Arthur Samuel's explanation as a "Field of study that gives computers the ability to learn without being explicitly programmed". Machine learning is concerned with the development and utilisation of algorithms and programmes, for example, to build prediction and forecast models, to group data, or to extract patterns from data for use with respect to some "downstream" task based on existing data (Park et al., 2018). If the data is too large or too complicated to be analysed by conventional techniques it is referred to as "Big data". It is possible to develop software or algorithm that learn to anticipate possible patterns in the future (Sagiroglu & Sinanc, 2013). There are many software tools available to support machine learning such as the libraries and tool kits available in the Python and R programming languages. The R programming language was used with respect to the work presented here because of the positive reputation it has as an algorithm development environment for machine learning (Hosseinzadeh Lotfi et al., 2020). Machine learning approaches can be extremely helpful in situations where a long-term perspective of individuals (patients) is to be considered in order to generate a reliable prognostic evaluation. Prognosis is a critical point of medical care. It supplied the most possible estimate of a person's likelihood of experiencing specific results based on both nonclinical and clinical characteristics. The prognosis is known as the expectation of a disease's development. It can also be used to anticipate how healthy individuals will perform in the future. For instance, cardiovascular risk factors could be used to estimate the prevalence of

heart disease in people of a certain age or geographic area. Machine learning could be used to forecast individuals' health outcomes and drug prescriptions.

Additionally, machine learning can serve a variety of functions in healthcare associations, including providing predictive analytics for healthcare providers, patient's medical history, and data for research and analysis needs. Also, machine learning has been utilised for predicting the possibility of developing diseases in the near future, diseases like cardiovascular disease, stroke, and diabetes (Alanazi, 2022).

In addition, it can be used for predicting the medications' side effects, which could be extremely helpful in preventing adverse drug reactions (Atias & Sharan, 2011). In particular, the Apriori algorithm (ARM) has been found to be an important tool for use in health care to investigate association rules between numerous factors such as medications and prescribing patterns (Abdullah et al., 2008). The following Table 1.3, displays the different machine learning algorithms that have been developed for use in healthcare settings.

Table 1.3 Shows different machine learning algorithms used in health care system (Uddin et al., 2019)

Machine Learning Algorithm	**Use in Healthcare Settings**
Decision tree (DT)	One of the oldest machine learning algorithms. Used to classify data based on tree structure.
Random forest (RF)	An ensemble of decision trees used to improve the accuracy of classifications.
Support vector machine (SVM)	Used to classify data by identifying a decision boundary. Typically used for binary classification
Artificial neural networks (ANNs)	A type of machine learning inspired by the human brain. It is used to identify complex patterns in data and make predictions. Much deep learning is founded on ANNs.
Association rule mining (ARM)	The discovery of relational rules in data that can be used for a variety of downstream tasks.

1.8 Association Rule Mining and the Apriori Algorithm

Association rule mining (ARM) is concerned with the identification of Association Rules (ARs) in binary valued (Yes/ No) data. An association rule expresses a relationship:

$$A \Rightarrow B$$

Where A+B are groups of data attributes called "item sets". The above AR is interpreted as "if A exists then B is also likely to exist". Likely hood is described in terms of a probability valve referred to as a "confidence" value. ARs of the form A ⇒ B are derived from frequent item sets. Groups of attributes that occur frequently in a given data set. Frequency in this context is defined in terms of a percentage of the records in the data set referred to as a "support" threshold. Given a frequent item set {a,b,c} We can derive six ARs from this :

$$a \Rightarrow bc$$
$$b \Rightarrow ac$$
$$c \Rightarrow ab$$
$$ab \Rightarrow c$$
$$ac \Rightarrow b$$
$$bc \Rightarrow a$$

These will have the same support values but are likely to have different confidence valves. The support of an item set A is calculated as follows:

$$\text{Support (A)} = \frac{\text{Number of records (transactions) in which A appears}}{\text{Total numbers of records in the data set}}$$

Confidence for a rule A ⇒ B is calculated as follows:

$$\text{Confidence (A} \Rightarrow \text{B)} = \frac{\text{Support (A U B)}}{\text{Support (A)}}$$

The Apriori algorithm was one of the first logarithms for discovering common frequent item sets, and consequently association rules from within data sets. In 1993 the Apriori algorithm was initially suggested for use in effective practice by Agrawal, Imielinski, and Swami, but it was not until 1994, the algorithm was developed and given the name Apriori (Borgelt & Kruse, 2002).

ARM is used extensively in many fields, for instance, information security and commercially. Kanza et al studied the ARM role in the medical field and applied it in the context of disease diagnosis and therapy (Gulzar et al., 2023). Wang used the Apriori algorithm to analyse the treatment of headaches in traditional Chinese medicine, which successfully assisted in deciding when to prescribe conventional medications to numerous headache patients. He also discovered fundamental guidelines among common Chinese medical conditions as well as relevant symptoms, which were analogous to the principles of clinical practice (Luo et al., 2021). In another algorithm approach, the Apriori algorithm was used to filter out the traditional Chinese medicine prescriptions with potential analgesic effects. A 311 clinical cases of chronic pain in rheumatoid arthritis (RA) were used to thoroughly examine and analyse the prescribing patterns in the treatment of RA pain. All compounded medication prescriptions were gathered from the "Second Affiliated Hospital of Zhejiang Chinese Medical University" and entered into the database of the "Rheumatism Intelligent Auxiliary diagnosis and treatment system" (Lai et al., 2022). Similarly, Yoosofan et al used ARM to find association among drugs in pharmacy (Yoosofan et al., 2015). Nowadays, the Apriori algorithm become one of the most efficient ways that contribute to improving various aspects of healthcare systems.

1.9 Aims and Objectives

This study aims to identify the relationship between multimorbidity and polypharmacy with the objective of examining medication use patterns. This could assist to study the possibilities to improve the benefits and avoid the risks associated with medication management in multimorbid patients.

1.9.1 Aim:

Multimorbidity and polypharmacy are common in the older persons, posing a challenge to the healthcare system by increasing the healthcare burden. While the literature explains the

incidence and consequences of polypharmacy and multimorbidity, however, the issue is still remains of serious concern with some aspects still not been covered sufficiently examined. Therefore, the aim of this thesis is to describe the changing patterns of medication prescription practice over the last 20 years in older people with a specific focus on cardiovascular and gastrointestinal diseases. Health informatics and machine learning approaches will be applied to assist in describing the changing in prescription patterns over time. To accomplish this aim, the objectives of this study are set out as follows.

1.9.2 Objectives:

- To identify older patients with multimorbidity with a specific focus on cardiovascular disease over the last 20 years.
- To determine older patients with multimorbidity and a specific focus on gastrointestinal disease over the last 20 years.
- To appraise the polypharmacy in cardiovascular and gastrointestinal diseases.
- To investigate the drug classes prescribed over time in cardiovascular disease and gastrointestinal disorders.
- To explore the majority of the drugs prescribed specificity in cardiovascular disease and gastrointestinal disorders.
- To compare the change in the prescription pattern of cardiovascular diseases in the period between 2001-2020.
- To compare the change in the prescription pattern of gastrointestinal diseases in the period between 2001-2020.
- To collect patient records on the CPRD dataset to apply machine learning strategies.
- To examine changing patterns of cardiovascular and gastrointestinal diseases over the last 20 years.

Chapter 2

Cardiovascular Disease

2.1 Introduction

Cardiovascular diseases are one of the main causes of mortality among older people. In fact, studies show that more than 80% of deaths are directly related to those who are 65 years old and above (Yazdanyar & Newman, 2009). It becomes obvious that people are subject to cardiovascular diseases as they proceed in life and grow older. A number of issues are related to this such as hypertension, changes in cholesterol levels, and the heart ability to pump blood appropriately.

They are a number of risk factors that could play a major role in developing heart diseases. These factors include smoking, bad diet, and lack of exercise. In addition, cardiovascular diseases are also directly linked to multimorbidity which is associated with polypharmacy in older patients (Villén et al., 2022). Polypharmacy is known as the use of five or more medications while multimorbidity is referring to having two or more chronic conditions.

Both multimorbidity and polypharmacy could increase the likelihood of developing cardiovascular diseases due to the potential possibility of adverse drug reactions, drug-drug interactions, and medication nonadherence (Glynn et al., 2008). In the long run, controlling the chronic condition could be challenging which leads to negative overall health impact on patients due to confusion and difficulties of providing the most appropriate mutable medications. Also for some patients, it can be quite to understand the treatment plan which results in an increase in healthcare costs and poor health outcomes.

2.1.1 Cardiovascular Diseases

Cardiovascular disease (CVD), is an illness that affects the heart and blood vessels, and is one of the main causes of death and disability in the world. It is the main contributor to early death and mortality, for instance, in the UK. At the time of writing, 7.6 million people in the United Kingdom are affected by CVD (British Heart Foundation, 2023), and, according to 2020 data from BHF, CVD accounted for 27% of all deaths in the United Kingdom (British Heart Foundation, 2020).

Notably, there are some clear factors that have been seen to increase the risk of CVD, such as high cholesterol, hypertension, smoking, and obesity. Other risk factors associated with CVD are age, family history, and gender, with the incidence of CVD increases with age in men and women. According to the American Heart Association (AHA), the incidence of CVD in U.S. males and females rises with age: 40% between the ages of 40 and 59, 75% between the ages of 60 and 79, and 86% in people over the age of 80 (Rodgers et al., 2019). In addition to this, a difference in the incidence of CVD has been noted in relation to gender: males have been documented to have a higher risk of cardiovascular disease than females (Gao et al., 2019).

CVD increases hospital admissions, and the annual cost of CVD to the UK economy is estimated to be at around £19 billion. Included in this estimate are costs associated with premature mortality and disability, among other expenditures (British Heart Foundation, 2023). Therefore, it is indisputable that CVD is contributing to the financial issues health services are currently facing, and is accordingly of great importance (nationally and internationally) to be prevented and managed appropriately.

2.1.2 Cardiovascular Disease in Older People

Cardiovascular disease is the most commonly diagnosed ailment in older people, and this may be because of age-related effects on the heart and blood vessels. For instance, the heartbeat changes in physical activity, and instances of strain are common. Indeed, these changes may increase a person's risk of heart disease.

Heart attacks, strokes, coronary heart disease (also known as heart disease), and heart failure are more common in older persons aged 65 and older than in younger people, and heart disease is also a major contributor to disability and significantly lowers the quality of life, restricting sufferers' activities (National Institute on Aging, 2018).

The cardiovascular system undergoes many additional changes as people get older. For instance, age-related changes in the electrical system can cause arrhythmias (irregular, fast, or slow heartbeats), which may lead to a pacemaker being required. Further, the valves may restrict blood flow out of the heart, and may also become incompetent — and both of these

pathologies can lead to heart failure with fluid accumulation in the body (i.e., the legs, feet, and abdomen) and the lungs. It is also possible that due to aging, the heart's chambers grow in size, and, despite the increasing size, a chamber's capacity for holding blood may decline when the heart wall thickens. The key factor contributing to the thickening of the heart wall (which raises the risk of atrial fibrillation, a frequent heart rhythm issue in older adults) is long-standing hypertension. Old people become more sensitive to salt, which may elevate blood pressure and/or induce ankle or foot swelling (oedema) (NIA, 2018, Pennacchini et al., 2015).

Of relevance, it has been demonstrated that cardiovascular disease is the leading cause of mortality in high-income countries, comprising a startling 27% of all deaths. This has a huge impact on people's lifestyles, as well as the overall country's economy as a whole (Feary et al., 2010).

2.1.3 Relationship to Polypharmacy and Multimorbidity

Patients with cardiovascular diseases and multimorbidity are at an increased risk of being administered multiple drugs (polypharmacy), with up to 82% of older patients being subjected to polypharmacy (Tefera et al., 2020). Not only this, but research on the composition of polypharmacy regimens (which included data from 7,730 participants in the English Longitudinal Study of Ageing) found that 90.6% of polypharmacy patients were on cardiovascular drugs (Slater et al., 2020). Polypharmacy in patients with cardiovascular disease has been linked with several factors, including increasing age and the presence of multiple morbidities, such as diabetes, hypertension, and dyslipidaemia (which all require numerous medications).

Moreover, multimorbidity in cardiovascular disease and polypharmacy have a strong correlation. For instance, a Scottish study on polypharmacy demonstrated that the mean number of drugs for patients with one condition of ischaemic heart disease was 3.7 while it was 8.0 for patients with ischaemic heart disease and additional co-conditions (Payne, Avery, et al., 2014). Notable, although cardiovascular diseases are the most common disease among older persons who use five or more drugs, polypharmacy is not always considered an inappropriate treatment. In some cases, using the polypharmacy approach becomes beneficial, necessary and suitable (Vrettos et al., 2017).

Indeed, there is much discourse in the field about this point of view, with some arguing that cardiovascular polypharmacy should not be assumed to be dangerous and that it represents poor care. Others however posit that the burden of polypharmacy has been underestimated (Tefera et al., 2020).

2.2 Methods

2.2.1 Study Design

A longitudinal evaluation in the Clinical Practice Research Datalink (CPRD) dataset (CPRD Aurum) was used to analyse electronic health records for the period between January 1, 2001, and December 30, 2020.

2.2.2 Data Source

Clinical Practice Research Datalink (CPRD)

Clinical Practice Research Datalink (CPRD) is a research service that supports prospective and retrospective medical and public health research. It is jointly supported by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research (Clinical Practice Research Datalink, 2022), and is one of the largest datasets of longitudinal medical records from primary care in the world. Notably, the small Value Added Medical Products (VAMP) dataset (created in London in 1987) expanded to become the General Practice Research Database (GPRD) in 1993 and then the CPRD in 2012 (Herrett et al., 2015). CPRD obtains anonymised patient data from a network of GP surgeries in the United Kingdom (CPRD, 2022), and several UK primary care practices can connect to hospital and death data through it (which is usually considered valid data for health events). This increases the validity and value of the CPRD (Arana et al., 2021).

CPRD's data has been utilised in two databases: CPRD GOLD and CPRD Aurum. 60 million patients are included in two CPRD datasets, including 18 million who are currently enrolled, and the data are obtained from a UK-wide network of more than 2,000 GP practices (CPRD, 2022). The difference between the two datasets is that CPRD GOLD comprises data from a separate GP software supplier called Vision, whilst CPRD Aurum contains data given by practices using the EMIS software.

These databases have been made available as independent data packages, since the data across the two systems is structured and coded differently (CPRD, 2022). These datasets cover patient records from various aspects, including demographics, diagnosis, referrals, test results, and prescription.

Clinical Practice Research Datalink (CPRD) Aurum Database

The current study data were derived from the CPRD Aurum, which is a huge population-based, prospectively composed, anonymised medical dataset that has been available for research since 2018. It is composed of eight main files (Wolf et al., 2019). For this study, three of these eight files were used to extract data: the patient file, observation file, and drug issue file. The patient file covers patient demographics and registration information in the practice, the observation file comprises the medical history information recorded on the practice system (such as symptoms, clinical measures, test results, and diagnoses) in addition to demographic data recorded, and the drug issue file provides information on all previously issued prescriptions by the GP system. This file contains information on all prescriptions (drugs and equipment) that have been issued by the practice (Wolf et al., 2019).

CPRD Aurum contains electronic patient records dating from 1988 that have been gathered using the EMIS® patient record software, and the data have been imported into EMIS from other systems (e.g., Vision® and SystmOne®). In the United Kingdom, GPs serve as the protector of NHS care, so providers of hospital and secondary care are compelled to report information on patients to the GP. Thus, primary care records include diagnoses and treatments made by physicians and consultants. In CPRD Aurum, observation and diagnosis data is recorded in EMIS Web®, and this data is then coded using a combination of SNOMED CT, Read Version 2, and local EMIS® codes to a single diagnostic code called 'MedCode' by CPRD. Meanwhile, drugs and equipment prescriptions files are in EMIS Web®, and this data is coded using the Dictionary of Medicines and Devices (DM+D), a subgroup of the SNOMED CT terminology, known as 'ProdCode', by CPRD (Persson et al., 2022).

2.2.3 Ethical Approval

The Health Research Authority has granted the Clinical Practice Research Datalink (CPRD) ethical authority to provide anonymised patient records for use in an observational study (Herrett et al., 2015). Further to this, all research employing CPRD data must obtain approval from the Independent Scientific Advisory Committee (ISAC) before the data is made available to researchers (CPRD, 2023). The ethical approval for the current study was obtained by (ISAC-MHRA), reference number 19_159_R1.

2.2.4 Study Population Criteria

Two main analyses were carried out in this study. Firstly, from the database of one million patients, the CPRD was used to identify and extract patients with cardiovascular disease. However, this list was then condensed to those who had cardiovascular disease alongside two or more chronic conditions, and two or more years of follow-ups. This reduced the total number of patients to 452,243. These patients were then filtered further based on the age of the multimorbidity, the second chronic condition, and the patient's age (whether they were 50 years and above). This additional filtering reduced the patient number to 241,907. After adjusting for the range between the years 2001 and 2020, the number of eligible patients for this study was 228,376 (used for the first group analysis). When this is filtered to those who had 20 years of follow-up appointments, it reduced the number of patients to 17,075 (used for the second group analysis). Please see the following figure for a representation of how the patients were filtered (Figure 2.1).

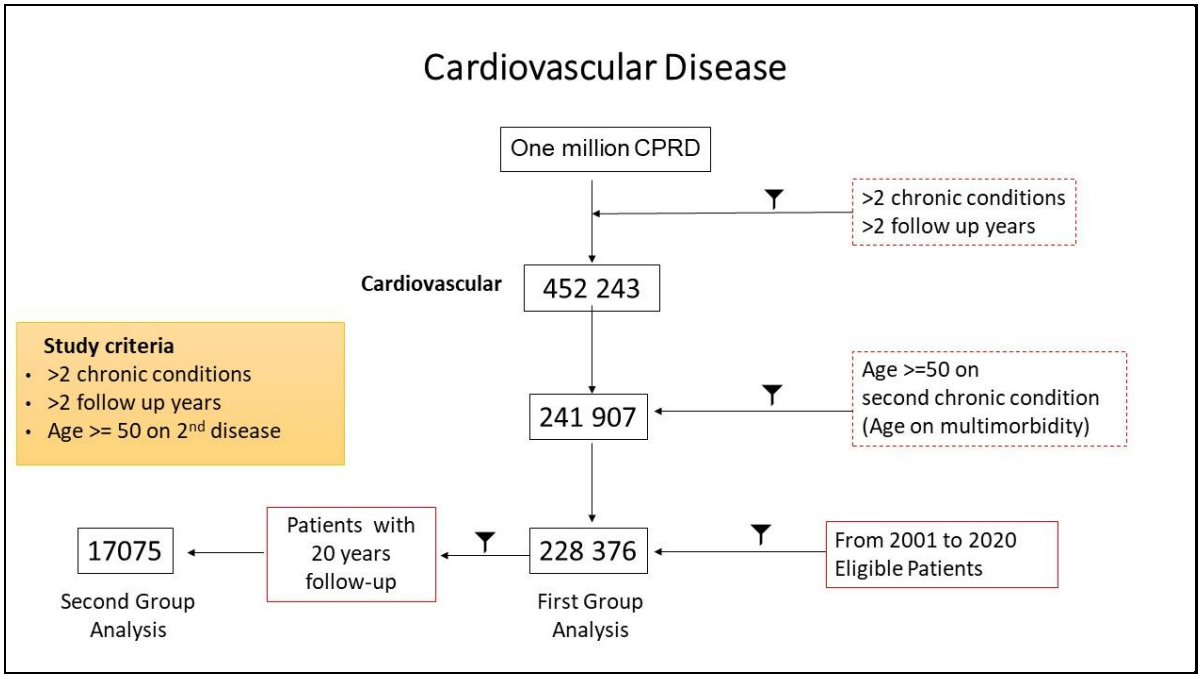

Figure 2.1: Population criteria from the CPRD database for the first and second group analysis

2.2.5 Data Collection

First, the medical records were filtered via cardiovascular diagnoses using MedCode. This meant that for the current study, a total of 19 cardiovascular diseases (CVD) were selected, in addition to a couple of subcategories. The cardiovascular conditions and subcategories were:

1. Atrioventricular block (Complete).
2. Atrioventricular block (Second Degree).
3. Coronary heart disease.
4. Dilated cardiomyopathy.
5. Heart failure.
6. Hypertension.
7. Hypertrophic cardiomyopathy.
8. Lipid disorder.
9. Myocardial infarction.

10. Non-rheumatic aortic valve disorders.
11. Non-rheumatic mitral valve disorders.
12. Cardiomyopathy.
13. Rheumatic valve disease.
14. Sick sinus syndrome.
15. Stable angina.
16. Unstable angina.
17. Atrial fibrillation.
18. Stroke.
19. Transient ischaemic attack.

Next, a list of all cardiovascular drugs that contain available information in the British National Formulary (BNF) in the chapter "Cardiovascular Disease" (2021) were created. After that, the drugs in the cardiovascular disease list were identified using the product code dictionary 'ProdCode' in CPRD, as shown in Figure 2.2. Finally, the medical files containing the medical history and diagnosis were identified in Medcode so the CVD patients with one or more disorders from 19 CVD-mentioned conditions, along with the current study original criteria, could be identified. Then, the prescription records were analysed by ProdCode (where the Medcode has all patients' CVD conditions), and then the extracted data from the Medcode and ProdCode dictionaries was merged together in the CPRD Aurum dataset so the required study groups could be obtained.

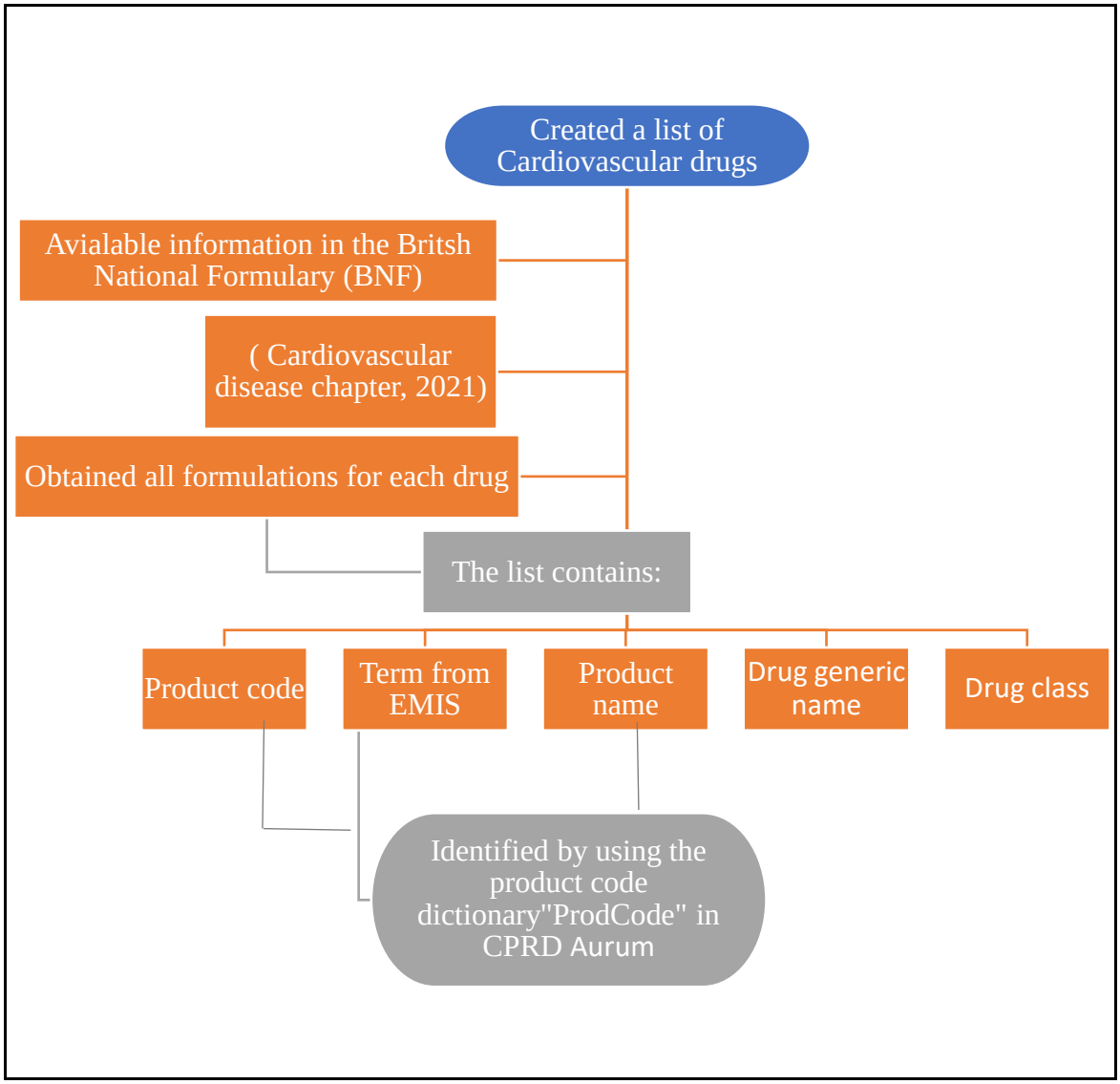

Figure 2.2: The Process of creating cardiovascular drugs, to be recognised by the product code dictionary in CPRD Aurum

2.2.6 Data Analysis

The data were analysed using R and machine learning (ARM) which was applied to the selected patient records. Two analyses were carried out. Firstly, the patients with cardiovascular disease (n = 228,376), who were all older patients aged 50 years or above with two or more chronic conditions and two or more years of follow-ups in the period between 2001-2020, were extracted. Following this, the major drug patterns for the prescribed drugs, along with the major drug classes trend, were analysed. The results were obtained via the preparation of the required CVD drugs list, which was done through the British National Formulary (BNF) in the cardiovascular disease chapter. This was applied and combined to the product code in the

CPRD dictionary so the required cardiovascular database trends in the period between 2001-2020 could be identified.

The patients have been segmented into five years snapshots. Each snapshot was taken as a point prevalence in a specific year (with five year intervals between each one snapshot and the other) as follows:

1. Snapshot One: 2001 (n = 33,484).
2. Snapshot Two: 2005 (n= 73,079).
3. Snapshot Three: 2010 (n = 121,945).
4. Snapshot Four: 2015 (n= 157,326).
5. Snapshot Five: 2020 (n = 150,055).

This was so the total unique drugs prescribed in each 5-year point prevalence, hereafter termed 'snapshot', could be compared. The result from the tested group samples of total unique drugs in the different snapshots was considered statically significant if the *P*-value identified was <0.05 by one-way ANOVA. Snapshot One (in 2001) and Snapshot Five (in 2020) were compared via the *T*-test. Furthermore, for the five snapshots, Pearson's Chi-squared test was used to identify any significant difference between the snapshots in terms of the number of drugs used, so as to identify the polypharmacy percentage in the tested study sample.

The same CVD patients were also tracked in the 20 years of follow-up (n = 17,075), and the leading drug prescribed was analysed to examine the major 'drug classes' trend between 2001-2020. Moreover, the Apriori algorithm was used to identify any associations among the medications in the dataset, including each drug's code, dosage, and generic name recorded in this database (Yoosofan et al., 2015). The study database notably comprises 804 cardiovascular drugs, and the CVD list was created using BNF and a product code dictionary. Then, the information in this dataset was transformed into a single format, and machine learning was used to facilitate the data analysis.

Subsequently, from these datasets, association rules were obtained. Thus, the Apriori algorithm (one of the approaches for determining association rules among medications) was used to

examine the change in drug prescription patterns over time. This technique has the advantage of decreasing search issues to an accessible size, and it also minimises the search scope.

2.2.7 Apriori Algorithm Analysis

One of the traditional algorithms used to identify Association Rules (ARs) between data items in a database, the Apriori algorithm was used in this research. An AR describes a relationship between two sets of frequently occurring items. The term item refers to a binary-valued attribute in the data set, an attribute that can have a value of Yes or No (exists or does not exist). For example, the items may be products that can be bought in a store (Yoosofan et al., 2015), or potential conditions/diseases. The Apriori algorithm is founded on two steps:

1. Identifying a common frequent item set.
2. Creating association rules based on the discovered sets.

There are various parameters for comparing association rules. The two most common are 'confidence' and 'lift'. The level of confidence is defined as the likelihood that a transaction (record) containing *x* also contains *y* following a condition (Trikha & Singh, 2014). In the context of this study, a transaction refers to a prescription pattern, and the 'lift' reflects the correlation between the association rules. The higher the lift (data >1), the higher the positive correlation it refers to. In the same way, the lower the lift (data <1), the more negative the correlation between the association rules (Lai et al., 2022). The count meanwhile refers to the number of transactions that includes all database transactions (Alfiqra & Khasanah, 2020). The current study used the Apriori algorithm implemented in R software to analyse the top 10 prescription patterns for the same people who have 20 years of follow-up by comparing Snapshot One (in the years 2001-2005) and Snapshot Two (in the years 2016- 2020) to examine the change of drug prescription patterns over time.

2.3 Results

2.3.1 Population Characteristics

The study population comprised 228,376 patients in the UK, all aged 50 years and older and diagnosed with cardiovascular diseases between 2001-2020. In accordance with the inclusion

criteria, all the patients with cardiovascular disease had two or more chronic conditions and two or more years of follow-up.

Table 2.1 shows the population characteristics by gender (107,619 females and 120,757 males). The mean age of the females was 65 years (SD 9; range 50-98), while the mean age of the males was 62 years (SD 8; range 50-98). Furthermore, 18% of the study population was aged 55-59 and was female, while 23% of the study population was aged 55-59 and was male. About 0.3% of the study population was female and 90+, and less than 0.1% was male and 90+. And finally, the mean number of comorbidities was six (SD 3; range 2-26) for both females and males.

Table 2.1: The population characteristics by gender (N = 228,376)

Characteristic		**Female N =107,619**	**Male N =120,757**
Comorbidities	Mean [SD]	6 (3)	6 (3)
Follow-up	Mean [SD]	18 (11)	17 (12)
Age	Mean [SD]	65 (9)	62 (8)
Age groups	***Number (%)**		
50-54 Years		17,231 (16%)	24,281 (20%)
55-59 Years		19,328 (18%)	27,469 (23%)
60-64 Years		20,036 (19%)	25,830 (21%)
65-69 Years		18,649 (17%)	20,243 (17%)
70-74 Years		14,955 (14%)	12,843 (11%)
75-79 Years		10,004 (9.3%)	6,438 (5.3%)
80-85 Years		7,072 (6.6%)	3,533 (2.9%)
90+ Years		344 (0.3%)	120 (<0.1%)
Ethnicity	***Number (%)**		
Asian or Asian British		3,065 (2.8%)	3,347 (2.8%)
Black or Black British		3,210 (3.0%)	3,104 (2.6%)
Chinese or Other Group		5,144 (4.8%)	5,395 (4.5%)
Mixed		177 (0.2%)	201 (0.2%)
White		74,183 (69%)	83,404 (69%)
Unknown		21,840 (20%)	25,306 (21%)

Table 2.2 depicts these population characteristics by age group. The 228,376 patients were all categorised into intervals (age 50-54, 55-59, 60-64, 65-69, 70-74, 80-85, and 90+), with the most populated age groups being 55-59 and 60-64 (46,797 and 45,866 patients, respectively). Most of the patients in these two age groups were male, with mean ages of 57 (SD1; range 55-59) and 62 (SD 1; range 60-64) in the age groups 55-59 and 60-64 respectively. Furthermore, the mean number of comorbidities in this age group was six (SD 3; range 2-26), and six (SD 3; range 2-24) in age groups 55-59 and 60-64 respectively.

Table 2.2: Population characteristics by age group (N = 228,376)

Characteristic	50-54 Years N = 41,512	55-59 Years N = 46,797	60-64 Years N = 45,866	65-69 Years N = 38,892	70-74 Years N = 27,798	75-79 Years N = 16,442	80-85 Years N = 10,605	90+ Years N = 464
Gender Number (%)								
Female	17,231 (42%)	19,328 (41%)	20,036 (44%)	18,649 (48%)	14,955 (54%)	10,004 (61%)	7,072 (67%)	344 (74%)
Male	24,281 (58%)	27,469 (59%)	25,830 (56%)	20,243 (52%)	12,843 (46%)	6,438 (39%)	3,533 (33%)	120 (26%)
Comorbidities Mean [SD]	6 (3)	6 (3)	6 (3)	6 (3)	6 (3)	6 (3)	6 (3)	4 (2)
Follow-up Mean [SD]	17 (11)	18 (11)	18 (11)	18 (12)	17 (11)	17 (11)	15 (11)	12 (11)
Age Mean [SD]	52 (1)	57 (1)	62 (1)	67 (1)	72 (1)	77 (1)	83 (2)	92 (2)
Ethnicity Number (%)								
Asian or Asian British	1,839 (4.4%)	1,527 (3.3%)	1,264 (2.8%)	859 (2.2%)	550 (2.0%)	254 (1.5%)	117 (1.1%)	2 (0.4%)
Black or Black British	1,863 (4.5%)	1,375 (2.9%)	1,105 (2.4%)	860 (2.2%)	613 (2.2%)	331 (2.0%)	165 (1.6%)	2 (0.4%)
Chinese or Other Group	2,472 (6.0%)	2,288 (4.9%)	2,032 (4.4%)	1,603 (4.1%)	1,110 (4.0%)	603 (3.7%)	1413 (3.9%)	18 (3.9%)
Mixed	107 (0.3%)	88 (0.2%)	72 (0.2%)	57 (0.1%)	32 (0.1%)	15 (<0.1%)	7 (<0.1%)	0 (0%)
White	27,070 (65%)	32,275 (69%)	32,397 (71%)	27,709 (71%)	19.459 (70%)	11,357 (69%)	7,019 (66%)	301 (65%)
Unknown	8,161 (20%)	9,244 (20%)	8,996 (20%)	7,804 (20%)	6,034 (22%)	3,882 (24%)	2,884 (27%)	141 (30%)

2.3.2 Disease Profile of the Study Population (N = 228,376)

Cardiovascular Diseases and Related Conditions

The disease profile shows that within the study sample of 228,376 patients, hypertension was the most common condition, occurring in around 70% of the total population, followed by lipid disorder. Meanwhile, only about 15% of the study population suffered from coronary heart disease, and the remaining studied cardiovascular diseases were even more uncommon among the study sample, as shown in Figure 2.3.

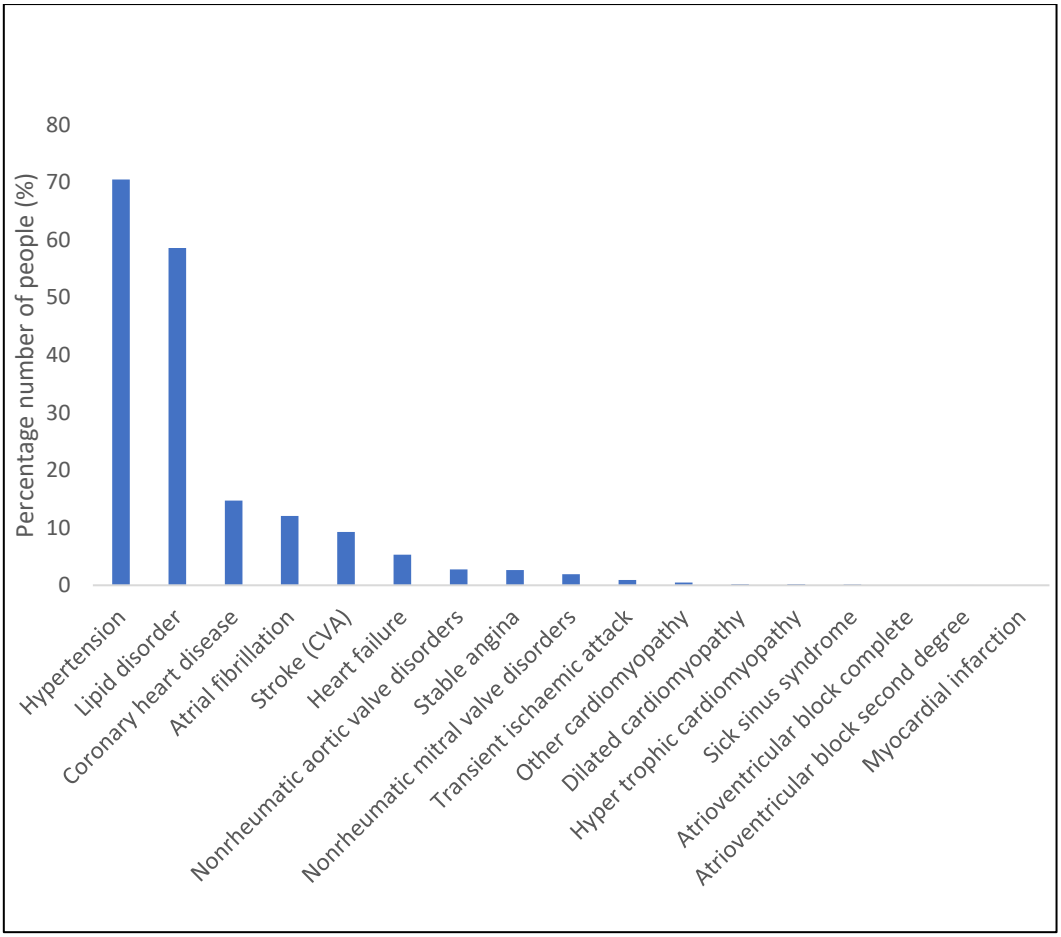

Figure 2.3: The subcategories for the conditions diagnosed in people with cardiovascular disease

Cardiovascular Conditions Alongside Long Term Diseases

Figure 2.4 indicates that hypertension was the most common condition in the patients (who all had cardiovascular disease and comorbidities), while allergic and chronic rhinitis were the two most uncommon conditions. To summarise, the most commonly suffered conditions were hypertension and lipid disorder, followed by chronic kidney disease, chronic pain disorder, and diabetes.

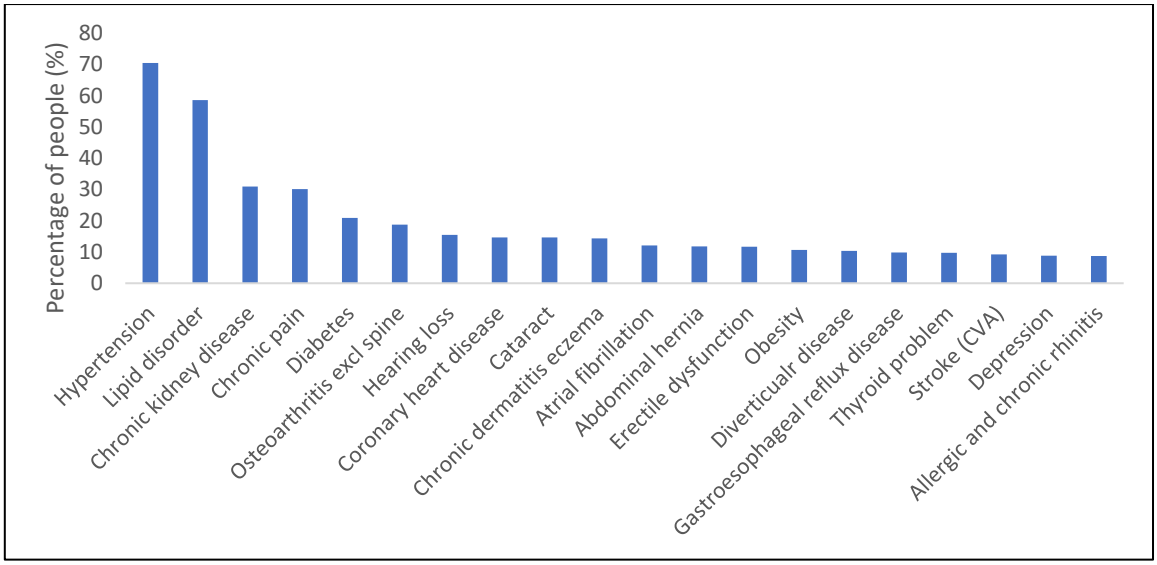

Figure 2.4: The cardiovascular conditions associated with other long term diseases

The correlation between the population sample's age groups and these comorbidities is illustrated in Figure 2.5. As can be seen, comorbidities were most common among the 65-79 age group.

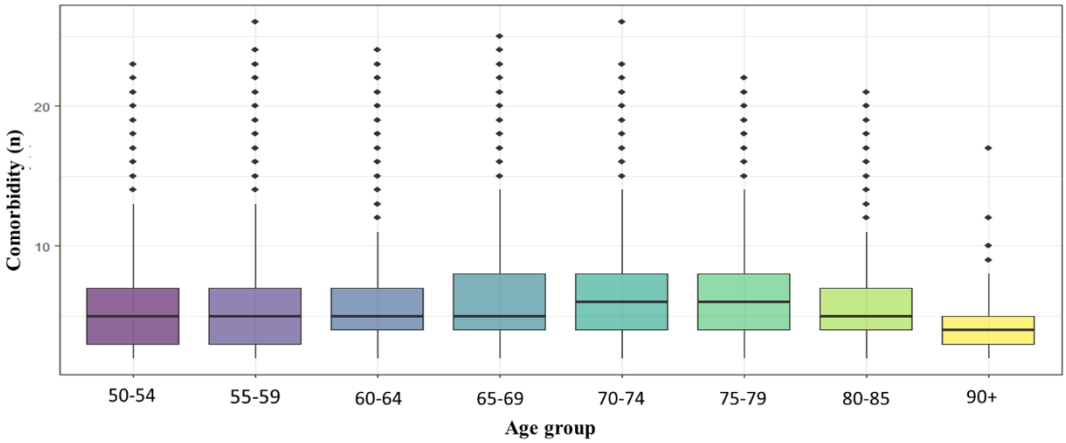

Figure 2.5: Relation between the age group and comorbidities (age group vs. comorbidity)

2.3.3 Prescription Pattern of Drugs Usage and Classes

Major Cardiovascular Drugs Prescribed Between 2001-2020

Table 2.3 (below) illustrates the drug count and percentage for each cardiovascular drug prescription in the period 2001-2020. As can be seen, simvastatin was the most frequently prescribed drug, followed by atorvastatin and ramipril, while lercanidipine was the least commonly prescribed.

Table 2.3: Major drugs prescribed to the study sample (N = 228,376)

Drug name	Count	Prescription (%)
Simvastatin	5441439	13.09
Atorvastatin	4339279	10.44
Ramipril	4136226	9.95
Amlodipine	4096866	9.85
Aspirin	3649614	8.78
Bendroflumethiazide	3348802	8.05
Atenolol	2176065	5.23
Lisinopril	1669993	4.02
Furosemide	1124407	2.70
Losartan	1119159	2.69
Perindopril	989378	2.38
Candesartan	982371	2.36
Clopidogrel	964323	2.32
Doxazosin	874592	2.10
Felodipine	832431	2.00
Warfarin	828173	1.99
Pravastatin	441172	1.06
Indapamide	400331	0.96
Digoxin	370669	0.89
Lercanidipine	352547	0.85

The Major Cardiovascular Drug Classes Trend

Trends in prescribing of the major cardiovascular drugs are shown in Figures 2.6 to 2.11. As can be seen for statins (Figure 2.6), angiotensin receptor blockers (Figure 2.7) and calcium channel blockers (Figure 2.8), while the trends were either downwards or variable for other drugs (Figures 2.9-2.11)

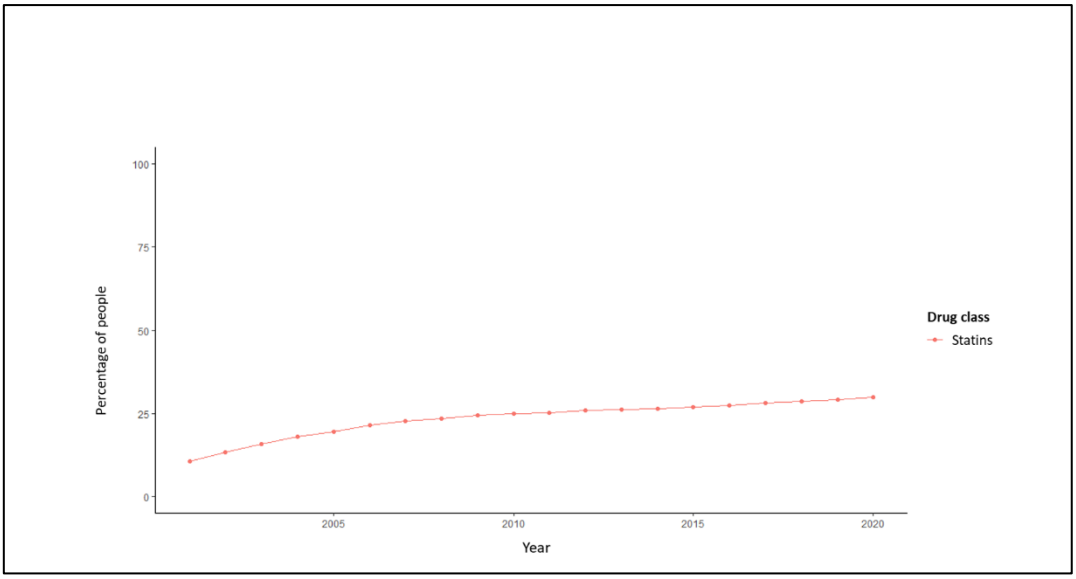

Figure 2.6: The percentage of people prescribed the statins drug class increased between 2001-2020

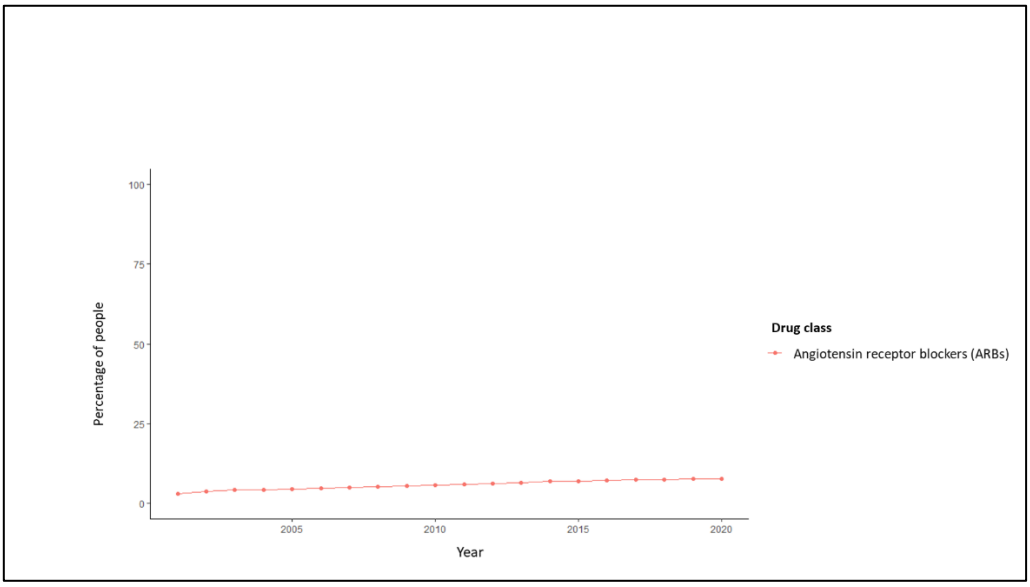

Figure 2.7: The percentage of people prescribed the angiotensin receptor blockers (ARBs) drug class increased in the period 2001-2020

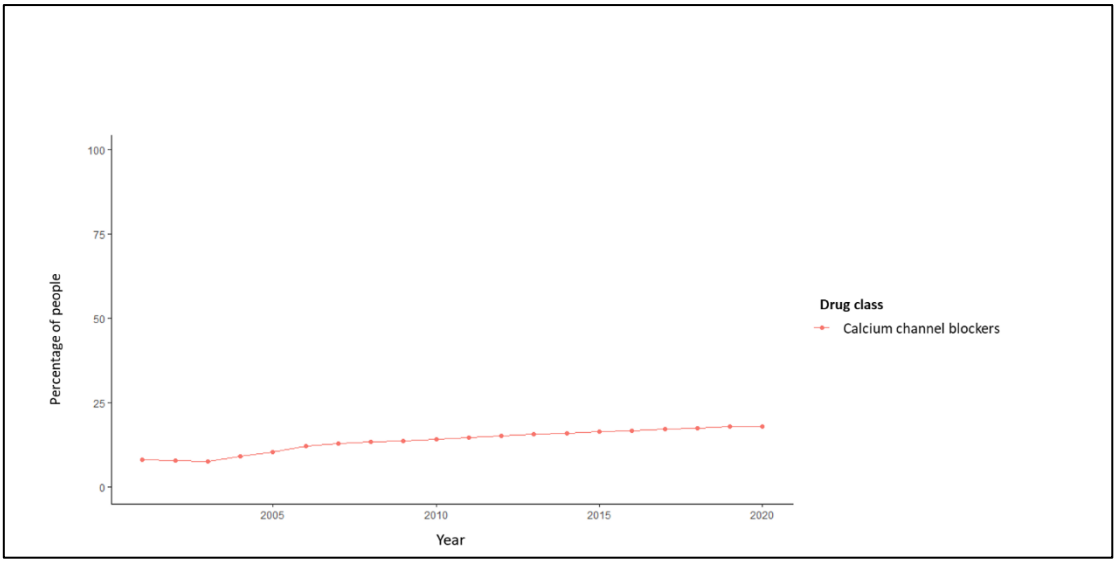

Figure 2.8: The percentage of patients prescribed calcium channel blockers rose dramatically in the period from 2003-2020

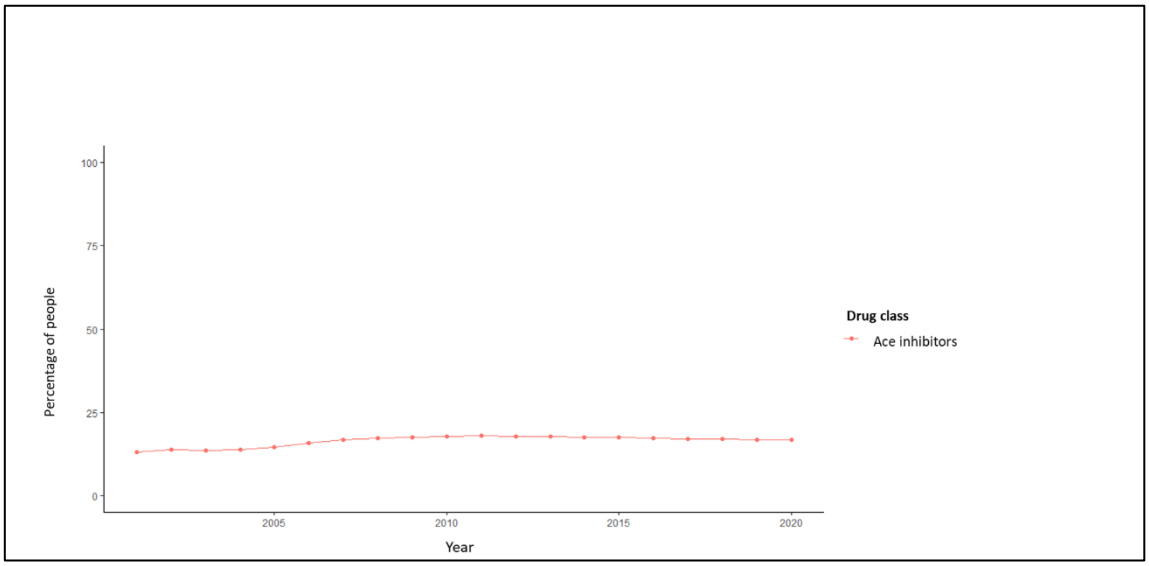

Figure 2.9: The percentage of people who used angiotensin-converting enzyme (ACE) inhibitors increased from 2005-2012 and then decreased constantly until 2020

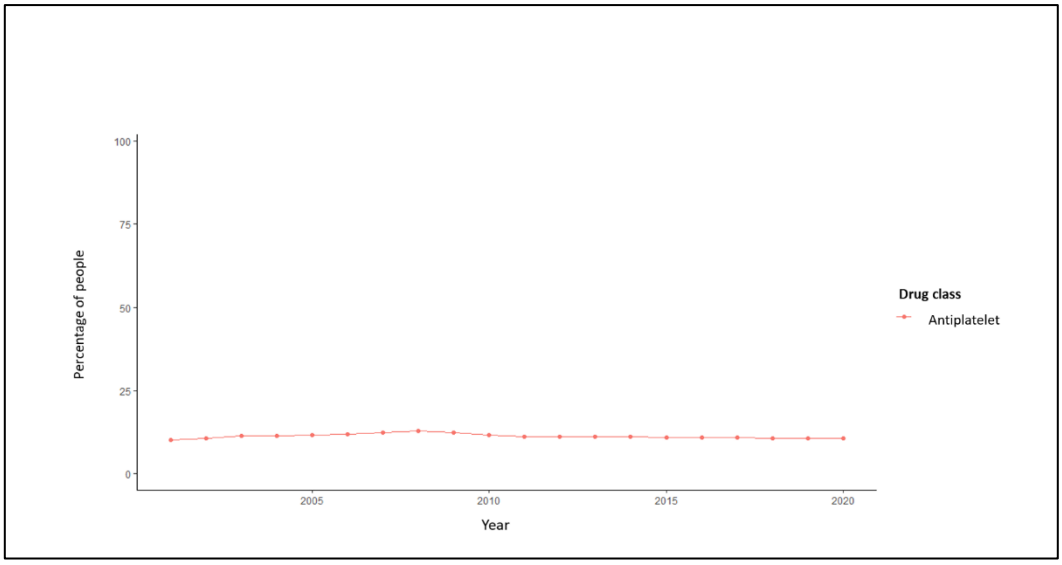

Figure 2.10: The percentage of people who used the antiplatelet drug class rose between 2001-2008 and then dropped until 2011

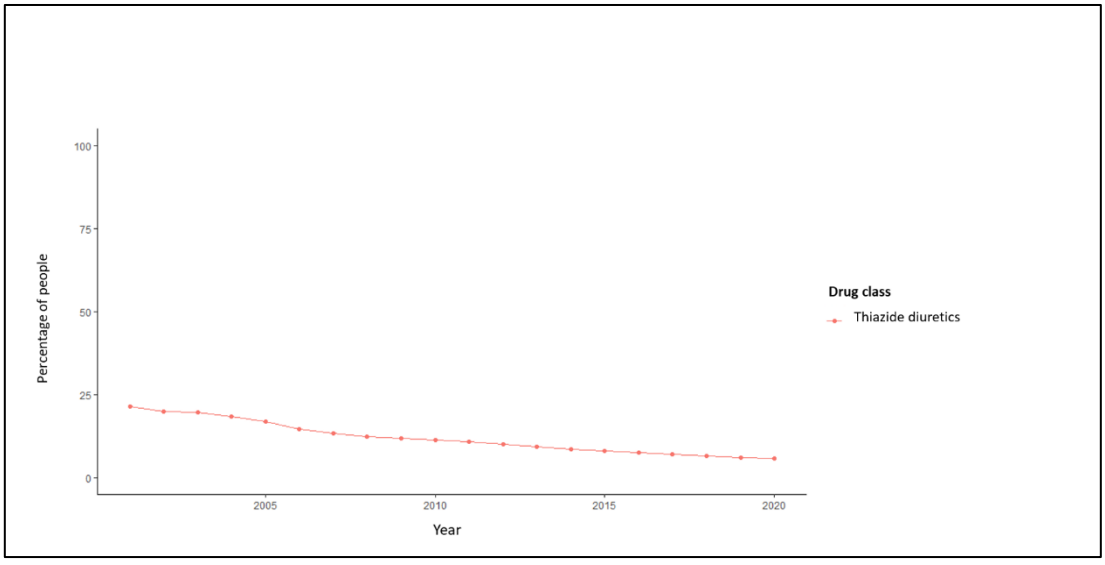

Figure 2.11: Thiazide diuretics started at a high value of around 22% and experienced a steep decline in the period between 2001-2020

Top Ten Drug Class Trends in the Period 2001-2020

Figure 2.12 depicts the most commonly prescribed drug classes. As can be seen, statins and calcium channel blockers were the most commonly prescribed drugs between 2001-2020, while oral anticoagulants were the least commonly prescribed drugs during the same period.

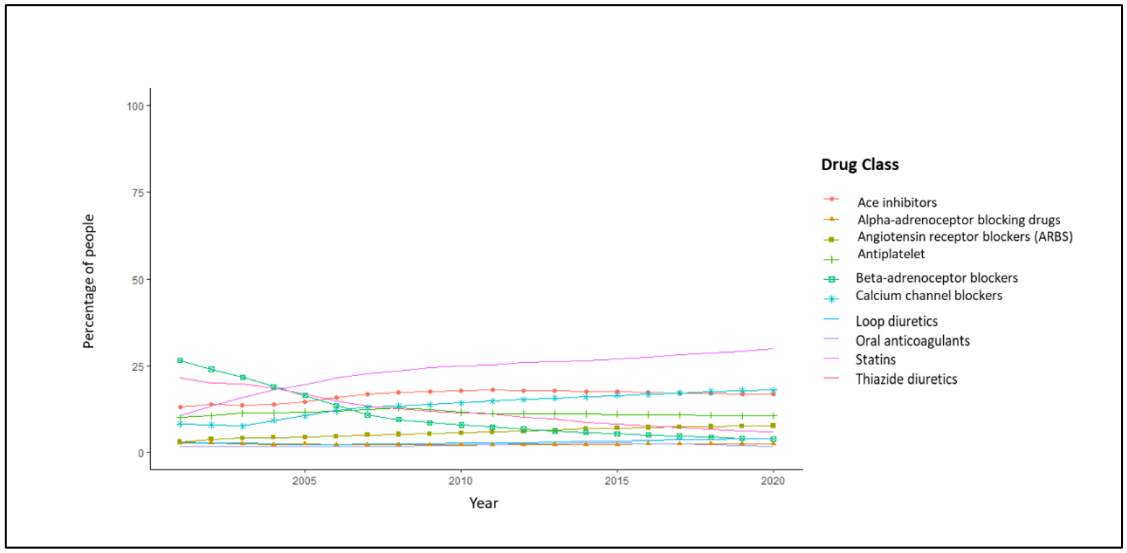

Figure 2.12: The top ten drug classes prescribed between 2001-2020

Most Commonly Prescribed Drugs in the Drug Class Trend

Within each drug class (Figure 2.13), there were differences in prescribing trends. The rate at which simvastatin was prescribed increased sharply between 2001-2010 and then declined from 2010. Meanwhile, atorvastatin fluctuated until 2015 and then increased dramatically until 2020.

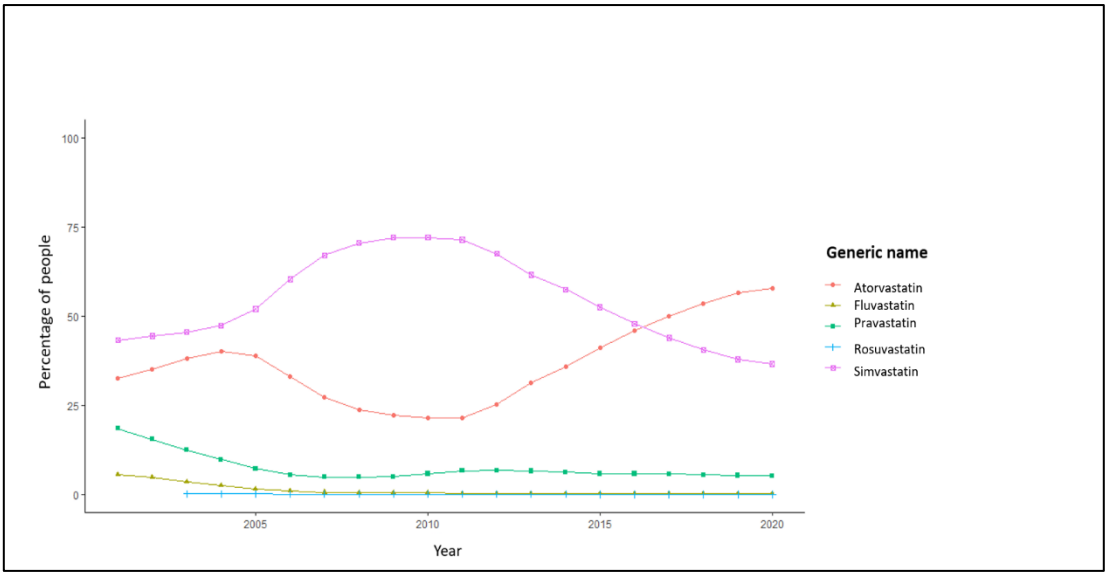

Figure 2.13: Most commonly prescribed medications in the statins drug class in 2001-2020

Figure 2.14 shows that aspirin started at a high prescription rate of around 90% before decreasing to around 60% over the course of the study period. On the other hand, clopidogrel started at a low number (around two percent) and then jumped dramatically to around 36% in 2020.

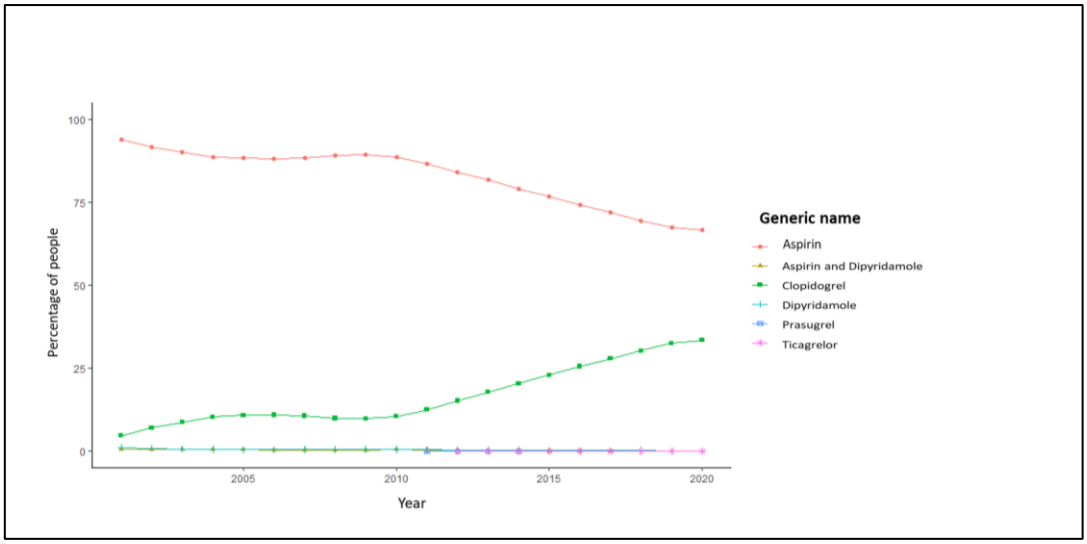

Figure 2.14: The most commonly prescribed medications in the antiplatelet drug class between 2001-2020

Figure 2.15 illustrates that amlodipine was the most commonly prescribed drug in the calcium channel blockers drug class, starting from around 30% in 2001 and dramatically increasing to around 79% in 2020.

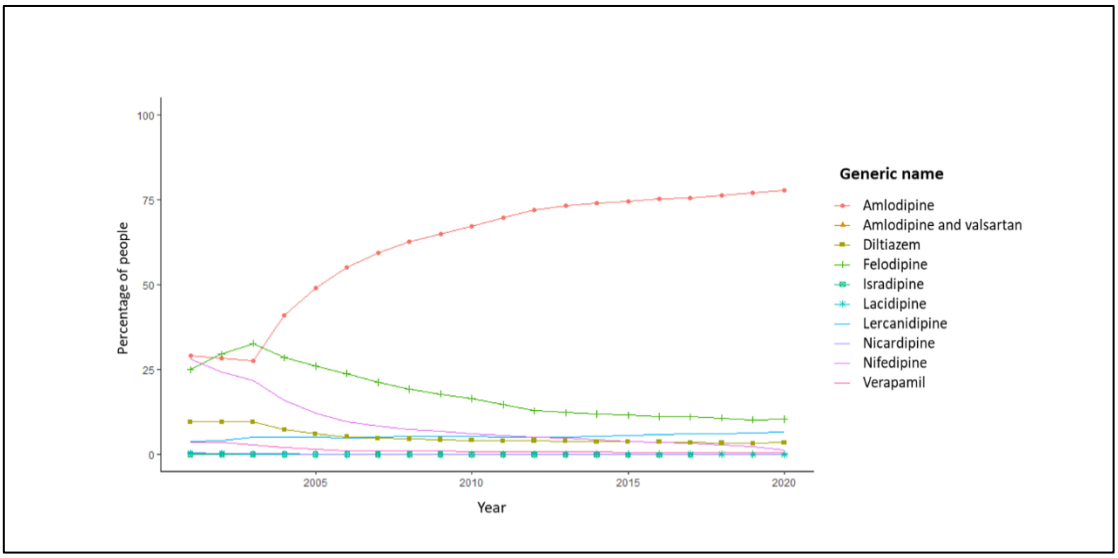

Figure 2.15: The most commonly prescribed drugs in the calcium channel blockers (CCB) drug class between 2001-2020

The most commonly prescribed ARBs drug was losartan, at around 53%, followed by candesartan, with a percentage of around 38% in 2020. The majority of the remaining drugs shown in Figure 2.16 remained steady between 2001-2020.

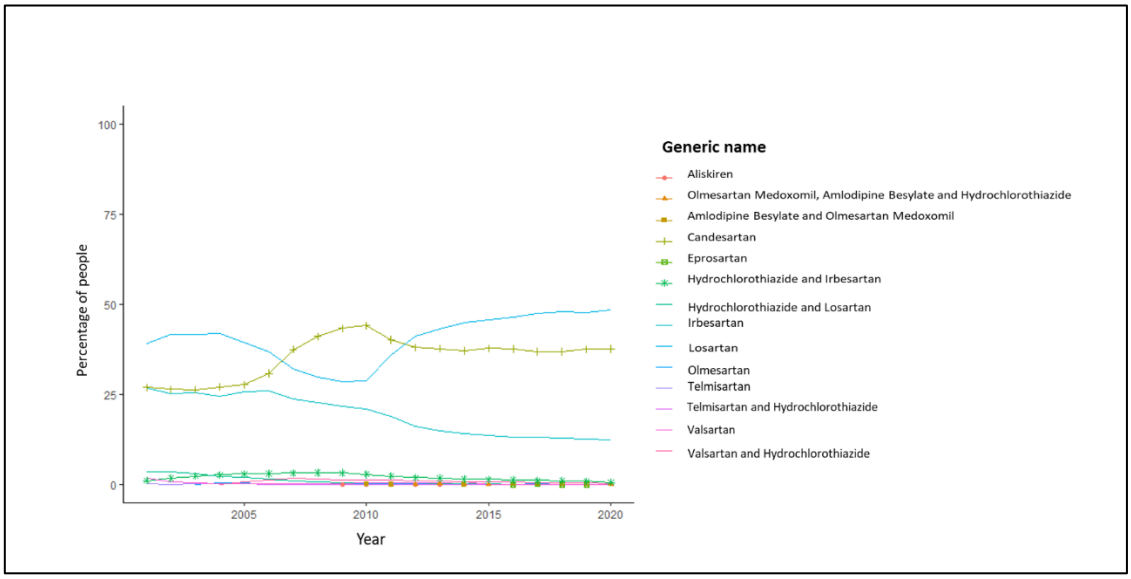

Figure 2.16: The most commonly prescribed drugs in the angiotensin receptor blockers (ARBs) drug class in the period 2001-2020

For the ACE inhibitors (Figure 2.17), ramipril started at 30% in 2001 and then increased sharply to 70% in 2020. Meanwhile, lisinopril started at around 48% in 2001 and then dropped to roughly 19% in 2020. Bendroflumethiazide was the most commonly prescribed drug in the thiazide diuretics drug class for the same study period (Figure 2.18).

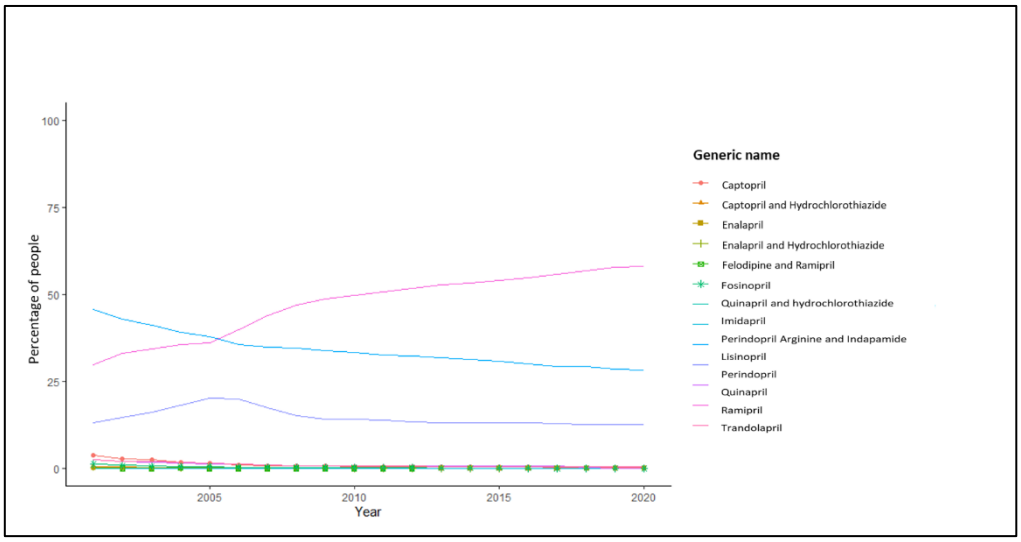

Figure 2.17: The most commonly prescribed angiotensin-converting enzyme (ACE) inhibitors between 2001-2020

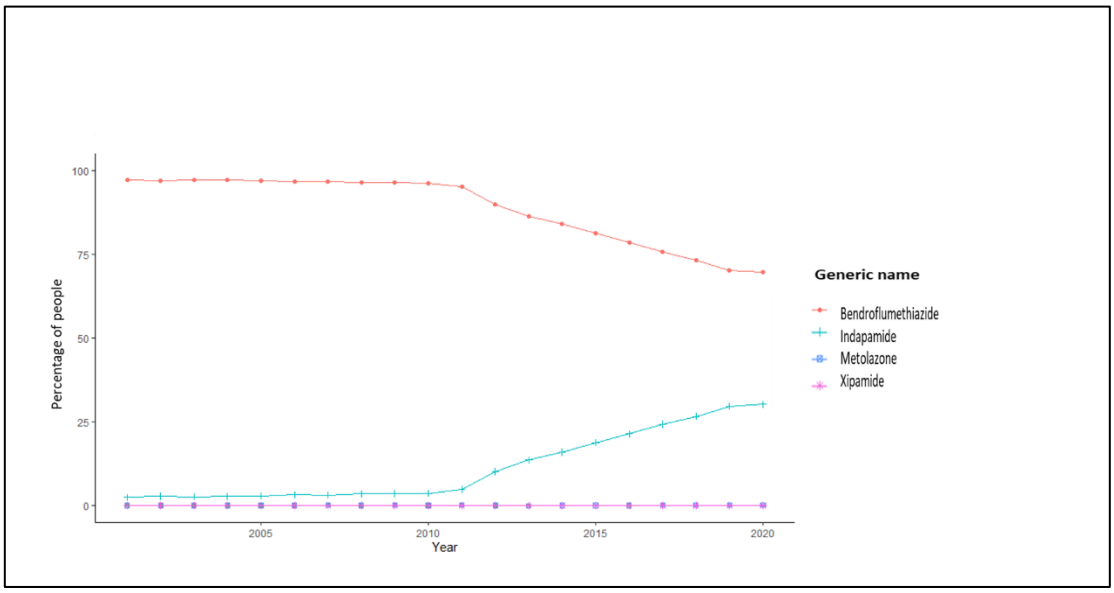

Figure 2.18: The most commonly prescribed thiazide diuretics between 2001-2020

Total Unique Drug Prescriptions from 2001-2020

The current study analysed the number of drugs prescribed to patients with the cardiovascular disease within five-year snapshots. These numbers were compared using Pearson's Chi-squared test, and the results showed that there is a statistically significant deferent in the number of the consumed drugs during the study period in five-year snapshots between 2001–2020 *P*-value (<0.001). In addition, a comparison between the total unique drugs in the five-year snapshots from 2001-2020 using the ANOVA test showed that there are statistically significant differences in the total unique drugs prescription in the five-year intervals between the tested groups (*P*- value <0.0001), as shown in the Tables 2.4 and 2.5 below.

Table 2.4: Drug consumption in five-year snapshots between 2001-2020

Characteristic	2001 N = 33,484	2005 N = 73,079	2010 N = 121,945	2015 N = 157,326	2020 N = 150,055
Number of drugs N(%)					
1	18,098 (54%)	25,973 (36%)	37,019 (30%)	45,594 (29%)	46,017 (31%)
2-4	14,538 (43%)	41,468 (57%)	74,323 (61%)	98,969 (63%)	96,040 (64%)
5-9	845 (2.5%)	5,617 (7.7%)	10,573 (8.7%)	12,739 (8.1%)	7,993 (5.3%)
10-15	3 (<0.1%)	21 (<0.1%)	30 (<0.1%)	24 (<0.1%)	5 (<0.1%)

Table 2.5: Total unique drugs analysis for five-year snapshots (2001, 2005, 2010, 2015, and 2020)

Year	Population count	Mean	Standard deviation	Median	Minimum drug	Maximum drug	Drug range
2001	33484	1.580904	0.860066	1	1	8	7
2005	73079	2.07756	1.189049	2	1	10	9
2010	121945	2.258043	1.244542	2	1	10	9
2015	157326	2.278231	1.225307	2	1	12	11
2020	150055	2.20058	1.15282	2	1	10	9

Comparison of Unique Drug Prescription in Snapshot One (2001) and Snapshot Five (2020)

The *T*-test was used to compare between the tested groups. This is to identify if there are statistically significant differences in the mean number of the total cardiovascular unique drugs at the beginning and the end of the study period (2001 and 2020) individually. The results in Table 2.6 show that there was a statistically significant increase (*P*-value <0.0001) in the mean of the total cardiovascular drugs prescription.

Table 2.6: Comparison of cardiovascular drug prescription in 2001 and 2020

Group	2001	2020
N	33484	150055
Mean	1.581	2.201
SEM	0.0047	0.002976

2.3.4 Population Characteristics of the cohort followed over 20 years (N = 17,075)

The study population (n = 17,075) in the UK was tracked and identified as having constant and continuous follow-up for the entire 20 years in the period between 2001 and 2020. The individual patients were also above the age of 50 years and had been diagnosed with cardiovascular diseases, together with two or more chronic conditions.

Table 2.7 shows the population characteristics of the same patients over the 20 years of follow-up. Specifically: there was a total number of 8,888 females and 8,187 males; the mean age was 64 years (SD 8; range 50-95) and the patients in the 65-69 age group represented 21% (n = 3,635) of the study population, as did the 60-64 year age group (n = 3,617). In contrast, the 90+ age group comprised 0.1% (n = 19) of the study population.

Table 2.7: Population characteristics of the same patients over 20 years of follow-up (N = 17, 075)

Characteristic	N = 17,075
Gender Number (%)	
Female	8,888 (52%)
Male	8,187 (48%)
Age Mean [SD]	64 (8)
Age Group Number (%)	
50-54 Years	2,060 (12%)
55-59 Years	3,221 (19%)
60-64 Years	3,617 (21%)
65-69 Years	3,635 (21%)
70-74 Years	2,545 (15%)
75-79 Years	1,327 (7.8%)
80-85 Years	651 (3.8%)
90+ Years	19 (0.1%)
Ethnicity Number (%)	
Asian or Asian British	315 (1.8%)
Black or Black British	337 (2.0%)
Chinese or Other Group	520 (3.0%)
Mixed	20 (0.1%)
White	12,400 (73%)
Unknown	3,483 (20%)

2.3.5 Prescription Pattern of Drug Usage and Drug Classes (N = 17,075)

The Major Drug Classes Trend

The two figures (Figures 2.19 and 2.20) show the percentage of people prescribed statins class Angiotensin Receptor Blockers (ARBs) over the tested study period. Both prescription rates increased sharply between 2001-2020.

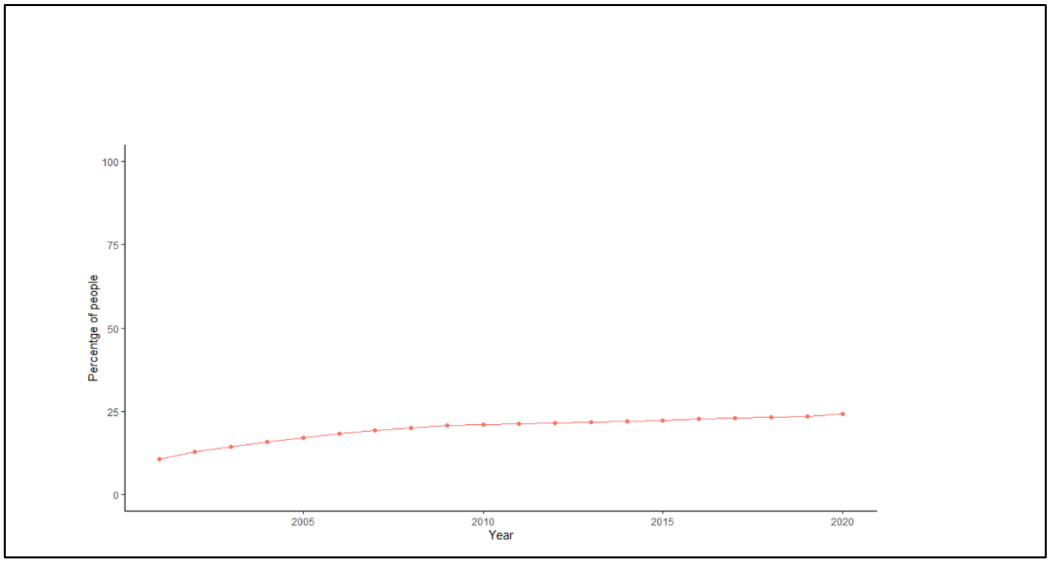

Figure 2.19: Percentage of people prescribed the statins between 2001-2020

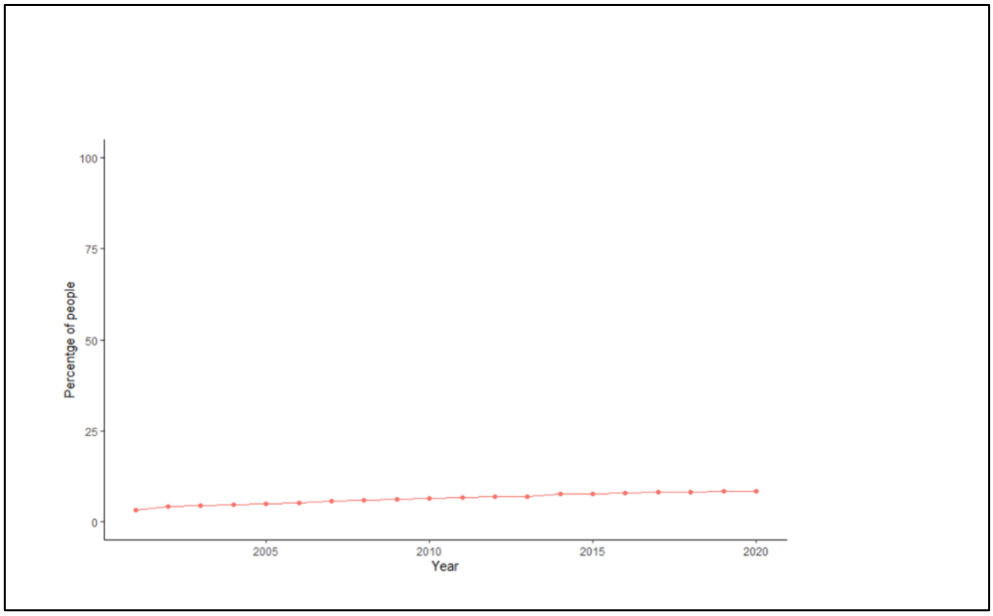

Figure 2.20: The percentage of people prescribed the angiotensin receptor blockers (ARBs) saw a noticeable increase between 2001-2020

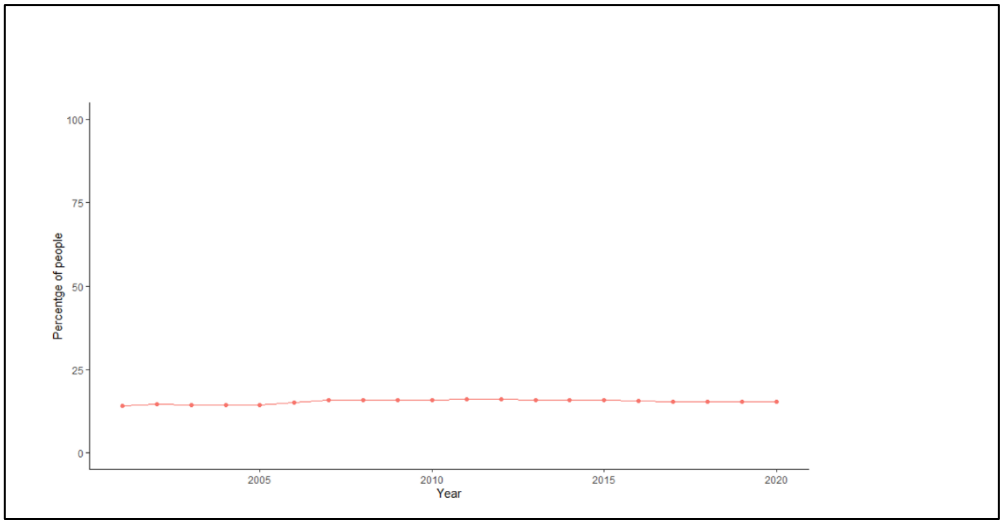

Figure 2.21: The percentage of people who used angiotensin-converting enzyme (ACE) inhibitors rose from 2004 to 2012 and then dropped until 2020

The calcium channel blockers drug class prescription rate sharply increased (as can be seen in Figure 2.22) throughout the study period. For antiplatelet drugs (Figure 2.23), there was a continues increase until 2009, from which point there is a sharp drop until 2020. Meanwhile, thiazide diuretics use started at a high rate of around 22% and then experienced a decline over the study period (Figure 2.24).

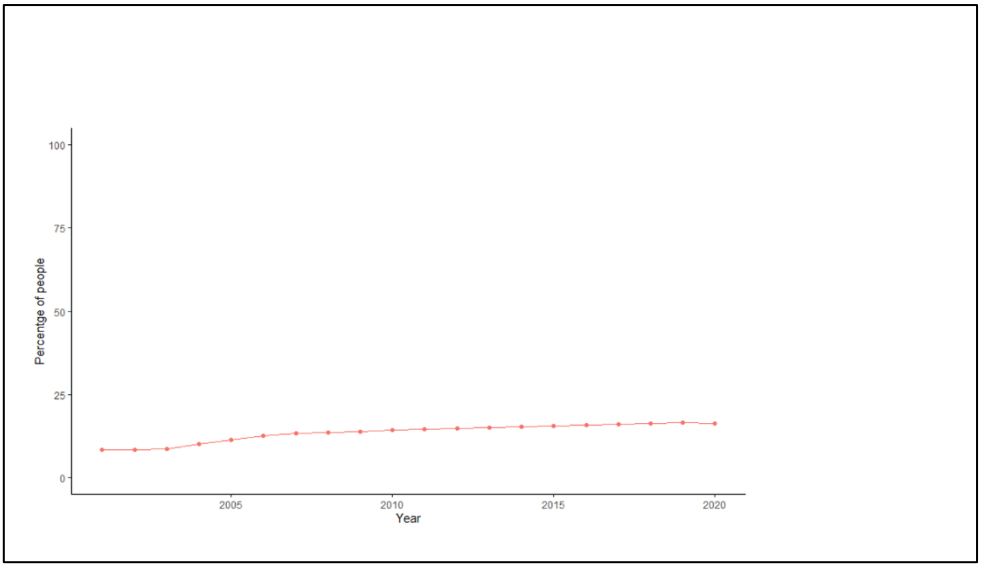

Figure 2.22: Calcium channel blockers' drug prescription throughout the study period

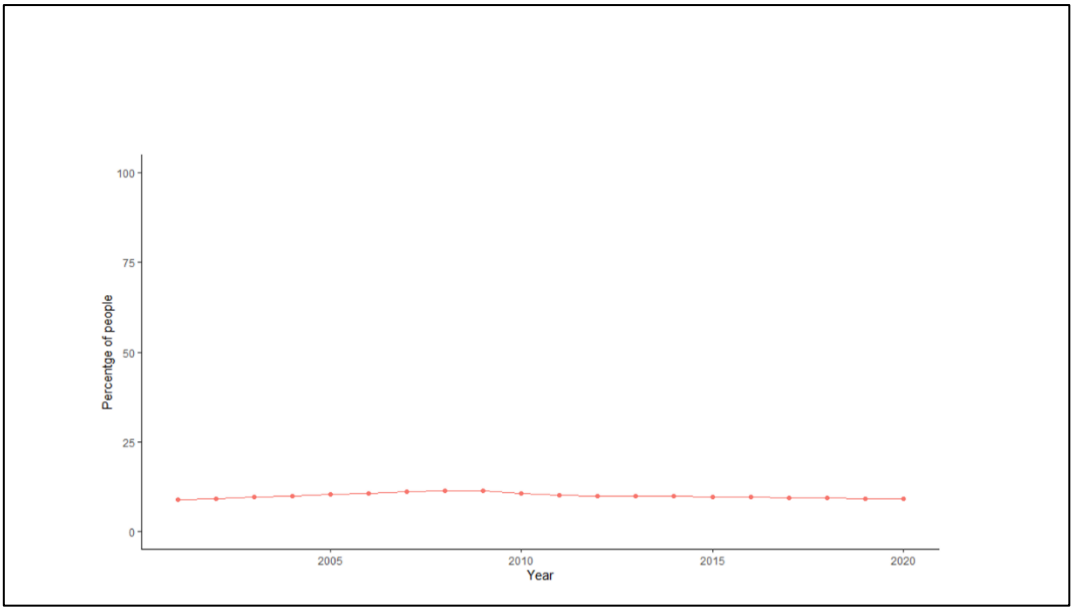

Figure 2.23: Antiplatelet drug class trend from 2001 until the end of the study period

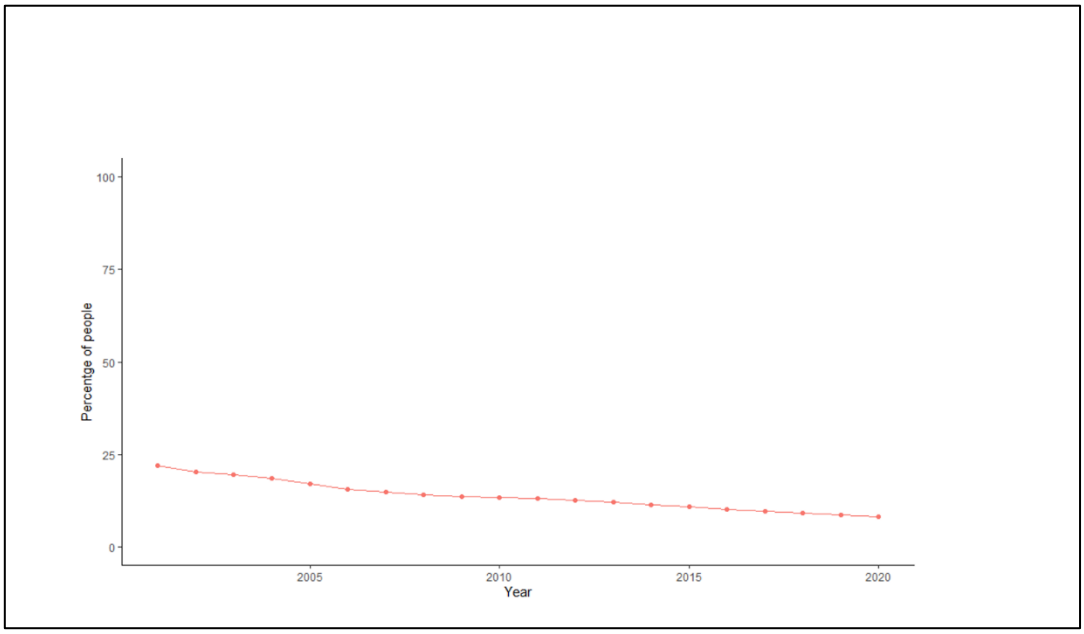

Figure 2.24: Thiazide diuretic use between 2001-2020

Figure 2.25 below shows that the most commonly prescribed drug class between 2001-2020 were statins, followed by calcium channel blockers.

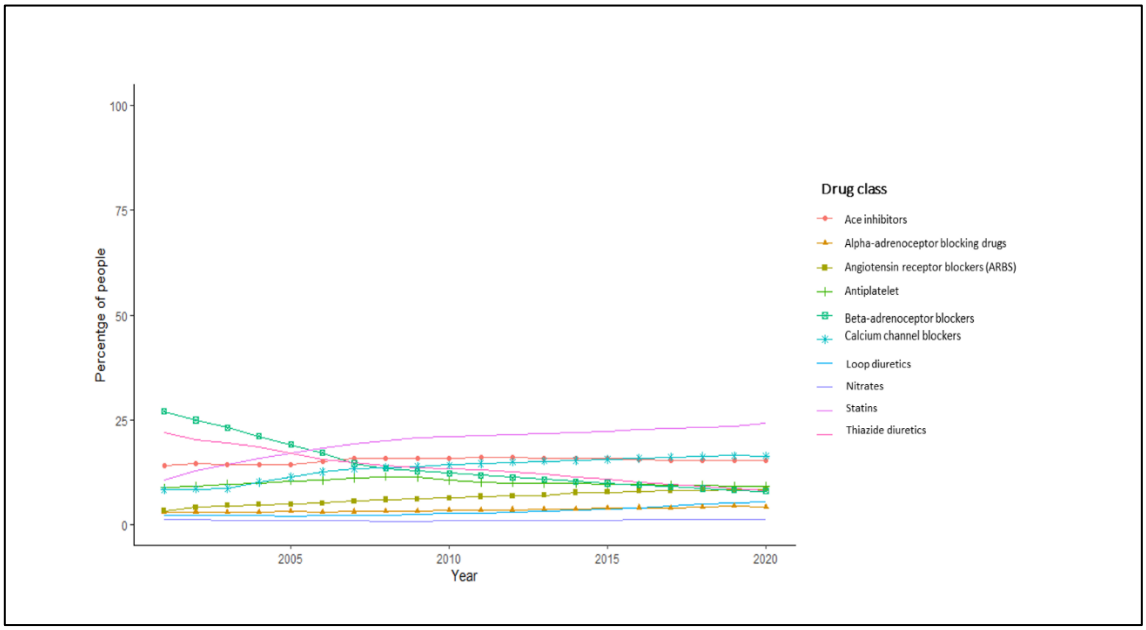

Figure 2.25: Top ten drug classes trend for the same patients for 20 years follow-up

Prescription Pattern Comparison at the Beginning and End of the Study Period

Tables 2.8 and 2.9 (below) show a comparison between the prescription patterns in two snapshots. The first snapshot spans the beginning of the study period (2001-2005), and the second is Snapshot Two (2016- 2020), the end of the study period. The analysis was carried out using the Apriori algorithm, where the sample size (number of records/transactions) was (n = 17,075). Aspirin, clopidogrel, and furosemide are associated with atorvastatin by a high probability of confidence with 72.3% and a high correlation with lift 2.55 as shown in Table 2.9. It was found that Atenolol, atorvastatin, and isosorbide are usually prescribed with aspirin at 66% of confidence, and the high-value coloration is 3.9. The same relation was illustrated in the period between 2001-2005. However, Table 2.9 illustrates that the drug combination has been substituted to atorvastatin instead of simvastatin in the period between 2016-2020.

Table 2.8: Top 10 patterns in the period 2001-2005

Antecedent	Consequent	Confidence (%)	Lift	Count
{Atenolol,Nicorandil}	{Aspirin}	0.625	4.56	940
{Atenolol,isosorbide,Simvastatin}	{Aspirin}	0.602	4.39	719
{Aspirin,Pravastatin,Ramipril}	{Atenolol}	0.584	1.87	746
{Atenolol,Pravastatin,Ramipril}	{Aspirin}	0.579	4.22	746
{Atenolol,isosorbide}	{Aspirin}	0.574	4.18	1783
{Aspirin,Nicorandil}	{Atenolol}	0.541	1.73	940
{Aspirin,isosorbide,Simvastatin}	{Atenolol}	0.540	1.72	719
{Atorvastatin,isosorbide}	{Aspirin}	0.539	3.93	721
{isosorbide,Simvastatin}	{Aspirin}	0.519	3.78	1332
{Digoxin}	{Warfarin}	0.465	20.54	3170

Table 2.9: Top 10 patterns in the period 2016-2020

Antecedent	Consequent	Confidence (%)	Lift	Count
{Amlodipine,Atenolol,Clopidogrel}	{Atorvastatin}	0.727	2.569	1632
{Aspirin,Clopidogrel,Furosemide}	{Atorvastatin}	0.723	2.555	1208
{Amlodipine,Clopidogrel,Losartan}	{Atorvastatin}	0.709	2.505	1316
{Amlodipine,Bendroflumethiazide,Clopidogrel}	{Atorvastatin}	0.695	2.457	1078
{Clopidogrel,Spironolactone}	{Atorvastatin}	0.689	2.434	1114
{Atenolol,Clopidogrel,Ramipril}	{Atorvastatin}	0.68	2.401	963
{Atenolol,Atorvastatin,isosorbide}	{Aspirin}	0.669	3.99	1185
{Amlodipine,Aspirin,Clopidogrel}	{Atorvastatin}	0.659	2.328	947
{Amlodipine,Nicorandil}	{Atorvastatin}	0.648	2.288	1452
{Clopidogrel,Furosemide,Ramipril}	{Atorvastatin}	0.638	2.254	1143

Table 2.10 (below) shows the change of pattern in sequence of two drugs being prescribed over time. The count refers to the number of prescriptions. The higher (greenest) the count number is the greater likelihood/chance that the two drugs are prescribed together. The following results draw a comparison between the first snapshot (2001–2005) and the second snapshot (2016–2020) to illustrate the two drugs most commonly prescribed together in these study periods**.** The results show that aspirin and atorvastatin were most commonly prescribed

together in snapshot two, though there was a lower correlation regarding them being prescribed together in Snapshot One (2001-2005).

Table 2.10: Change of pattern in sequence of two drugs being prescribed over Time

Rule	2001-2005	2016-2020
{Aspirin} => {Atorvastatin}	16183	58905
{Atorvastatin} => {Ramipril}	8007	57471
{Ramipril} => {Simvastatin}	9146	48466
{Aspirin} => {Simvastatin}	21823	44115
{Atenolol} => {Simvastatin}	22946	39902
{Amlodipine} => {Aspirin}	5680	39465
{Amlodipine} => {Simvastatin}	4255	38978
{Simvastatin} => {Bendroflumethiazide}	14805	38545
{Aspirin} => {Ramipril}	12257	38016
{Ramipril} => {Aspirin}	12257	38016
{Amlodipine} => {Atenolol}	9615	36778
{Atorvastatin} => {Atenolol}	15440	36778
{Amlodipine} => {Bendroflumethiazide}	9780	35482
{Atorvastatin} => {Bendroflumethiazide}	12085	35371
{Ramipril} => {Bendroflumethiazide}	16575	28562
{Ramipril} => {Atenolol}	14984	28187

High count **Low count**

2.4 Discussion

2.4.1 Population Characteristics and Diseases Profile

In the study population, the number of males was higher than females (120,757 and 107,619, respectively) because the incidence and occurrence of cardiovascular disease is usually higher in males than in females of an identical age (Wakabayashi, 2017). Moreover, the 90+ age group was extremely small compared to the other age groups in this study, potentially because fewer individuals are expected to live over 90 years old. Additionally, the majority of the population's ethnicity was white, which is likely largely due to the fact that the study took place in the United Kingdom. Another reason for this (and a study limitation), however, could be that the ethnicity coding in the CPRD may not be accurate: typically, when the ethnicity of the patient is missing, they will refer to them as 'White' on the record (since this is the ethnicity that represents the majority of population in the UK).

The study illustrates that 70% of cardiovascular disease sufferers also suffer from hypertension, while 58% of the population were recorded to have lipid disorder. These two conditions are subcategories of cardiovascular disease (an 'umbrella' term). Hypertension is the most common condition, and was a main contributing cause to over 670,000 deaths in the United

States in 2020 (Centers for Disease Control and Prevention, 2023). It is also a major risk factor in various cardiovascular diseases, including coronary artery disease, atrial fibrillation, heart failure, peripheral arterial disease, cerebrovascular disease, and aortic aneurysm (Tackling & Borhade, 2022). Further, lipid disorder is a predominant risk factor for CVD (Boucheniata et al., 2022), and is probably the single biggest risk factor, although it is not considered a disease of the heart or cardiovascular system, but a metabolic state.

Notably, 14.7% of the study population suffer from coronary heart disease, and, indeed, these results may be generalisable to a wider population, since this is already known to be the most common type of CVD: in 2020, approximately two out of every ten deaths from coronary heart disease occurred in adults under the age of 65 due to that type of heart illness (CDC, 2022).

Conversely, the prevalence of stable angina among the study population was quite minimal; it was limited to around three percent of the study population. This could be related to some kind of coding issue, since people are often not coded as suffering from angina, but from a heart attack, and are discharged from the hospital with this diagnosis. Some GP practices also add this to patients' records, and it is for this reason that only looking at a GP record can be misleading. It could be more helpful and precise to look at the hospital data at a later stage, since it could represent accurate details about the patient's actual condition. Coding may be different in general practices compared to hospitals, and so this is one of the CPRD's limitation that needs to be taken into consideration.

Comorbidity is defined as the existence of one or more co-occurring chronic illnesses alongside an index disease (Buddeke et al., 2019), and this study's results presented the top 20 comorbidities within CVD patients. Here, 70% of the study population also suffered from hypertension, 58% from lipid disorder, 30.9% from chronic kidney disease, 30.1% from chronic pain, and 20% from diabetes. These numbers highlight the fact that hypertension and lipid disorders represent serious risk factors for causing CVD. In addition, chronic kidney disease (CKD) raises the risk of cardiovascular disease (CVD), and, similarly, cardiovascular disease may promote CKD, creating a vicious cycle. This is because heart failure promotes kidney function reduction, and atherosclerosis works to promote renovascular disease progression. As a consequence, as renal function reduces, a number of cardiovascular risk

factors (such as volume expansion, calcium-phosphate metabolism disturbances, hypertension, and dyslipidaemia) may be exacerbated—which can aggravate CVD, as well as other related diseases. This accordingly leads to an increase in polypharmacy (Weiner et al., 2006).

The study shows that the number of comorbidities suffered by the study sample increased with the subjects' age, especially in the 65-69, 70-74, and 75-79 age groups. Indeed, most chronic conditions become more widespread as patients grow older. It is known, for example, that patients are 60% more likely to develop two or more significant conditions when they are 75-79 years old (Day, 2017). However, perhaps counterintuitively, this study's results showed that the number of comorbidities declined in the age groups 80-85 and 90+—although notably, there were much fewer participants in these groups compared with the other age groups, which maty account for this finding. Additionally, the mortality rate is higher in the older persons groups. For instance, Yazdanyar & Newman have demonstrated that approximately 40% of cardiovascular deaths occur in people over 85 years old, the main reasons for this fatality rate being associated with heart failure, coronary heart disease, and stroke. Further to this, the mortality rate in the 75-84 age group is twice as high as that in the 65-74 age group (Yazdanyar & Newman, 2009). It is also noted that people with lots of comorbidities tend to die younger, and usually, people who live up to the age of 90 are those who do not have long-term chronic conditions. These people were able to live a healthy life, and get the chance to engage in more activities that assist in decreasing the chances of them acquiring the normally expected comorbidities.

2.4.2 The Prescription Pattern of Drug Usage and Classes

The results indicate that the two most common medicines prescribed were statins, with simvastatin and atorvastatin ranking the highest at 13% and 10%, respectively. These types of drugs are usually used for both primary and secondary disease prevention, and they have an excellent long-term safety record. Indeed, a huge proportion of people use these medications due to their effectiveness in treating and preventing cardiovascular diseases (Obialo et al., 2018). Their wide usage may also be due to their low cost and widespread availability (Lazar et al., 2011). 9.9% of the study population used ramipril, which is typically used to treat high blood pressure and is important in CVD since it can help reduce the risk of myocardial infarction and stroke by lowering blood pressure and improving blood flow. It has also proven

to be efficient and effective for patients aged 55 and over who are at a higher risk of developing ischaemic cardiovascular events due to a history of coronary artery disease, stroke, or diabetes (with patient-controlled blood pressure) (Warner & Perry, 2002). In addition, 9.8% of the study sample were prescribed amlodipine. This drug is recommended and effective for treating hypertension and stable angina, and it has directly contributed to there being fewer hospital admissions for unstable angina and revascularisation. Amlodipine has also shown benefits in preventing stroke (Fares et al., 2016). Furthermore, the results showed 8.7% of the study population used aspirin, and the evidence demonstrated that using aspirin for secondary CVD prevention was associated with a reduced risk of stroke and myocardial infarction (Davidson et al., 2022). Relevantly, 1.99% of the study sample were prescribed warfarin. Although the remaining direct oral anticoagulants were included in the analysed drugs, however, they did not appear in the obtained list as the study highlighted only the top 20 of the major drugs prescribed in the study period. This could be because warfarin has a long history of use and physicians are familiar with its effectiveness while DOACs are relatively new drugs.

Major Cardiovascular Drug Classes Trend

The study identified the most commonly prescribed drug classes for cardiovascular disease in UK primary care between 2001-2020. The prescribing patterns have changed over time: statins have dramatically increased over time. Toth & Banach have identified that over the course of four decades of intensive research that statins are both safe and effective, in both primary and secondary prevention, and have been shown to reduce cardiovascular events and mortality (Toth & Banach, 2019).

The use of calcium channel blockers (CCBs) has also increased over the study period. Several studies and meta-analyses have shown that CCBs reduce hypertension, cardiovascular morbidity, and death, while also improving vasculature and renal function (Alcocer et al., 2010). It has been required by the National Institute for Health and Care Excellence guidelines to use CCBs as a first-line treatment for patients who have hypertension and over 55 years old (National Institute for Health and Care Excellence, 2022).

By contrast, beta-adrenoceptor blockers and thiazide diuretics started at a high prescription rate at the beginning of the current study before seeing a sharp decrease until 2020. Beta-adrenoceptor blockers seem to be a risky drug class for the treating of hypertension when people get older, possibly because of physiologic changes in older people. The identified potential negative effects include low cardiac output, slow heart rate, and decreased renal blood flow, which are associated with an increase in the risk factors (Vögele et al., 2017). Indeed, it was largely because of these adverse effects that it has seen a sharp drop in its prescription rate over the years. Similarly for thiazides, hypokalaemia, hyponatremia, and acute kidney injury are potential adverse side effects, and this can be associated with increased morbidity, mortality, and overall healthcare costs (Makam et al., 2014).

Prescribed Drugs in the Drug Class Trend

The results show that the atorvastatin was most popular statin from 2012, and, indeed, a similar conclusion was reached by Adams in 2012 (the first update published in this regard). Accordingly, atorvastatin is one of the most commonly prescribed drugs and statins worldwide (Adams et al., 2015). Conversely, simvastatin use has rapid decreased between 2010-2020, potentially because it is less potent than atorvastatin, and may be involved in more drug interactions (Pasupathi et al., 2009).

Regarding the antiplatelet drugs: the study showed that aspirin use has been declining from 2010, and this correlates with people ceasing to use it in primary prevention in older individuals because of the risk of bleeding (Berger, 2022). Additionally, the use of aspirin in atrial fibrillation has stopped, as it is not as effective as oral anticoagulants (Hsu et al., 2016).

Clopidogrel prescription use increased between 2010-2020. In 2015, Jiang *et al*. found that clopidogrel was not only highly prescribed, but the second largest marketing branded drug in the U.S. in 2010. Indeed, clopidogrel is effective and safe for many patients, and is used to decrease arteriosclerotic events in individuals with recent myocardial infarction (MI), stroke, or well-established peripheral arterial disease (Jiang et al., 2015).

In relation to calcium channel blockers, amlodipine was found to be the most popular, with its use increasing quickly over the last two decades. Large randomised controlled trials have demonstrated that calcium channel blockers are effective for reducing cardiovascular events, with good safety and effectiveness for reducing blood pressure (Fares et al., 2016). Meanwhile, when it comes to angiotensin receptor blockers (ARBs), the study results showed losartan was frequently used to treat cardiovascular illnesses such as hypertension, myocardial infarction, and heart failure (Xu et al., 2009). Further, the study found that angiotensin converting enzyme (ACE) inhibitors (in particular ramipril) have been more commonly prescribed from 2004. To compare the results to previous studies: according to the findings of the HOPE (Heart Outcomes Prevention Evaluation) trial, ramipril is the only ACE inhibitor authorised for the prevention of cardiovascular events in patients with elevated risk without evidence of heart failure or left-ventricular dysfunction (Vuong & Annis, 2003).

When it comes to thiazide diuretics drugs, the results show that in 2001, bendroflumethiazide was used by around 98%, but the use dropped between 2010-2020. Thiazide-like diuretics (e.g., indapamide) were, however, the most popular by 2010. This may be because of changes in guidelines: the most recent 2018 European Society of Cardiology and European Society of Hypertension ESC/ESH guidelines and NICE guidelines recommend thiazide-like diuretics over thiazide diuretics for a number of reasons (Burnier et al., 2019; NICE, 2022), including duration of action, ability to reduce blood pressure, and long-term cardiovascular endpoint benefits. Additionally, the American Diabetes Association preferred thiazide-like diuretics (such as indapamide) for high blood pressure patients with diabetes due to their longer effective diuresis and effectiveness in cardiovascular event reduction (Burnier et al., 2019).

Total Unique Drug Prescriptions from 2001-2020

Cardiovascular drug use was studied according to five-year intervals, starting from 2001 and ending in 2020. The study showed that most older persons take two to four drugs, and the results found a considerable increase in this, from 43% in 2001 to 64% in 2020, which could be due to the increase in multimorbidity. In the same vein, polypharmacy (those taking five and more drugs) has increased between 2005 (7.7%) and 2015 (8.1%). Similarly, Zhang et al.'s study showed that polypharmacy increased from 16.9% to 19% between 2006-2014 (Zhang et al., 2020). Clearly, a limitation of our study is that we are focusing on cardiovascular drugs,

and it is likely that these patients were also taking a range of non-cardiovascular medications, which add to the polypharmacy burden. Nevertheless, it is clear that polypharmacy has become more common between 2005 and 2016—a result that is easily explained by the fact that there are more patients with multimorbidity.

The study found that in 2001 the drug range number was seven, and this increased by 2010 to nine—and then increased even further in 2015 to 11 drugs. In a similar study reported by the United Nations' office on drugs and crime, it was concluded that the number of people who used drugs all around the world in 2017 was 30% higher than that in 2009 (United Nations Office on Drugs and Crime, 2019). This is consistent with our finding, and shows that the healthcare burden has been increasing during recent years, both economically and clinically.

It is interesting to note there was a decrease in 2020 to a drug range of nine drugs. Such findings could be directly related to the COVID-19 pandemic, as more than 27,000 patients in the United Kingdom stopped using some of their prescribed drugs for (e.g., blood pressure drugs) during this time (British Heart Foundation, 2023). This could be directly related to the patient's difficulties in attending primary care to get their prescribed drugs because of public panic, curfew, and other reasons associated with the precautionary measures. As a result, a study by British Heart Foundation have reported a possible increase in the fatality rate among the older persons due to heart attacks and strokes, with an increase in the risk of cardiovascular disease (British Heart Foundation, 2023).

The study results show the significant differences between 2001 and 2020 because the total number of drugs used and drug prescription patterns in cardiovascular disease have changed significantly over time. The increase in number of drugs increases the possibility of drug-drug interaction along with illnesses, hospitalisations, health system spending, and mortality (Villén et al., 2022), but obviously there are also benefits associated with improvements in cardiovascular end-points. At an individual level, the balance between improving prognosis and reducing unintended harms is become more complex with the increasing prevalence of multimorbidity.

2.4.3 Cardiovascular Patients in 20 Years of Follow-Up

The study classified and analysed patients who had 20 years of follow-up. These patients (n = 17,075) represented around 7.5% of the current study population. The number of people having 20 years of follow-up decreased due to number of reasons including deaths of patients as they aged, change in GPs as a result of home moves, and loss to follow up. High mortality rates are seen in cardiovascular disease patients, especially in the older persons (Villén et al., 2022).

Over the 20 years of follow-up, the most commonly prescribed drug classes were still statins, followed by calcium channel blockers. The least commonly prescribed drug classes, meanwhile, was nitrates. Interestingly, the top two prescribed drugs remain the same for both study samples (n = 228,376 and n = 17,075) at the end of the 20 years of follow-up. As highlighted previously, this might be related to the fact that the most commonly prescribed drugs, statins, are one of the most efficient treatment options for with lipid disorders and for lowering cardiovascular (CV) risk in both primary and secondary prevention (Toth & Banach, 2019), and of course, because hyperlipidaemia is a highly prevalent condition. Calcium channel blockers (CCBs) are one of the most widely used cardiovascular medications in adults because they are used to treat a wide range of clinical conditions, including high blood pressure, vasospasm, and supraventricular tachycardia (Chakraborty & Hamilton, 2022).

Comparison of the Prescriptions Between Snapshots for the 20-Year Follow-Up Patients

The top 10 prescription patterns in the same population over 20 years of follow-up (n = 17,075) was identified in the period between 2001-2005 and sorted by confidence. The results show that atenolol and nicorandil are associated with co-prescription with aspirin with high confidence (62%), which is not surprising given that these are used for the treatment of Ischemic heart disease (IHD). Overall, there were 940 prescription patterns found in the present study, largely because of the disease patterns and the evidence for the benefit of multiple treatments. For instance, if atenolol, isosorbide, and simvastatin are prescribed, aspirin will be prescribed with a confidence of 60%.

Lleva et al. have previously shown that digoxin use is associated with warfarin to treat atrial fibrillation, and, similarly, this study found a high correlation with lift of 20.54 and 46% confidence alongside a high-value number for the pattern, which was observed with a count of 3,170 (Lleva et al., 2009). In addition, the top 10 prescription patterns in the period 2016-2020

was amlodipine, atenolol, and clopidogrel: these drugs are frequently prescribed together with atorvastatin, with a high validity of confidence at 72%. These medications have been shown to be prescribed as combinations for the management of coronary artery disease symptoms, specifically stable angina (Rosendorff et al., 2015). Using a combination of calcium channel blockers with beta-blockers is a requirement that has been recommended by NICE guidelines for coronary artery disease (NICE, 2016).

Atenolol, atorvastatin, and isosorbide are usually prescribed with aspirin. It could be noticed that the drug combination has been substituted to atorvastatin instead of simvastatin in the period between 2016-2020. This could be related to the fact that atorvastatin proved to be more effective in controlling/managing the cholesterol level within stable angina patients (Manfrini et al., 2020). This is relevant to the several attempts and various ongoing studies that assist in improving the currently available medication, and it could also contribute to enhancing the overall older patient's lifestyle from many aspects, including significant efforts on the multimorbidity and polypharmacy fields to minimise the drug-drug interaction (and possible side effects).

The study findings highlighted how the drug patterns have changed over time, focusing on two periods: Snapshot One (between 2001-2005) and Snapshot Two (between 2016-2020). Aspirin and atorvastatin were less correlated in Snapshot One, with the results finding 16,183 patterns, whereas in Snapshot Two there was a substantial jump to 58,905 patterns. This is in keeping with increasing evidence of the effectiveness of this combination. A similar pattern of findings was observed in 2018 by Zhang et al. They highlighted that aspirin and atorvastatin have synergistic effects in ischemic stroke therapy, and that these medications play major roles in lipid regulation and atherosclerotic plaque reduction. They can also improve the patient's quality of life and prognosis (Z. Zhang et al., 2018).

The study results also show that atorvastatin is also commonly used with ramipril, with a sharp increase between 2016-2020 (57,471 times) in comparison with the first snapshot (8,007 times). A combination of statins and ACE inhibitors reduces cardiovascular events more than when they are prescribed separately (Koh et al., 2015). There was a similar finding with respect to amlodipine and aspirin changing from 5,680 prescriptions to 39,465 prescriptions. This is consistent with the fact that CCB treatment and aspirin usage has been shown to be beneficial

in stable coronary artery disease (Kodesh et al., 2021). Our results suggest that physicians tend to follow therapy guidelines in clinical practice. These multi-drug regimens have undoubtedly been important in improving the prognosis in patients with cardiovascular disease.

The introduction of pertinent revisions to various guidelines causes continuous adjustments in prescription rates. For instance, updates to the National Institute for Health and Care Excellence guidelines for hypertension and coronary artery disease often result from a thorough analysis of the available data and agreement among experts. Publication, evidence review, consultation, cost-effectiveness analysis, implementation, monitoring, and evaluation are just a few of the various aspects of the process. For example, NICE guidelines use a mapping exercise to identify the gap in recommendations for hypertension prescription. By enhancing treatment plans and drug selections, these components seek to reflect the most recent evidence-based practices and enhance patient care. They are essential in directing clinical decision-making, assuring the provision of high-quality, and assist for low-cost healthcare (NICE, 2022).

In summary, the study provided a comprehensive assessment of cardiovascular drug use over a 20 year period. In general, there has been an increase in numbers of drugs being used per patient, which at least is partially related to the increasing prevalence of multimorbidity. While this polypharmacy may be appropriate, and evidence-based, at a population level, at an individual level, when taken together with non-cardiovascular drugs being used in these patients (which we did not assess), there may be an increased risk of drug-drug interactions, and potential harms. This highlights the complexities involved in extrapolating from population-based guidelines to individual patients with complex multimorbidity patterns now being seen in clinical practice.

Chapter 3

Gastrointestinal Disease

3.1 Introduction

There is an increased risk of gastrointestinal (GI) diseases with age. The management of GI diseases in older people, such as diagnostic and therapeutic interventions, is further complicated by the presence of polypharmacy, comorbidities, and a limited life expectancy (Dumic et al., 2019).

Gastrointestinal disease management in older persons required a multidisciplinary approach including geriatric, gastroenterology as well as primary healthcare providers. It is highly expected for older people with multimorbidity to develop gastrointestinal diseases (Firth & Prather, 2002). This is due to the interaction and complexity of their medications. Older persons are more subject to the risk of various gastrointestinal diseases including colorectal cancer, diverticulitis, and inflammatory bowel disease (J. Wang et al., 2019).

Moreover, polypharmacy is related to a higher risk of drug interactions and adverse drug events (including those affecting the GI system). Medications used to treat chronic conditions such as diabetes, hypertension, and heart disease can contribute to GI complications, such as diarrhoea, peptic ulcer disease, nausea, and vomiting (Goriacko & Veltri, 2021).

Managing GI diseases in older patients with multimorbidity and polypharmacy requires a collaborative approach amongst healthcare professionals. Treatment plans should prioritise the most necessary medications with the fewest potential adverse effects. Medications that can exacerbate GI symptoms should be replaced or adjusted whenever possible. In addition, non-pharmacologic treatments such as dietary adjustments, exercise, and stress-reducing techniques may be beneficial for older patients with GI diseases.

3.1.1 Gastrointestinal Disease

Gastrointestinal (GI) disease affects the GI tract, which extends from the mouth to the anus. The mouth, oesophagus, stomach, small intestine, large intestine and anus are the organs that make up the GI tract. Globally, GI diseases are very common and cause serious morbidity and

considerable healthcare costs, and are responsible for almost 8 million deaths annually over the world (Chan et al., 2019).

Gastrointestinal diseases have a significant effect on patients and healthcare organisations. In the United States, the expenditure on these disorders amounts to US $135.9 billion (Peery et al., 2019). In addition there are 54.4 million visits with a main diagnosis of a GI disorder, with the most common complaint being abdominal pain with 16.5 million annual visits, followed by gastroesophageal reflux disease with more than 5.6 million visits. There are more than 40.7 million ambulatory visits for GI symptoms annually, including more than 21.8 million visits for abdominal pain, while 4.7 million visits are attributable to vomiting and 3.4 million visits to diarrhoea. GI disease contributes to more than 3.0 million hospital admissions annually at a cost of US $31 billion. Furthermore, Peery et al. (2019) showed that one in seven patients who are admitted to the hospital are highly expected to return within 30 days (Peery et al., 2019). These facts highlight the importance of considering gastrointestinal diseases as one of the major contributors to the burden in healthcare both clinically and financially.

3.1.2 Gastrointestinal Disease in Older People

In older persons, gastrointestinal system function can be affected in various ways, including through alterations in gut motility, enzyme, and hormone release, digestion, and absorption. Some gastrointestinal (GI) diseases are more prevalent in older persons such as Gastroesophageal reflux disease (GERD), for example, which is defined as a condition that occurs when the reflux of stomach contents creates bothersome symptoms and/or complications. According to research conducted by Moore et al., which included over 10,000 people in nursing homes, GERD affects roughly 23% of the aging population (Moore et al., 2012). It has also been identified that constipation is also more common amongst older persons. The estimated prevalence of constipation is 40% for old people in general and up to 50% for nursing care residents. Constipation amongst the older persons becomes more common because of reduced mobility, cognitive impairment, dietary changes, comorbidities, and polypharmacy (particularly the use of opioid and anticholinergic drugs) (Dumic et al., 2019). Consequently, polypharmacy and multimorbidity could have a major effect on GI disorders.

The majority of ulcers in the older persons are driven by H. pylori infection or are otherwise related to taking Non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (Lanas & Chan, 2017). The incidence and mortality of Peptic Ulcer Disease (PUD) in the older persons was always relatively high in contrast to the general population (Dumic et al., 2019). The main causes of this include an increased risk of H. pylori infection in the older persons, increased NSAID/aspirin use, and polypharmacy, which includes drugs like anticoagulants, selective serotonin reuptake inhibitors (SSRIs), and oral steroids that are linked to an increased risk of PUD. Reduced blood flow through the GI system and decreased secretion of essential components of the gastrointestinal defence mechanisms, such as bicarbonates and prostaglandins, are major physiologic alterations related to aging that contribute to such incidents (Dumic et al., 2019).

3.1.3 Relationship to Polypharmacy and Multimorbidity

Numerous comorbidities that become more common in older people can impair digestive function and the immune system of the gastrointestinal tract (Soenen et al., 2016). Typical examples include type 2 diabetes and degenerative diseases of the central nervous system, such as Parkinson's disease. These diseases can affect the enteric nervous system, gastrointestinal motility, and small intestinal permeability (Nguyen et al., 2022). This can in turn affect nutrient absorption and digestion in addition to defence against ingested pathogens. There may also be effects on postprandial blood pressure and appetite control (Soenen et al., 2016).

The gastrointestinal system (GIS) plays an important role in the metabolism and absorption of medications. In older people, GI diseases may impact on drug absorption, and rarely on the metabolism of drugs, especially with more advanced stages of liver disease. Inevitably the combination of multimorbidity and polypharmacy in the older persons may predispose to more complicated medical journeys, increase the risk of complications and thereby adverse outcomes (Dumic et al., 2019).

Epidemiological studies to evaluate the amount of polypharmacy and potentially inappropriate medication (PIM) use in older patients (65 years or older) have shown that upper gastrointestinal disease (adjusted OR=2.02, 95% CI 1.23–3.34, *P*=0.006) was found to be a

major predictor of polypharmacy. The analysis identified that patients on polypharmacy were more likely to have more comorbidities (OR=1.28, 95 percent CI 1.15–1.42, *P*<0.001) particularly of upper gastrointestinal conditions (including gastric ulcer, gastritis, oesophagitis/ulcer, duodenal ulcer or gastroesophageal reflux disease, OR=2.51, 95% CI 1.56–4.04, *P*<0.001) (Y. Wang et al., 2016).

In a study carried out by MacRae et al. (2021), 32.3 % of home care residents (n = 1444/4468) were found to have "excessive" polypharmacy (more than 10 medications), which was more prevalent in people aged 70–74 years old (MacRae et al., 2021). The most commonly prescribed medicines for residents were for the central nervous system followed by the gastrointestinal and cardiovascular systems. The most commonly prescribed drug classes included osmotic laxatives (36.3%), proton pump inhibitors (35.8%) and statins (27.3%), prescribed in over one-fifth of people (MacRae et al., 2021).

Given the prevalence and high burden caused by GI diseases, particularly in the older patients, the aim of this study was to evaluate the prescription of drugs used to treated GI diseases, and how this has changed over a 20-year period, and also to look at the patterns of prescribing for GI diseases.

3.2 Methods

3.2.1 Study Design

A longitudinal evaluation in the Clinical Practice Research Datalink (CPRD) dataset, CPRD Aurum, was carried out analysing electronic health records between January 1, 2001 and December 30, 2020.

3.2.2 Data Source

Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD) is a research database that facilitates both prospective and retrospective medicine and health-related research. The Medicines and

Healthcare Products Regulatory Agency and the National Institute for Health Research both support it in the UK (CPRD, 2022). The CPRD is one of the largest global data sources of longitudinal medical records from primary care (Herrett et al., 2015). As mentioned in the previous chapter, the CPRD is categorised into two databases (GOLD and Aurum) and these data sets cover the needed patients records.

Clinical Practice Research Datalink (CPRD) Aurum Database

Data records for the current study were obtained from the CPRD Aurum. The CPRD Aurum is an enormous population-based, prospective longitudinally constructed, anonymized health data set that has been available for research since 2018. It comprises of eight files (Wolf et al., 2019). For this study, data were extracted from three files: the patient file, the observation file, and the drug issue file.

The patient file contains information about the patient's demographic characteristics and registration with the GP. The observation file also contains medical-history information recorded on the practice system, such as symptoms, clinical measures, lab results, and diagnoses, along with demographic data. The drug issue file contains data on all prescriptions (medication and devices) issued by the GP system (Wolf et al., 2019). CPRD Aurum has recorded data from 1988, gathered with the use of EMIS software. As highlighted earlier, there are two main codes known as 'MedCode' and 'ProdCode' by CPRD.

3.2.3 Ethical Approval

The Clinical Practice Research Datalink (CPRD) has ethical approval to provide anonymised patient records for use in observational studies (Herrett et al., 2015). This is granted by The Health Research Authority. Furthermore, in addition to this ethical permission, all research employing CPRD data must obtain approval from the Independent Scientific Advisory Committee (ISAC) before data are made available to researchers (CPRD, 2021). Ethical approval for the study was obtained by (ISAC-MHRA), reference number (19_159_R1).

3.2.4 Study Population Criteria

Two main analyses were carried out in the gastrointestinal study. Firstly, from one million patients in the database, CPRD was used to identify and extract patients with gastrointestinal diseases. The patients evaluated not only had gastrointestinal disease, but also two or more chronic conditions. In addition, we only included patients with two or more years of follow-up. This reduced the total number of patients to 285,510. These patients were filtered further based on the age of multimorbidity (which refer to the second chronic condition whether they were 50 years and above). This additional filtering reduced the patient number to 126,047. After adjusting for year range between 2001 and 2020, the number of eligible patients for this study was 111,355 (used for the first group analysis). The same patients were filtered further to those who had 20 years of follow-up appointments. This reduced the number of patients to 3110 and this was used for the second group analysis. Figure 3.1 shows how the patients were filtered:

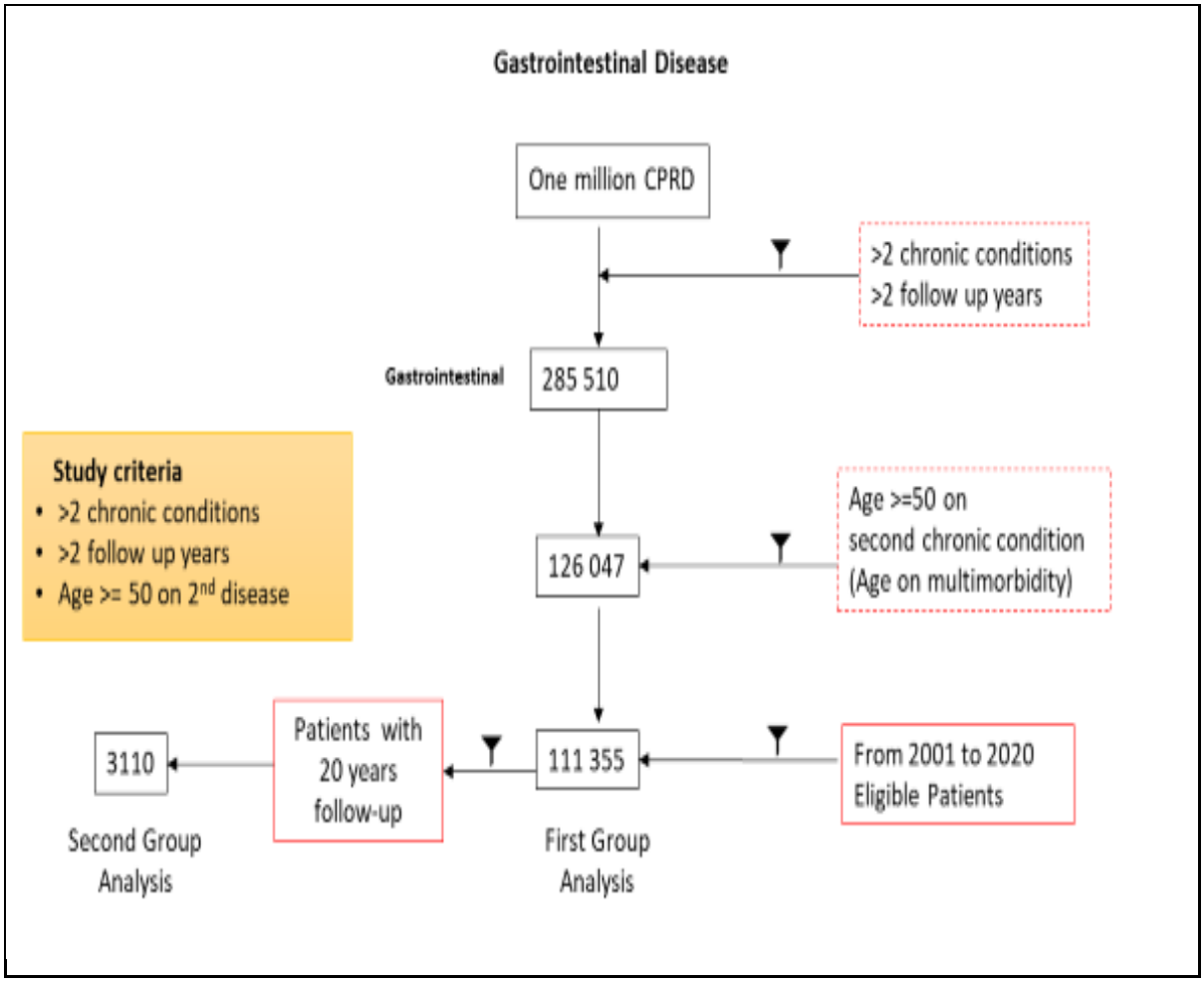

Figure 3.1 Population criteria from CPRD database for first and second-group analysis

3.2.5 Data Collection

First, the medical records were used to identify gastrointestinal diagnoses, notably through the application of MedCode. For the current analysis, 19 gastrointestinal disorders were selected. These were as follows:

1. Abdominal hernia.
2. Alcoholic liver disease.
3. Angiodysplasia of colon.
4. Anorectal prolapse.
5. Barrett's oesophagus.
6. Cholelithiasis.
7. Chronic liver disease and viral hepatitis.
8. Coeliac disease.
9. Colonic polyp.
10. Diverticular disease.
11. Fatty liver.
12. Gastritis and duodenitis.
13. Gastroesophageal reflux disease (GERD)
14. Inflammatory bowel disease (Crohn's Disease).
15. Inflammatory bowel disease (Ulcerative Colitis).
16. Oesophageal varices.
17. Chronic constipation.
18. Hiatal hernia.
19. Irritable bowel syndrome (IBS).

Next, a list of all gastrointestinal drugs contained in the British National Formulary (BNF) in the chapter 'Gastrointestinal disease' (2021) was created. Subsequently, the drugs in the gastrointestinal disease list were identified using the product code dictionary 'ProdCode' in CPRD, as shown in Figure 3.2.

Finally, the medical files containing the medical background and diagnosis in 'Medcode' were identified in order to extract patients with one or more disorders from 19 GI conditions, as mentioned earlier, along with the required criteria. Subsequently, the prescription records were analysed in 'ProdCode' (where the Medcode has all patients' GI conditions), and the extracted data from these code dictionaries merged together in the CPRD Aurum dataset to obtain the required groups needed for the study.

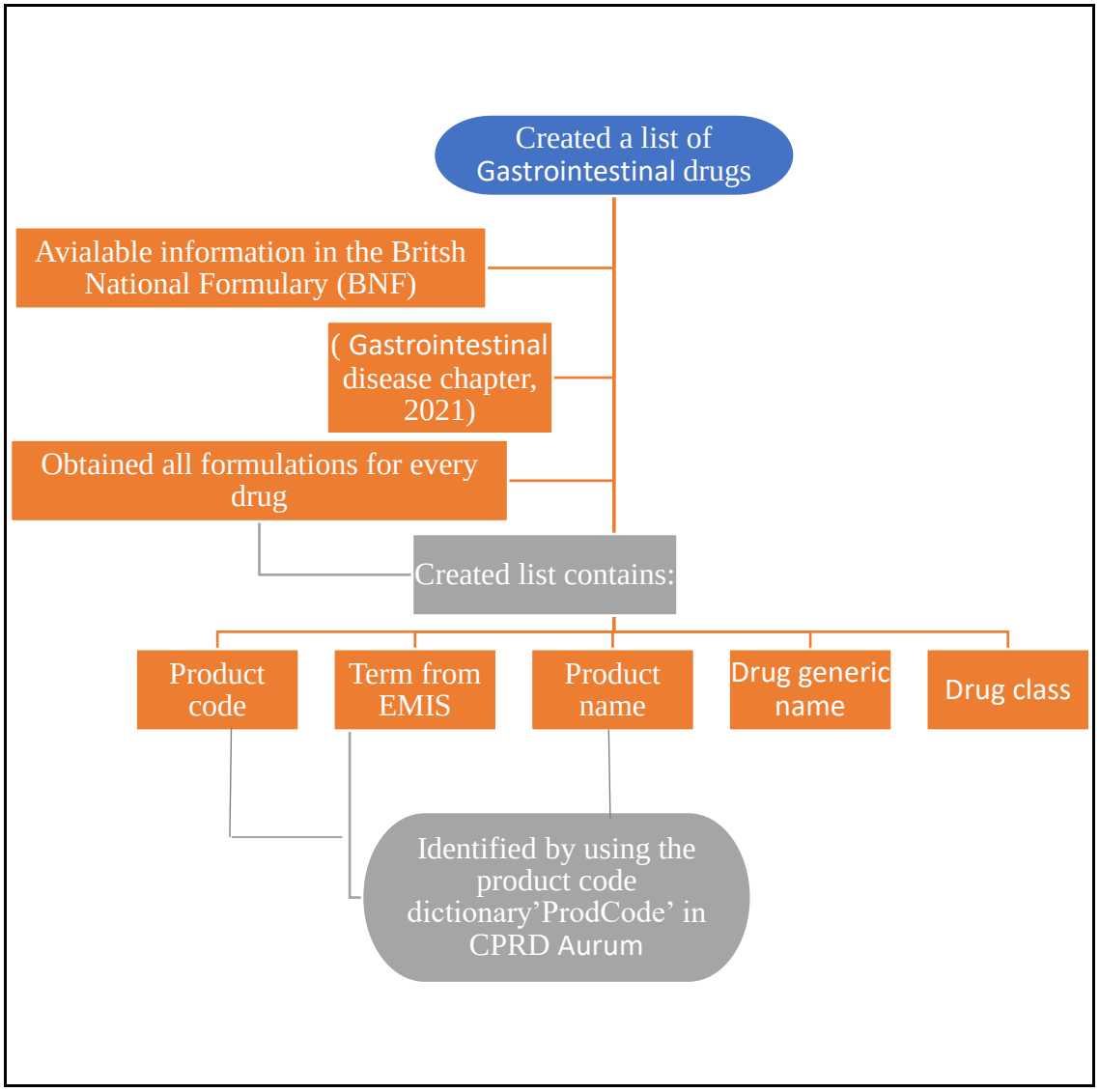

Figure 3.2: The process of creating gastrointestinal drugs to be recognized by the product code dictionary in CPRD Aurum

3.2.6 Data Analysis

The data were analysed utilising R and machine learning. This was carried out on the selected patient records, firstly in the total number (n=111,355) of patients with GI disorders who were above the age of 50 years and had two or more chronic conditions with two or more years of follow-up, in the period between 2001 to 2020.

Following this, the major drug patterns for the prescribed drugs, along with the major drug classes, were analysed. The results were obtained by preparing the required Gastrointestinal drugs list from the British National Formulary (BNF) gastrointestinal disease chapter (2021). This was applied and combined with the product code in the CPRD dictionary. This was to examine and identify the required gastrointestinal database trends in the period between 2001 to 2020.

The patients were segmented into five-year snapshots. Each snapshot was evaluated individually in a specific year (with five-year intervals between each snapshot and the other) as follows:

- Snapshot One: 2001 (n= 13,377).
- Snapshot Two: 2005 (n= 24,250).
- Snapshot Three: 2010 (n= 44,230).
- Snapshot Four: 2015 (n= 59,900).
- Snapshot Five: 2020 (n= 49,958).

This was to enable the total number of unique drugs prescribed at every single point in the five-year intervals, hereafter termed ‘snapshot’, could be compared. The results from the tested group samples of total unique drugs in the different snapshots was considered statically significant if the *P*-value identified was <0.05 using one-way ANOVA. Snapshot One in 2001 and Snapshot Five in 2020 were compared via *T*-test. Furthermore, for the five snapshots, Pearson's Chi-squared test was used to identify any significant difference between the snapshots in terms of the number of drugs used. This is to identify the polypharmacy percentage in the tested study sample.

After that, the same GI patients were also tracked over the twenty years of follow-up (n=3110). The leading drugs prescribed were analysed to examine the major drug classes in the period between 2001–2020. The Apriori algorithm was used to find associations amongst the medications in the dataset containing relevant information for each drug's code, drug dosage, and generic name that should be recorded in this database (Yoosofan et al., 2015). The study database comprised 636 GI drug items. The GI drugs list was created using BNF and a product code dictionary. Then, the information in this dataset was transformed into a single format. Subsequently, from these data sets, association rules were obtained. Thus, the Apriori algorithm, which is one of the approaches for determining association rules amongst medications, in addition, to examining the change in prescribing patterns over time was then utilised in this study.

3.2.7 Apriori Algorithm Analysis

The Apriori algorithm was used to identify frequent item sets and discover Association Rules (ARs) based on the discovered sets. There are some well-known concepts for comparing the prescribing patterns and identified ARs, such as 'Confidence' and 'Lift', which are different measures of the level of correlation between the previous and succeeding items.

The level of confidence is defined as the likelihood that a transaction containing X also contains Y (Trikha & Singh, 2014). In this context, a transaction refers to a prescription pattern. In addition, 'Lift' reflects the correlation between the association rules. The higher the number (data >1), the higher the positive correlation will be. Similarly, the lower the number (data <1), the greater the negative correlation between the association rules (Lai et al., 2022). The count refers to the number of transactions that include all database transactions (Alfiqra & Khasanah, 2020).

In this study an Apriori algorithm implemented in the R programming language was used to identify and analyse the top 10 prescription patterns in the period between 2001 to 2005 (hereafter termed 'snapshot one') and in the period between 2016 to 2020 (hereafter termed 'snapshot two'). This was to examine the changes in prescribing patterns over time.

3.3 Results

3.3.1 Population Characteristics

The study population comprised 111,355 people in the UK, aged 50 years and older, and diagnosed with gastrointestinal diseases in the period between 2001 to 2020. According to the inclusion criteria, all included patients must have had two or more chronic conditions alongside two or more years of follow-up.

Table 3.1 shows the population characteristics by gender with a total number of 51,523 females and 59,832 males. The mean age of the females was 63 years (SD 9; range 50-97) and for males, it was 62 years (SD 8; range 50-98). Patients aged between 55-59 represented 20% of females and 23% of males, but, in the group aged 90+, 0.2% were females and less than 0.1% were males. The mean number of comorbidities in females and males were 7 (SD 3; range 2-26) and 6 (SD 3; range 2-24), respectively.

Table 3.1: The population characteristics by gender (N=111,355)

Characteristic	Female, N = 51,523	Male, N = 59,832
Comorbidities Mean [SD]	7 (3)	6 (3)
Follow-up Mean [SD]	18 (11)	18 (12)
Age Mean [SD]	63 (9)	62 (8)
Age groups* Number (%)		
50-54 Years	10,777 (21%)	13,035 (22%)
55-59 Years	10,472 (20%)	13,784 (23%)
60-64 Years	9,782 (19%)	12,532 (21%)
65-69 Years	8,073 (16%)	9,491 (16%)
70-74 Years	6,123 (12%)	5,998 (10%)
75-79 Years	3,705 (7.2%)	3,206 (5.4%)
80-85 Years	2,494 (4.8%)	1,749 (2.9%)
90+ Years	97 (0.2%)	37 (<0.1%)
Ethnicity* Number (%)		
Asian or Asian British	1,451 (2.8%)	1,475 (2.5%)
Black or Black British	1,242 (2.4%)	1,143 (1.9%)
Chinese or Other Group	2,321 (4.5%)	2,516 (4.2%)
Mixed	78 (0.2%)	85 (0.1%)
White	36,643 (71%)	42,458 (71%)
Unknown	9,788 (19%)	12,155 (20%)

Table 3.2 shows the population characteristics by age group of the 111,355 patients categorised into intervals: 50–54, 55–59, 60–64, 65–69, 70–74, 80–85, and 90+. The highest number in the population were in the 50–54 and 55–59 year age groups (23,812 and 24,256, respectively). The number of males was highest in these two age groups with mean ages of 52 (SD 1; range 50-54) and 57 (SD 1; range 55-59) in the age groups 50–54 and 55–59, respectively. The mean number of comorbidities was 6 (SD 3; range 2-23) for both groups.

Table 3.2: Population characteristics by age group (N=111,355)

Characteristic	50-54 Years N = 23,812	55-59 Years N = 24,256	60-64 Years N = 22,314	65-69 Years N = 17,564	70-74 Years N = 12,121	75-79 Years N = 6,911	80-85 Years N = 4,243	90+ Years N = 134
Gender Number (%)								
Female Mean [SD]	10,777 (45%)	10,472 (43%)	9,782 (44%)	8,073 (46%)	6,123 (51%)	3,705 (54%)	2,494 (59%)	97 (72%)
Male Mean [SD]	13,035 (55%)	13,784 (57%)	12,532 (56%)	9,491 (54%)	5,998 (49%)	3,206 (46%)	1,749 (41%)	37 (28%)
Comorbidities Mean [SD]	6 (3)	6 (3)	6 (3)	7 (3)	7 (3)	7 (3)	6 (3)	5 (2)
Follow-up Mean [SD]	17 (11)	18 (11)	18 (12)	18 (12)	18 (11)	18 (12)	16 (11)	13 (11)
Age Mean [SD]	52 (1)	57 (1)	62 (1)	67 (1)	72 (1)	77 (1)	83 (2)	92 (2)
Ethnicity Number (%)								
Asian or Asian British	837 (3.5%)	673 (2.8%)	587 (2.6%)	391 (2.2%)	277 (2.3%)	111 (1.6%)	49 (1.2%)	1 (0.7%)
Black or Black British	772 (3.2%)	493 (2.0%)	394 (1.8%)	335 (1.9%)	217 (1.8%)	116 (1.7%)	56 (1.3%)	2 (1.5%)
Chinese or Other Group	1,250 (5.2%)	1,095 (4.5%)	903 (4.0%)	721 (4.1%)	451 (3.7%)	241 (3.5%)	169 (4.0%)	7 (5.2%)
Mixed	52 (0.2%)	44 (0.2%)	25 (0.1%)	20 (0.1%)	13 (0.1%)	6 (<0.1%)	3 (<0.1%)	0 (0%)
White	16,403 (69%)	17,410 (72%)	16,315 (73%)	12,760 (73%)	8,549 (71%)	4,830 (70%)	2,752 (65%)	82 (61%)
Unknown	4,498 (19%)	4,541 (19%)	4,090 (18%)	3,337 (19%)	2,614 (22%)	1,607 (23%)	1,214 (29%)	42 (31%)

3.3.2 *Disease Profiles of the Study Population (N=111 355)*

Gastrointestinal Diseases and Related Conditions

The gastrointestinal disease profile showed that gastroesophageal reflux disease ranked as the highest disease condition with around 32 percent of the total population followed by abdominal hernia. After that, there was a dramatic drop in the population of gastrointestinal patients from 20 percent to around 5 percent for Barrett's Oesophagus. Then, the population showed a slight decrease from 5 percent to approximately one percent for the remaining gastrointestinal diseases, as shown in Figure 3.3.

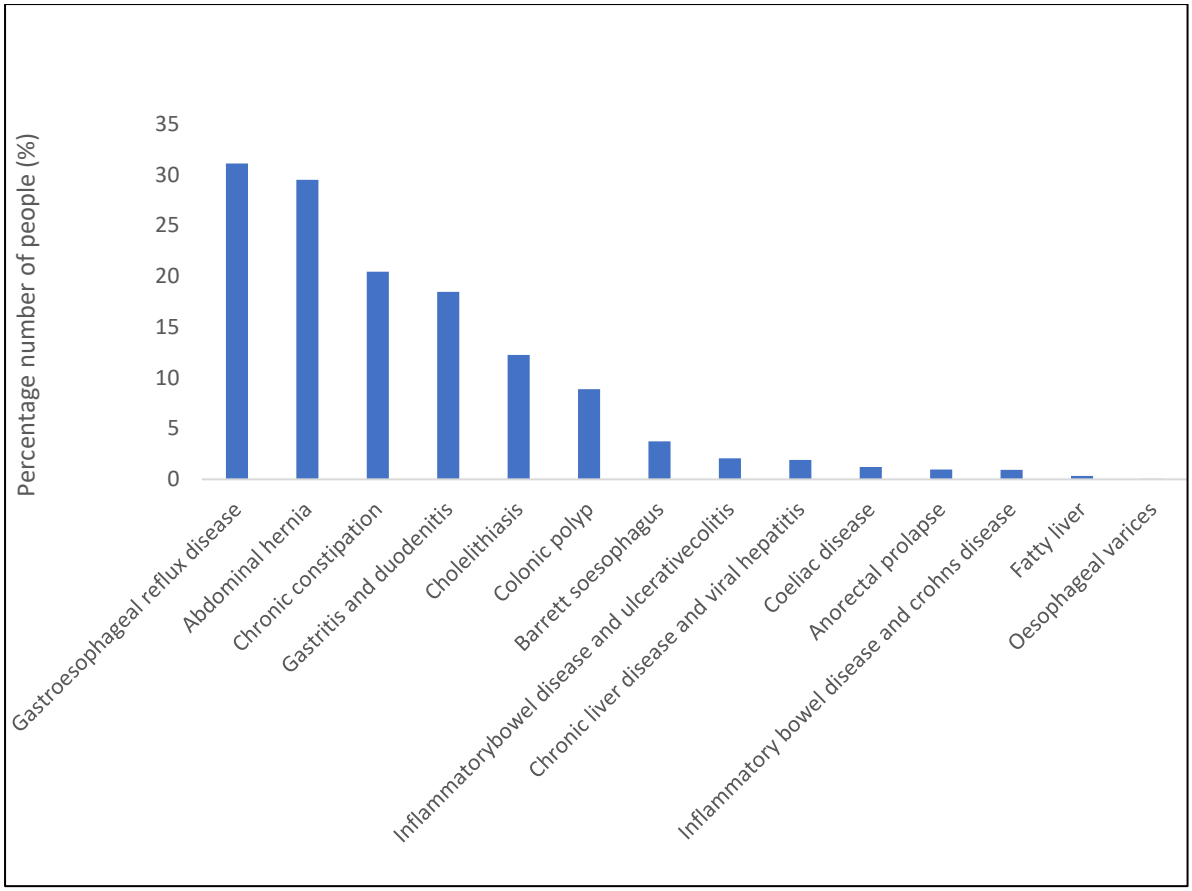

Figure 3.3: The majority of conditions related to gastrointestinal disease

Gastrointestinal Conditions Alongside Long-Term Diseases

Figure 3.4 shows that hypertension was the most common disease in patients with gastrointestinal diseases, whilst allergic and chronic rhinitis was the lowest. Lipid disorders chronic pain disorder and gastroesophageal reflux disease were also common. As presented in the below figure, some patients could have one GI disease along with another GI disorder at the same time.

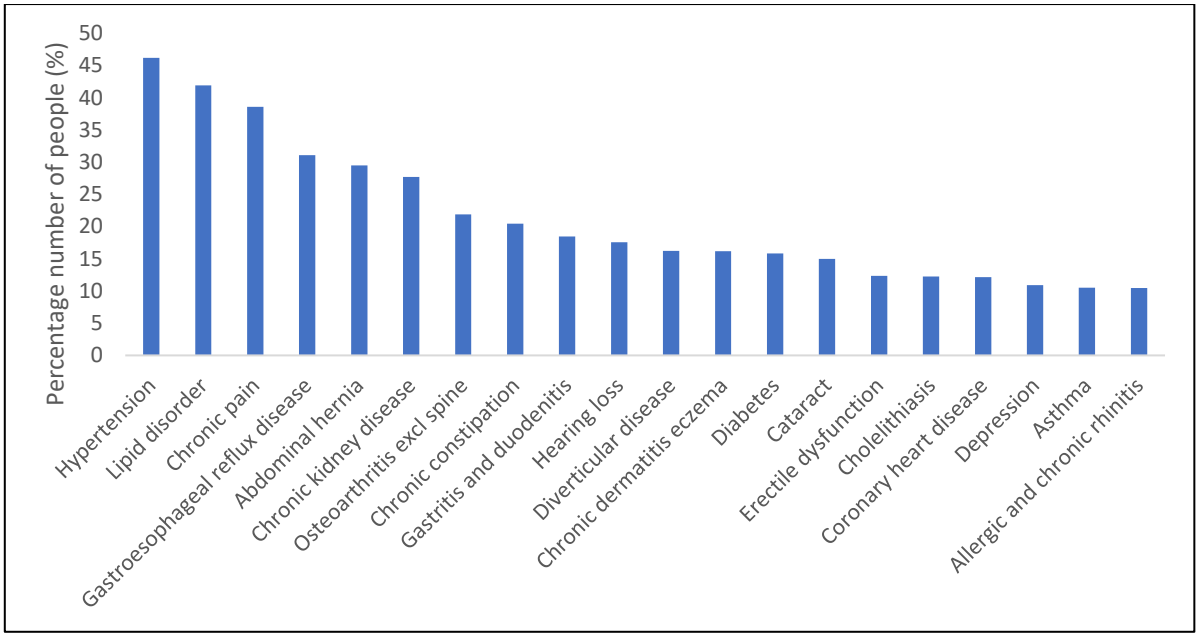

Figure 3.4: The gastrointestinal conditions associated with other long term diseases

The correlation between age groups and comorbidity can be seen in Figure 3.5. The number of comorbidities was the highest among the groups between the ages of 65–79 years old.

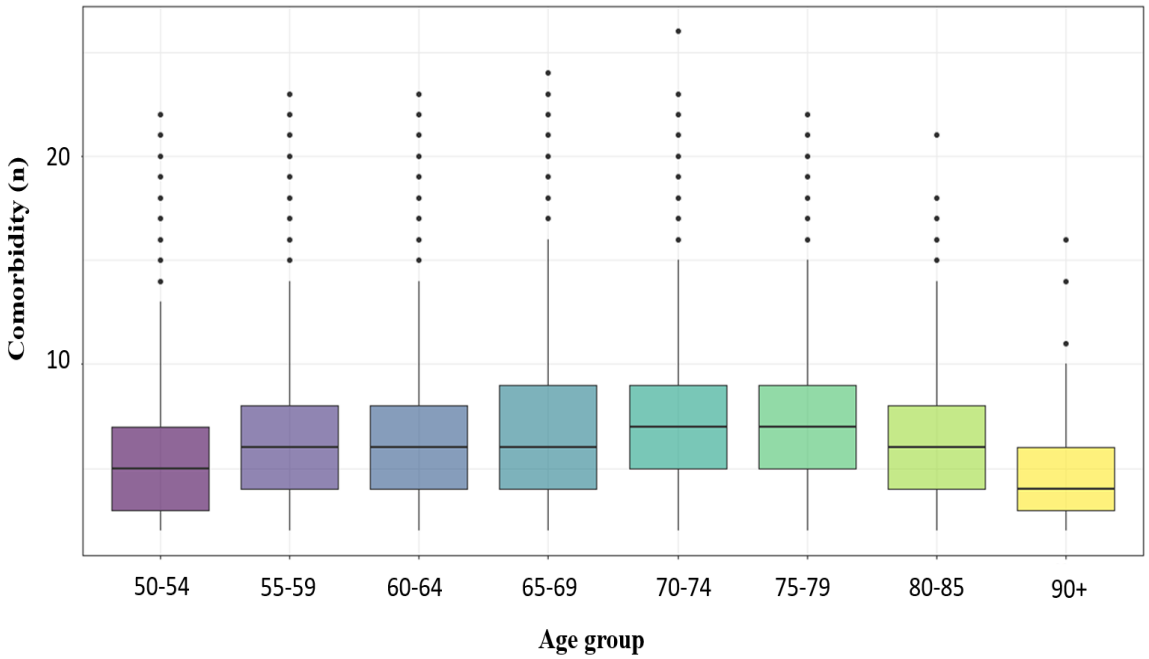

Figure 3.5: Relation between age group and comorbidities (age group vs. comorbidity)

3.3.3 Prescriptions Pattern of Drugs Usage and Classes

Major Gastrointestinal Drugs Prescribed in the Period 2001–2020

Table 3.3 below illustrates the drug count and percentage for each gastrointestinal drug prescription in the period between 2001 and 2020. Omeprazole was the most frequently prescribed drug, followed by lansoprazole and prednisolone, whereas rabeprazole was the least commonly prescribed drug.

Table 3.3: Major drugs prescribed to the study sample (N=111 355)

Drug name	Count	Percentage%
Omeprazole	2060210	31
Lansoprazole	1531898	23
Prednisolone	359706	5
Ranitidine	319195	5
Lactulose	262815	4
Beclometasone	178096	3
Senna	224015	3
Esomeprazole	164786	2
Ispaghula husk	149015	2
Loperamide	99718	2
Mebeverine hydrochloride	123744	2
Azathioprine	52927	1
Bisacodyl	69868	1
Calcium carbonate, Sodium alginate,Sodium bicarbonate	72732	1
Hyoscine butylbromide	55740	1
Macrogol	64531	1
Mesalazine	88754	1
Methotrexate	98999	1
Pantoprazole	89049	1
Rabeprazole	65358	1

The Major Gastrointestinal Drug Classes

Trends in prescribing of the major gastrointestinal drug classes are shown in Figures 3.6 to 3.9. As can be seen for proton pump inhibitors in Figure 3.6., there was a substantial increase in the period between 2001–2020. However, for the other gastrointestinal drug classes, there was either a fluctuation or a dramatic decrease in the same study period, as shown in Figures 3.7–3.9.

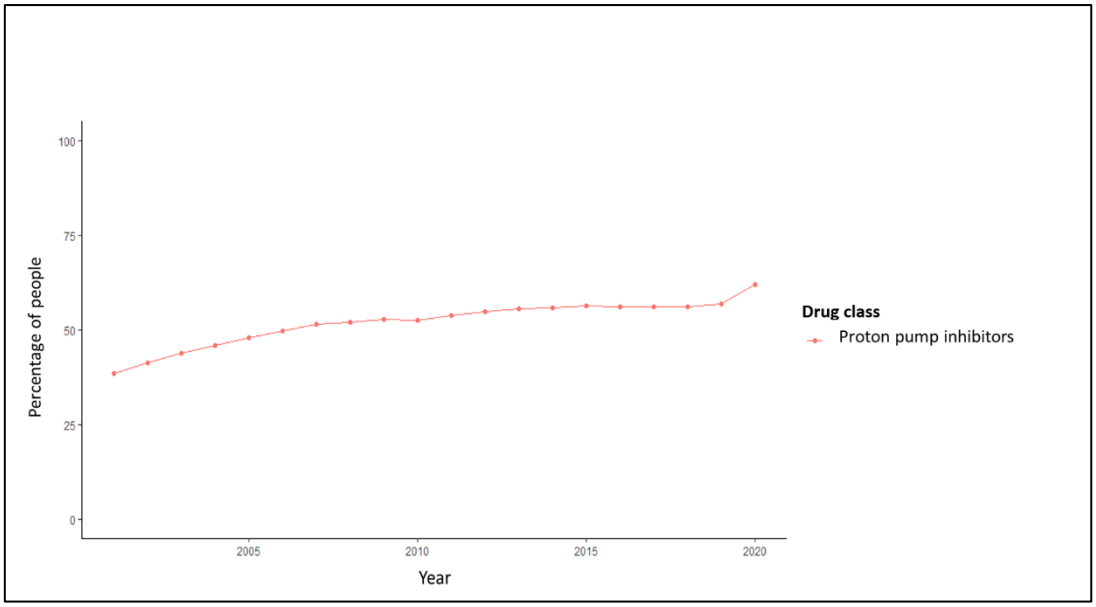

Figure 3.6: The percentage of patients prescribed proton pump inhibitors rose dramatically in the period from 2001–2020

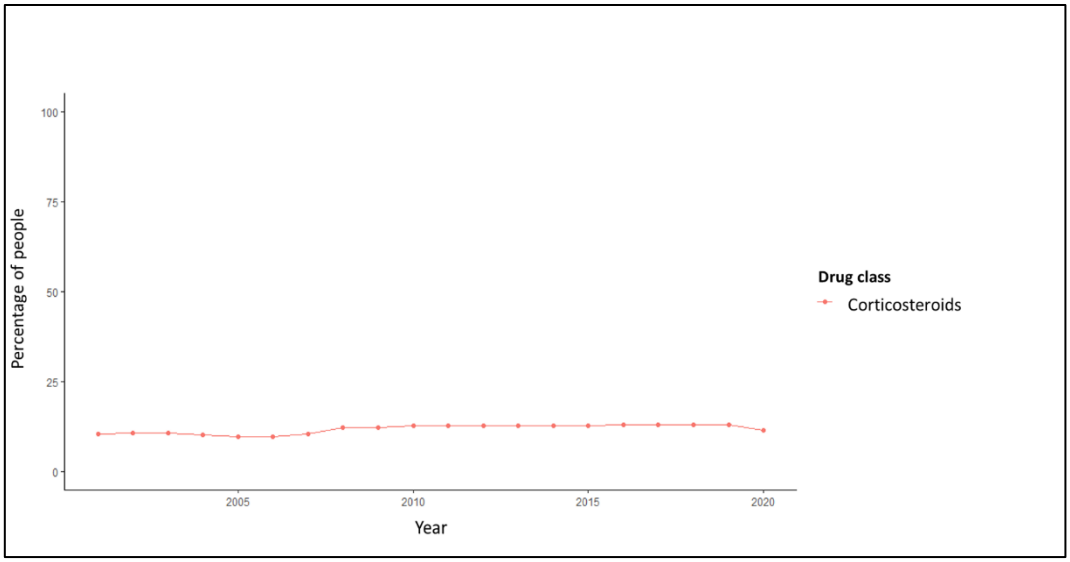

Figure 3.7: The percentage of people prescribed corticosteroids increased in the period between 2006 and 2010 then experienced a fluctuation, until a notable drop in 2018–2020

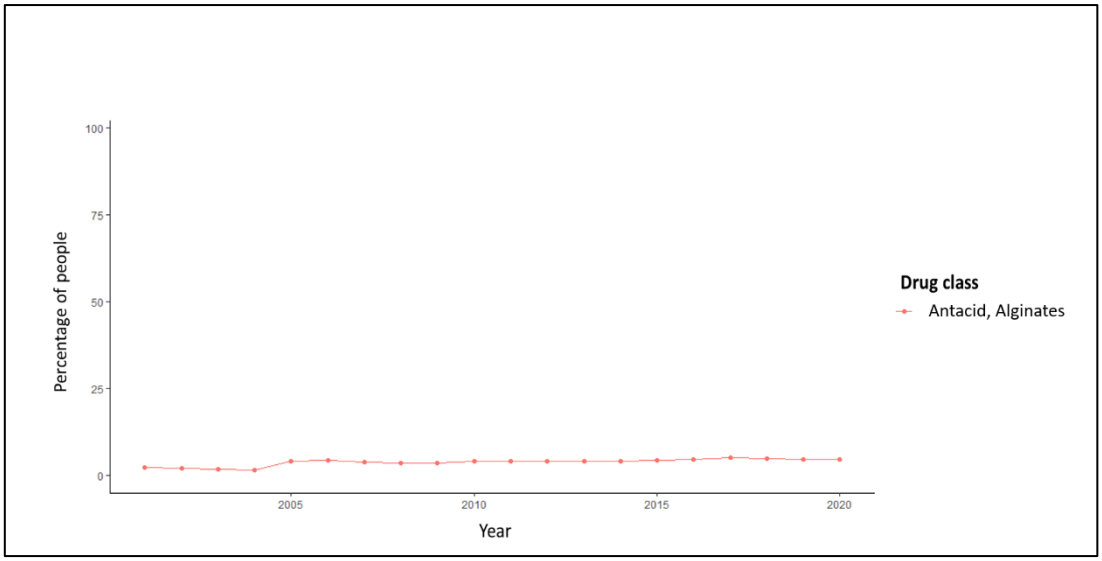

Figure 3.8: The percentage of people who used the antacid alginates drug class rose between 2004 and 2006 and then dropped until 2009, with a subsequent increase until 2017

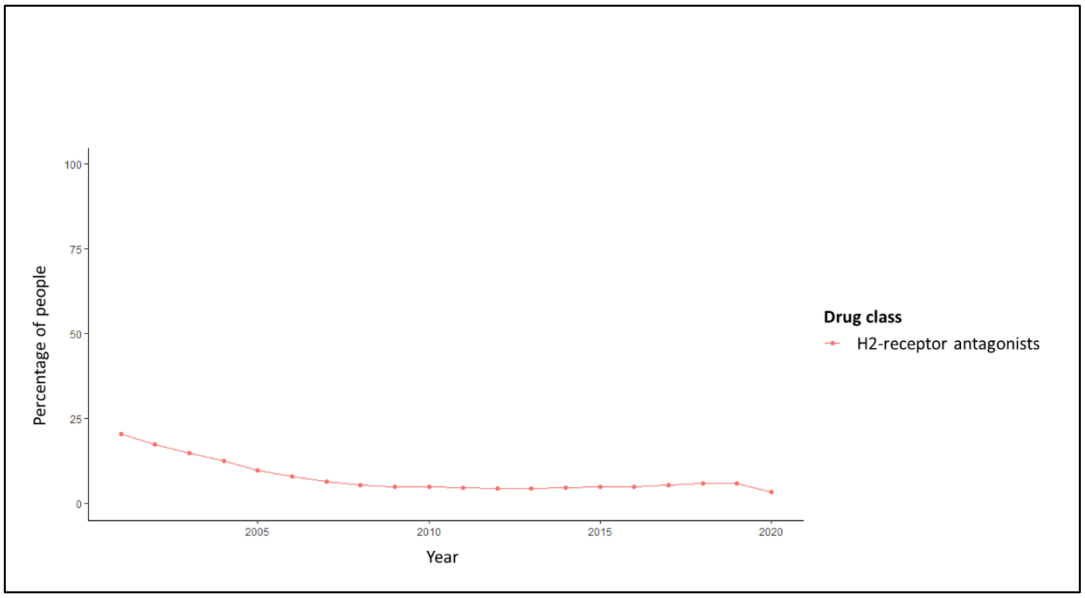

Figure 3.9: H2-receptor antagonists started at a high value of around 22% in 2002, with steep decline in the period 2002–2020

Top Ten Drug Classes Trends in the Period 2001–2020

Figure 3.10 depicts the most commonly prescribed drug classes. The Figure shows that the most prescribed drug class was proton pump inhibitors followed by corticosteroids in the period between 2001 and 2020. However, H2-receptor antagonists started at a high value of 20 percent in 2001 and then dropped to 3.5 percent in 2020. Generally, the remaining drug classes remained steady during the current study period.

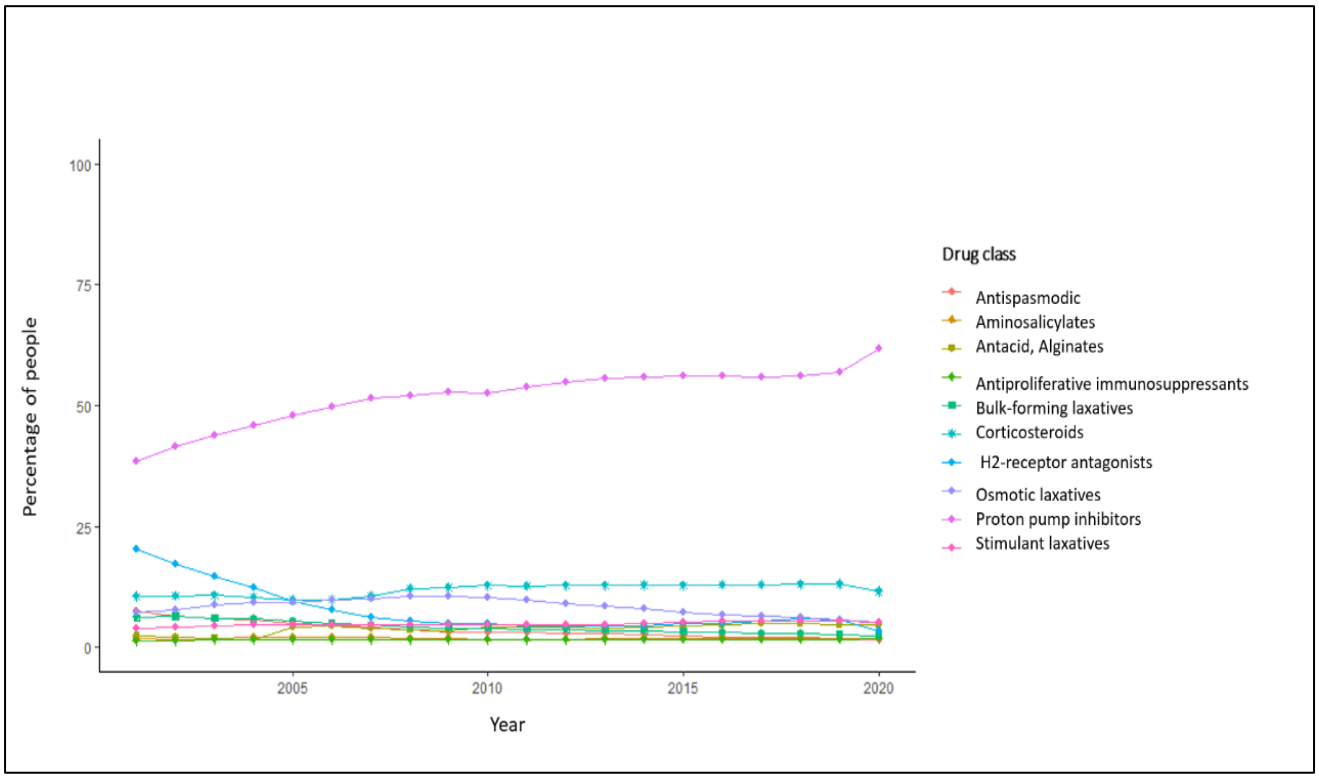

Figure 3.10: The top ten drug classes prescribed between 2001-2020

Most Commonly Prescribed Drugs in the Drug Class Trend

There were differences in drug prescription trends within each drug class (Figure 3.11). The rate at which omeprazole was prescribed increased sharply between 2003 and 2020. Lansoprazole declined from 2003 until 2005, and then remained relatively constant up until 2020.

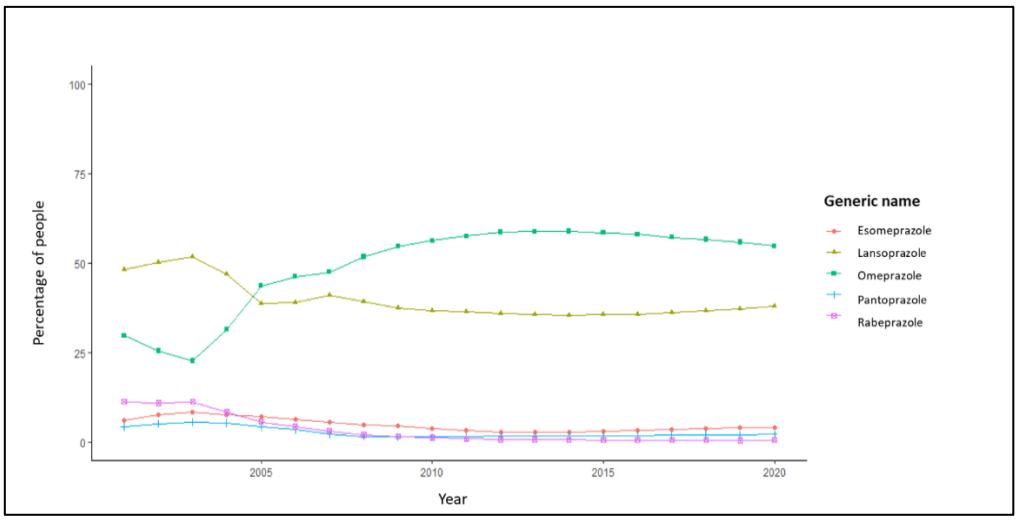

Figure 3.11: Most commonly prescribed medications in proton pump inhibitors drug class in 2001–2020

Figure 3.12 shows that prednisolone started at a high prescription rate of around 88% before decreasing to around 56% in 2010. After that, there was a slight increase up to 63% until the end of the course of the study period. On the other hand, beclomethasone started at a low number (around ten percent) and increased slightly to approximately 15% in 2006 and then jumped dramatically to around 35% in 2020.

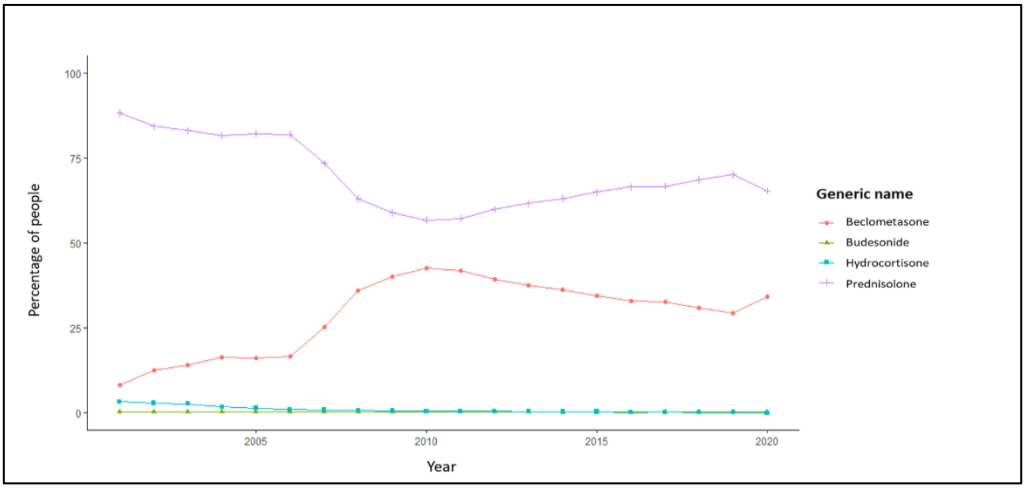

Figure 3.12: Most commonly prescribed medications in corticosteroids drug class between 2001 and 2020

Figure 3.13 demonstrates that ranitidine was the most commonly prescribed drug in the H2-receptor antagonist drug class, starting from around 62% and rose constantly to around 99% in 2018. It then falls suddenly to around 77% in the period between 2018 and 2020.

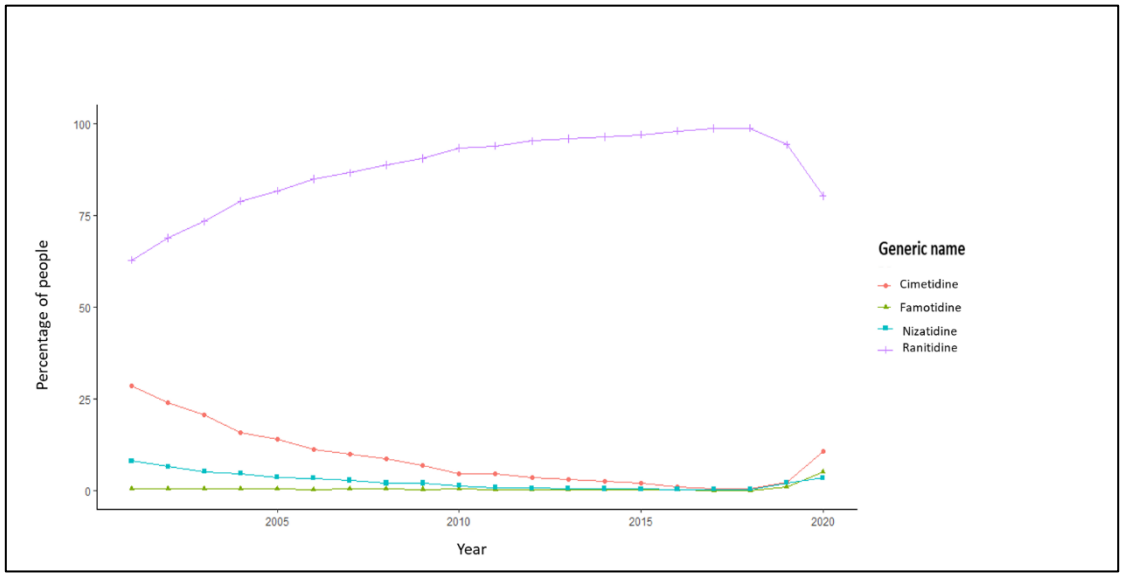

Figure 3.13: The most commonly prescribed drugs in the H2-receptor antagonists drug class between 2001 and 2020

Total Unique Drug Prescriptions from 2001–2020

The current study analysed the number of drugs prescribed to patients with gastrointestinal disease in five-year snapshots. These numbers were compared using Pearson's Chi-squared test, with the results showing statistically significant differences in the number of consumed drugs in the five-year snapshots from 2001–2020 (*P*-value <0.001). Also, the comparison between total unique drugs in the five-year snapshots from 2001–2020 using a one ANOVA test showed a statistically significant difference in the total number of unique drugs prescribed in the five-year intervals between the tested groups (*P*-value <0.0001), as shown in Tables 3.4 and 3.5 below.

Table 3.4: Drug consumption in five-year snapshots between 2001 and 2020

Characteristic	2001 N = 13,377	2005 N = 24,250	2010 N = 44,230	2015 N = 59,900	2020 N = 49,958
Number of drugs N(%)					
1	9,757 (73%)	16,546 (68%)	28,341 (64%)	37,598 (63%)	33,721 (68%)
2-4	3,545 (27%)	7,408 (31%)	15,241 (34%)	21,389 (36%)	15,798 (32%)
5-9	75 (0.6%)	295 (1.2%)	645 (1.5%)	906 (1.5%)	435 (0.9%)
10-15	0 (0%)	1 (<0.1%)	3 (<0.1%)	7 (<0.1%)	4 (<0.1%)

Table 3.5: Total unique drugs analysis for five-year snapshots (2001, 2005, 2010, 2015 and 2020)

Year	Population count	Mean	Standard deviation	Median	Minimum drug	Maximum drug	Drug range
2001	13377	1.152127	0.424065	1	1	7	6
2005	24250	1.223093	0.513782	1	1	8	7
2010	44230	1.270224	0.565666	1	1	7	6
2015	59900	1.294992	0.592325	1	1	8	7
2020	49958	1.284399	0.585833	1	1	8	7

Comparison of Unique Drug Prescription in Snapshot One (2001) and Snapshot Five (2020)

The *T*-test was used to compare the mean number of unique gastrointestinal drugs at the beginning and the end of the study periods (2001 and 2020). The results in Table 3.6 show that that there was a statistically significant (*P*-value <0.0001) difference in the mean number of the unique gastrointestinal drug prescriptions between 2001 and 2020.

Table 3.6: Comparison of gastrointestinal total unique drug prescriptions between 2001 and 2020

Group	2001	2020
N	13377	49958
Mean	1.152	1.284
Difference between means ± SEM	0.1323 ± 0.005409	

3.3.4 Population Characteristics of the Cohort Followed over 20 years (N= 3110)

The study population comprising 3,110 patients was tracked and identified as having constant and continuous follow-up for the entire 20 years in the period between 2001 and 2020. The individual patients were also equal to or above the age of 50 years and had been diagnosed with gastrointestinal diseases together with two or more chronic conditions.

Table 3.7 shows the population characteristic of the same patients over the 20 years of follow-up, with a total number of females (n=1,526) and males (n=1,584). The mean age was 63 years (SD 8; range 50-95). Most of the patients were in the age group 60–64 years (655 (21%) of the study population) followed by the age group 55 to 59 years which represented 618 (20%) of the population. In contrast, in the age group 90+, only 1 person (<0.1%) comprised the study population. In addition, the majority of people were white representing 74% of the study sample.

Table 3.7: Population characteristics of the same patients over 20 years of follow-up (N=3110)

Characteristic	**N = 3,110**
Gender Number (%)	
Female	1,526 (49%)
Male	1,584 (51%)
Age Mean [SD]	63 (8)
Age Group Number (%)	
50-54 Years	530 (17%)
55-59 Years	618 (20%)
60-64 Years	655 (21%)
65-69 Years	598 (19%)
70-74 Years	463 (15%)
75-79 Years	181 (5.8%)
80-85 Years	64 (2.1%)
90+ Years	1 (<0.1%)
Ethnicity Number (%)	
Asian or Asian British	65 (2.1%)
Black or Black British	25 (0.8%)
Chinese or Other Group	99 (3.2%)
Mixed	5 (0.2%)
White	2,315 (74%)
Unknown	601 (19%)

3.3.5 Prescription Pattern of Drug Usage and Drug Classes (N=3110)

The Major Drug Classes Trend

For this study sample, trends in prescribing of the major gastrointestinal drug classes are shown in Figures 3.14 –3.17. The proton pump inhibitors (Figure 3.14) showed a rapid surge in the period between 2001 to 2020 from around 49 percent to 59 percent. However, the remaining trends for the gastrointestinal drug classes were either experiencing variable fluctuation or a dramatic drop until the end of the study period, as shown in Figures 3.15–3.17.

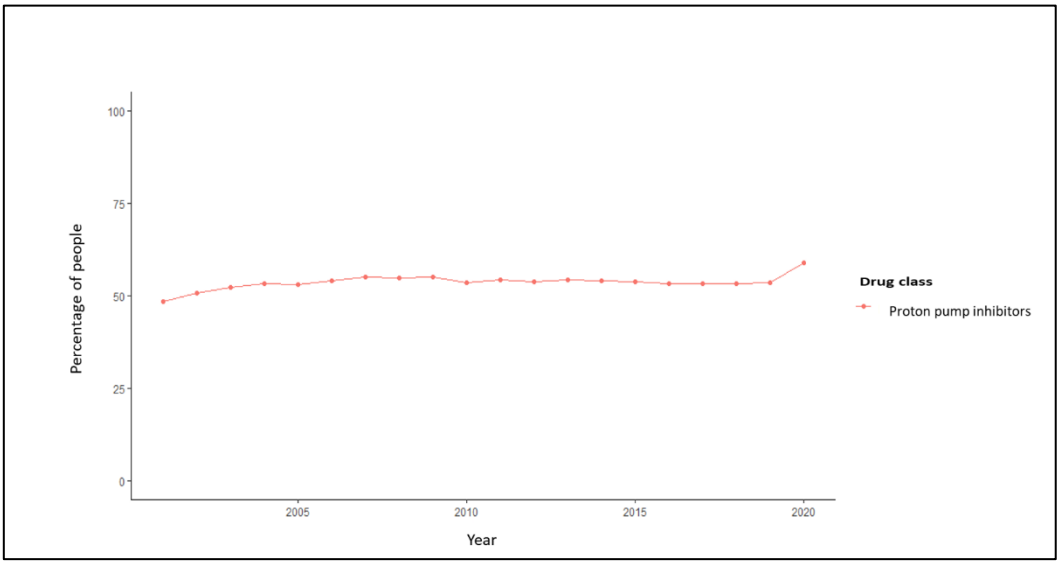

Figure 3.14: Proton pump inhibitors trend from 2001 until the end of the study period

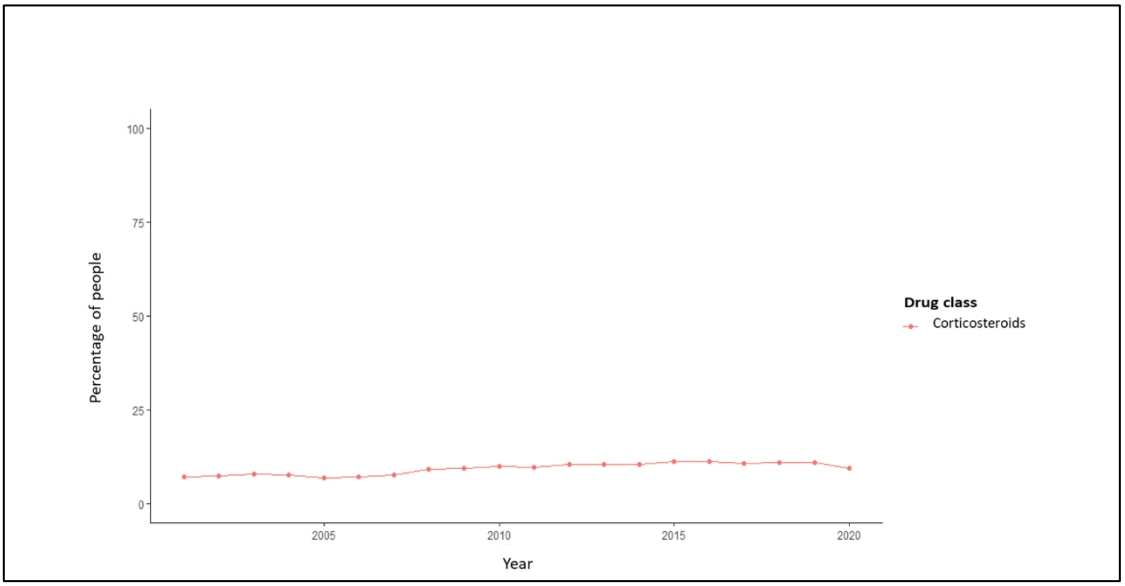

Figure 3.15: Percentage of people prescribed the corticosteroids between 2001 and 2020

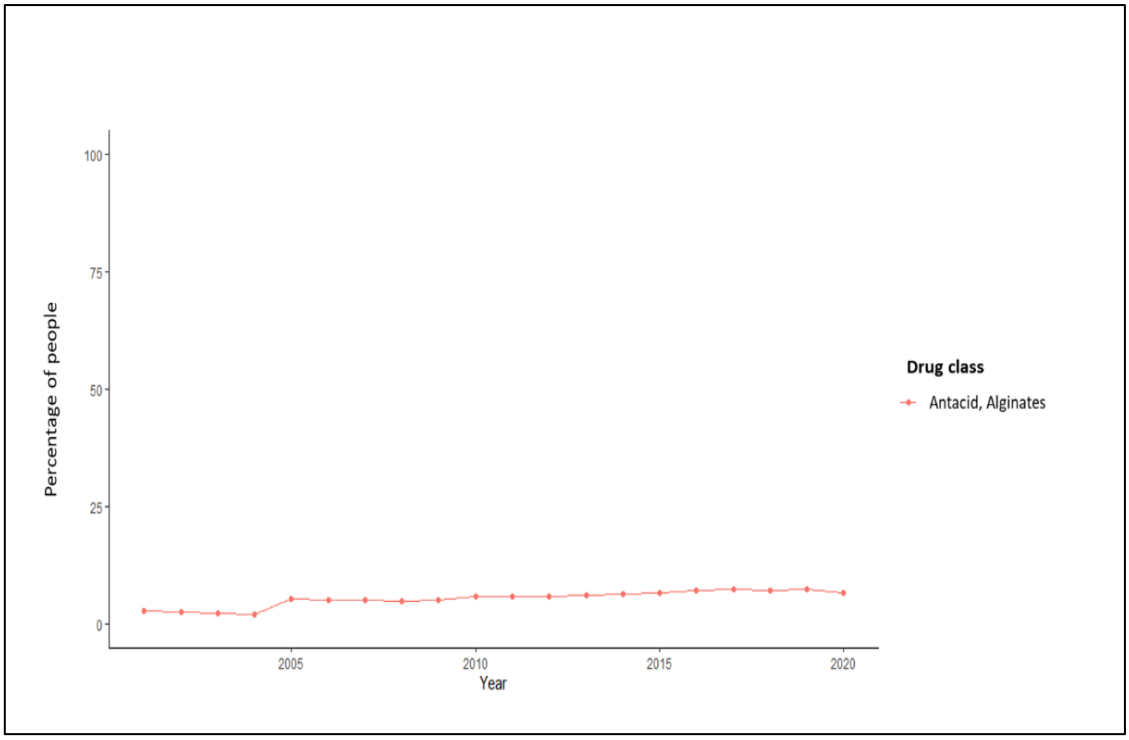

Figure 3.16: The percentage of people prescribed the antacid, alginate between 2001 and 2020

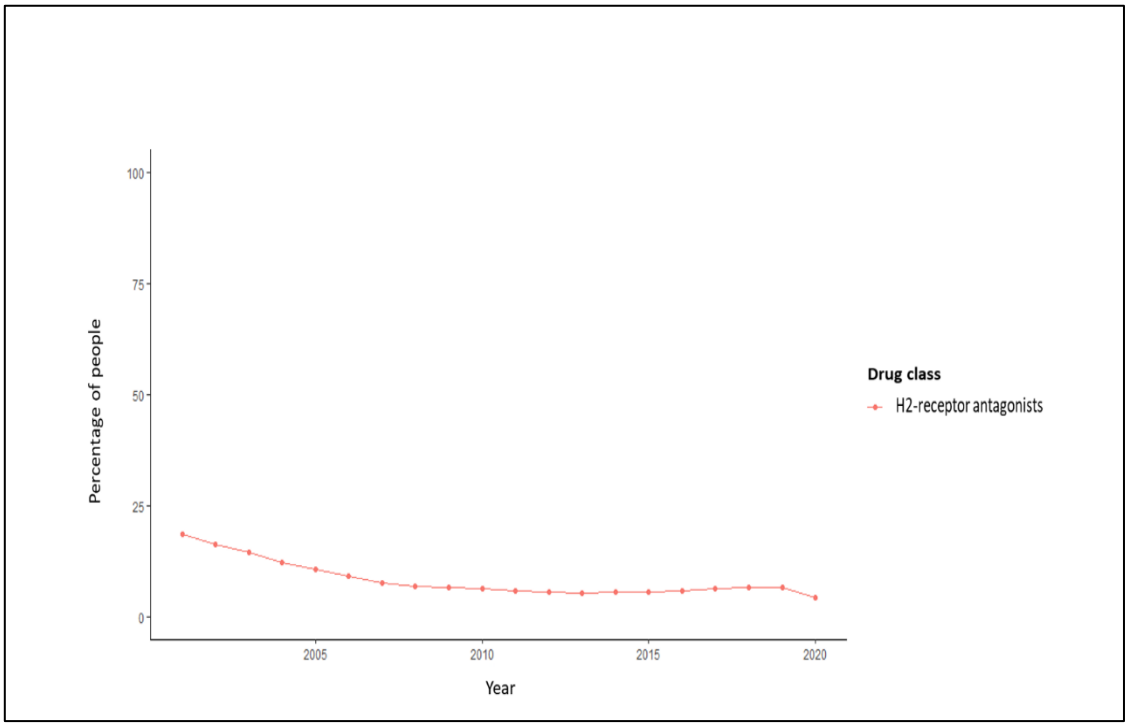

Figure 3.17: H2-receptor antagonists drug prescription throughout the study period

Figure 3.18 shows that the most commonly prescribed drug classes between 2001 and 2020 were proton pump inhibitors, followed by corticosteroids.

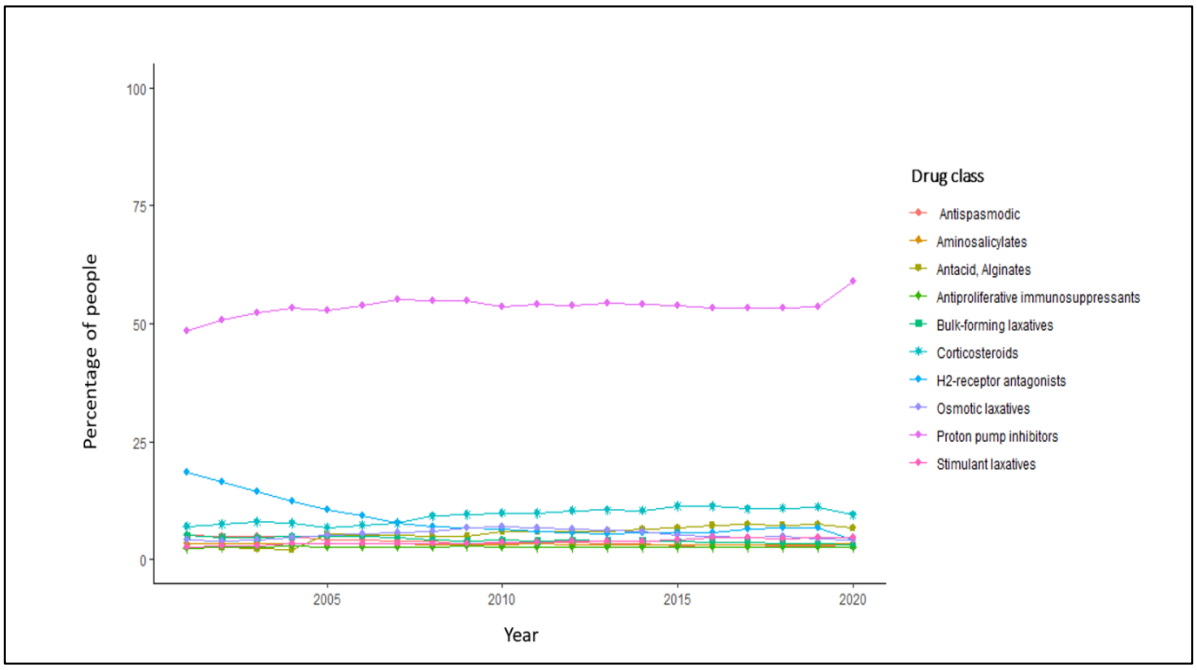

Figure 3.18: Top ten drug classes trend for the same patients for 20 years follow-up

Prescription Pattern Comparison at the Beginning and End of the Study Period

Tables 3.8 and 3.9 show a comparison between the prescription patterns in the two snapshots. This was to compare the top 10 prescription patterns along five-year periods ('snapshots'). The first snapshot was at the beginning of the study period (2001–2005), whilst the second snapshot (2016–2020) was at the end of the study period. The analysis was carried out using the Apriori algorithm to compare the most frequent drugs prescribed together at both the beginning and the end of the study periods (2001–200, and 2016–2020) in the available sample size (n = 3,110).

The results show that azathioprine was associated with prednisolone prescription with a confidence of 25%. In this study period, high confidence was identified with 404 counts of prescribing azathioprine and prednisolone together, as shown in Table 3.8.

Table 3.8: Top 10 patterns in the period 2001-2005

Antecedent	Consequent	Confidence (%)	Lift	Count
{Azathioprine}	{Prednisolone}	0.25	5.25	404
{Senna}	{Lansoprazole}	0.19	0.63	424
{Alverine citrate}	{Ispaghula husk}	0.16	4.44	152
{Mebeverine hydrochloride}	{Ispaghula husk}	0.16	4.39	656
{Methotrexate}	{Lansoprazole}	0.16	0.53	332
{Methotrexate}	{Prednisolone}	0.15	3.16	319
{Methotrexate}	{Sulfasalazine}	0.13	5.1	280
{Senna}	{Lactulose}	0.12	4.52	279
{Prednisolone}	{Lansoprazole}	0.11	0.36	611
{Mebeverine hydrochloride}	{Lansoprazole}	0.11	0.35	429

In addition, Table 3.9 illustrate the top 10 prescription patterns in the period 2016 to 2020 were prednisolone and senna, which were frequently prescribed together with lansoprazole, with a high confidence at 100% and a high correlation with a lift value 104.69.

Table 3.9: Top 10 patterns in the period 2016-2020

Antecedent	Consequent	Confidence (%)	Lift	Count
{Prednisolone,Senna}	{Lansoprazole}	1	104.69	342
{Lactulose,Senna}	{Lansoprazole}	0.89	463.36	203
{Methotrexate}	{Lansoprazole}	0.16	4.6	676
{Sulfasalazine}	{Lansoprazole}	0.16	2.44	492
{Alverine citrate}	{Omeprazole}	0.16	6.47	212
{Methotrexate}	{Lansoprazole}	0.16	4.6	676
{Sulfasalazine}	{Lansoprazole}	0.16	2.44	492
{Prednisolone}	{Omeprazole}	0.13	2.25	1457
{Mebeverine hydrochloride}	{Ispaghula husk}	0.12	3.45	603
{Lactulose}	{Senna}	0.11	4.47	486

Table 3.10 shows the correlation pattern for prescribing sequence over time. The count refers to the number of prescriptions. The highest (greenest) the count number the greater likelihood/chance that the two drugs are prescribed together. The following results draw a comparison between the first snapshot (2001–2005) and the last snapshot (2016–2020) to illustrate the two drugs most commonly prescribed together in these study periods. The results show that lansoprazole and prednisolone were most commonly prescribed together between

2016 and 2020, though there was a lower correlation regarding prescription count together in the period 2001–2005.

Table 3.10: Change of pattern in sequence of two drugs being prescribed over time

Rule	2001-2005	2016-2020
{Prednisolone} => {Lansoprazole}	611	2089
{Senna} => {Lansoprazole}	424	1870
{Mebeverine hydrochloride} => {Lansoprazole}	429	1499
{Lactulose} => {Lansoprazole}	326	709
{Methotrexate} => {Lansoprazole}	332	676
{Mebeverine hydrochloride} => {Ispaghula husk}	656	603
{Azathioprine} => {Prednisolone}	404	246

High count **Low count**

3.4 Discussion

3.4.1 Population Characteristics and Diseases Profile

In the present study, the number of people who had gastrointestinal disease was higher in both females and males in the age groups 50–54, 55–59, and 60–64 years old. Another study conducted by Dawoodi et al. (2022) showed that people with gastrointestinal diseases who are aged 55–64 years were highly affected. However, this was due to the fact that the 55-64 year old group were to those who were younger than 44 years old (Dawoodi et al., 2022). In the current study, the population of people with gastrointestinal diseases decreased with age in both males and females which could be linked to the increased mortality rate in the older persons with multimorbidity (Nguyen et al., 2022; Zazzara et al., 2023).

The majority of the population studied were categorised as white, which is perhaps not surprising as the study is conducted in CPRD which covers the whole of the UK population. However, there may also be some inaccuracies as when the ethnicity of the patient is missing, patients will be referred to as being ‘White’ (since this is the ethnicity that represents the majority of the population in the UK). Therefore a limitation of our study is that we cannot necessarily extrapolate the results to other ethnic groups living in the UK.

The study shows that the most common gastrointestinal disease was gastroesophageal reflux disease (GERD). GERD is one of the most common gastrointestinal disorders, affecting approximately 20% of adults in Western culture. According to a systematic review carried out by El-Serag et al., the prevalence of GERD in the United States ranged from 18.1% to 27.8% (Antunes et al., 2022). In another study, it has been shown that GERD was the most common outpatient diagnosis, with nearly 9 million visits in 2009 (Peery et al., 2012). The present study also showed that the second most common GI disease was abdominal hernia. This can confirmed from other publications, which indicate that there are more than one million abdominal hernia surgeries every year in the United States. This is equivalent to around 0.3% of the US population (Qin et al., 2021). Approximately 20% of the present study population had chronic constipation. This is consistent with Liu (2011) who stated that chronic constipation affects 15-25% of the general population (L. W. C. Liu, 2011).

In patients with GI disease, 46% also suffered from hypertension, with 41% also suffering from lipid disorders. These numbers highlight the fact that hypertension and lipid disorders represent the most common comorbidities in old people, particular in those over the age of 50 years (Davis et al., 2011).

Our study also shows that the number of patients suffering from comorbidities increased with age, especially in the age range between 65–69, 70–74, and 75–79 years. This is consistent with Divo et al. who showed that the number of chronic comorbidities increase with age and was highest in people aged 65 years and older (Divo et al., 2014). In our study, there was a steep decrease in the sample size for the age group 80+ years. This is due to the high mortality rate in those with multimorbidity, and indeed, many people who live to this age may be living healthier lives with the fewest long-term comorbidities.

3.4.2 The Prescriptions Pattern of Drugs Usage and Classes

The top most common medicines prescribed were proton-pump inhibitors (PPIs). Omeprazole and lansoprazole ranked the highest at 31% and 23%, respectively. Omeprazole has been found to be effective and can be used to manage and treat a variety of gastrointestinal conditions (Shah & Gossman, 2022). In addition, in line with a previous study, the most commonly used

PPIs to treat GERD symptoms were omeprazole and lansoprazole, with studies have shown that the omeprazole and lansoprazole are effective in relieving the symptoms of both heartburn and regurgitation with no significant difference between the two drugs. However, it has been suggested that omeprazole is more effective than lansoprazole in reducing gastric acidity (Javed et al., 2020), but whether this is of clinical significance, or a true finding, is debateable.

A total of five percent of the study population used prednisolone. This type of drug is typically used to treat Crohn's disease. Moreover, corticosteroids (usually prednisolone) continue to be utilised as first-line therapy, with immunotherapies serving as corticosteroid-sparing agents (Mak et al., 2019). In the most commonly used drugs list was ranitidine used by 5% of people. This drug is used for the treatment and prevention of a wide range of gastrointestinal diseases associated with gastric acid secretion. Ranitidine was considered a first-line agent when suppressing gastric acid secretion because it was shown to be beneficial with high efficacy and tolerability profiles (Grant et al., 2012). However, its used has been surpassed by proton pump inhibitors which explains why the use of ranitidine has declined over the last 10 years or so. In addition, the more recent decline in use may be because of shortages in medicine supply as a result of the identification of nitrosamine impurities in ranitidine formulations.

Major Gastrointestinal Drug Classes Trend

The study identified the major drug class most commonly prescribed for gastrointestinal diseases in UK primary care for the period 2001–2020 was proton-pump inhibitors. This is consistent with another study which showed an increase over a 14 year duration period (Torres-Bondia et al., 2022).

The use of corticosteroids has also increased over the period from 2001–2010. A similar conclusion was reached by Blackwell et al. (2021) in a study involving 20 Pennsylvania hospitals. In this study, steroid use increased to 63.7% during 2001–2010 in comparison to the period 1991–2000, where the percentage was 36.3% (Blackwell et al., 2021). In comparison, the H2-receptors antagonists and antispasmodic drugs were highly prescribed at the beginning of the study period, and then there was a decrease up to 2020. H2-Receptors antagonist has been linked to the central nervous system adverse effects such as anxiety, delirium, confusion,

difficulty speaking, or hallucinations (Nugent et al., 2022), but it is likely that most of the decrease is because of the availability and effectiveness of PPIs. The decrease in antispasmodic prescribing is likely to be due to the increasing realisation that they contribute to the anticholinergic burden which has been associated with falls, delirium and cognitive impairment especially in the older persons (Spence et al., 2015).

Prescribed Drugs in the Drug Class Trend

The results show that omeprazole was most commonly prescribed with a rapid increase from 2003 onwards. A similar pattern of results was obtained by Torres-Bondia et al. (2022), where lansoprazole, pantoprazole, and rabeprazole all showed a decline with slightly different evolutions over the period 2002–2015. With the exception of omeprazole, the remaining PPIs had a higher dispensing prevalence in 2015 than in 2002 (Torres-Bondia et al., 2022). In 2020, Pereira et al. (2020) illustrated that the most common and highest used drug to treat gastrointestinal diseases was omeprazole (Pereira et al., 2020).

In the corticosteroids drug class, the study showed that prednisolone was the most commonly used followed by beclometasone. Both corticosteroid types (prednisolone and beclomethasone) are used to treat inflammation in a variety of ailments, including inflammatory bowel disease (IBD). Prednisolone started at a high value of around 88% at the beginning of the study period and then decreased to 63% at the end of the study period. One possible reason for this decrease in prednisolone usage may be due to its side effects, which include weight gain, and elevated risk of infection (Barrett et al., 2018). In contrast, beclometasone started with a minimal value followed by a dramatic increase over the study period until 2020. This could be because of its effectiveness in treating IBD as well as its availability as a topical formulation (Rizzello et al., 2018). Additionally, advances in treatment options for gastrointestinal diseases may have also played a role in decreasing the use of prednisolone. For example, newer biological therapies have been developed that target specific inflammatory pathways, and these are being increasingly used. However, many of these newer biologics may be prescribed in secondary care, and hence may not be recorded in the GP prescribing, which represents a limitation of our analysis.

Total Unique Drug Prescriptions from 2001–2020

Drugs used for gastrointestinal diseases were studied in individual segments at five-year interval, starting from 2001 and ending in 2020. The study shows that the majority of people sample were taking only one gastrointestinal drug. The number of people taking five gastrointestinal drugs understandably was small.

A similar pattern of results was obtained in the United States (69.0%) and Canada (65.5%); nearly 7 in 10 adults aged 40 to 79 used at least one drug, and roughly 1 in 5 used at least five prescription drugs (22.4% in the United States and 18.8% in Canada) (Hales et al., 2019.). An obvious limitation of the present study is that it is focusing in gastrointestinal drugs, and it is likely that this study sample is also taking a range of non-gastrointestinal medications, which add to the polypharmacy burden. The current study found that the GI drugs range in 2001 was six, which has slightly increased in 2020 to seven drugs. The total number of drugs used and drug prescription patterns in gastrointestinal diseases have changed significantly over time indicating an increase in gastrointestinal drug usage, as well as the contribution of GI disease to the overall multimorbidity burden in the population.

3.4.3 Gastrointestinal Patients in 20 Years of Follow-Up

The study classified and analysed 3,110 patients who had 20 years of follow-up, which represents around 2.8% of the current study population. In 20 years of follow-up, the most commonly prescribed drug classes were still proton pump inhibitors (PPIs), followed by corticosteroids. The least commonly prescribed drug class, on the other hand, was an antiproliferative immunosuppressant. Interestingly, the top two prescribed drugs remained the same for both study samples (n=111,355, and n=3,110) at the end of the 20 years of follow reflecting the disease epidemiology which is unlikely to have changed over this time period.

In a similar study conducted in France, the key findings were that the PPIs were the most commonly prescribed drug class, reported in 25.7 million people, corresponding to 130 million prescriptions dispensed per year (Tuppin et al., 2019). Interestingly, from 2001 to 2010, steroid use increased to 63.7% in comparison to the period 2000 and before (Blackwell et al., 2021).

Meanwhile, research has shown that antiproliferative immunosuppressant agents are used less commonly in the treatment of IBD patients in East China (Huang et al., 2009).

Comparison of the Prescriptions Between Snapshots for the 20-Year Follow-Up Patients

The top 10 prescription patterns in the same population over 20 years of follow-up were sorted by confidence. The results show that azathioprine is associated with prednisolone with a confidence of 25%, with a count of 404 prescriptions. These medications show efficacy in combined treatment protocols for patients with active Crohn's disease (CD), outperforming prednisolone alone (Ewe et al., 2016).

Senna was occasionally prescribed with lansoprazole. Specifically, if senna was prescribed, lansoprazole will also be prescribed with a confidence of 19%. The present study found a correlation with lift of 0.63, which is less than one. This indicates that the drugs appear less often prescribed together than expected. Ogasawara et al has also reported that constipation is linked to gastroesophageal reflux disease (GERD) in the United States, reporting that 28.3% of GERD patients had constipation (Ogasawara et al., 2022). Our results also show that methotrexate is frequently prescribed with sulfasalazine, with a correlation, a lift value of 5.1 and 13% confidence with a 280 prescription count. It has been reported that these drugs are often used to treat inflammatory bowel disease (IBD) (Litou et al., 2019). Prescribing these drugs together could provide synergistic effect, leading to improved symptoms control and overall disease management.

The top 10 prescription patterns in the period 2016–2020 showed that prednisolone, and senna were the most frequently prescribed drugs together with lansoprazole, with a confidence value of 100% and high correlation with a lift value of 104.69. These medications are prescribed as combinations to manage side effects related to prednisolone. That is because corticosteroids can increase the risk of gastrointestinal ulcers or gastrointestinal bleeding. This is the reason why it is advisable to prescribe lansoprazole to protect the stomach lining and reduce stomach acid (Munson et al., 2012).

A common side effect of PPIs like lansoprazole is constipation. In some cases, senna may be prescribed along with lansoprazole to help relieve constipation. Lactulose and senna were prescribed together with lansoprazole with a high probability of confidence (89%) and a high correlation with a lift value of 463.36. Lactulose and senna are commonly prescribed together to treat constipation which can be caused by lansoprazole. Since the present study is focusing on older patients, our findings are in line with the fact that constipation is more common amongst the older persons (Fragakis et al., 2018).The study findings also highlight how drug patterns have changed over time, with a particular emphasis on the comparison of two periods. Snapshot One was between 2001 and 2005, while Snapshot Two was between 2016 and 2020. The results were sorted by the number of occurrences.

We also evaluated changes in prescribing patterns between Snapshot One (2001-2005) and the end of the study period (2016-2020). Prednisolone and lansoprazole were prescribed together 611 times in the period spanning 2001–2005, while there was a jump to 2,089 prescriptions of the two together in the period of 2016–2020. This is keeping with the guidelines which now recommend the co-prescription of these two drugs to reduce the adverse effects associated with corticosteroids (Munson et al., 2012).

In conclusion, an evaluation was undertaken of the use of gastrointestinal drugs over a 20-year period. Overall, there was an increase in the number of drugs used for each patient in the study population. This could be partially related to the increase in multimorbidity in the UK population. The study highlights how GI drug prescribing has evolved over two decades and contributes to the overall polypharmacy burden which is being seen in the population.

Chapter Four

Final Discussion

4.1 Aims Addressed

This thesis aims to describe the changing patterns of medication prescription practice in older people over the last 20 years, focusing on cardiovascular and gastrointestinal diseases. Health informatics and machine learning approaches were used to help describe how prescription patterns changed over time.

4.2 Summary of Main Findings

The data analysis was performed using R software on selected patient records. Chapter Two covers cardiovascular patterns, focusing on two groups of people aged 50 years and older with cardiovascular diseases between 2001 and 2020 in the UK.

In the first cardiovascular patient group (n= 228,376), all older patients aged 50 years or above with two or more chronic conditions and two or more years of follow-ups between 2001 and 2020, were extracted. The study findings highlighted the major drugs prescribed were simvastatin followed by atorvastatin which was confirmed by another study that highlighted that these were the most prescribed drugs within the same study period (J. Wang et al., 2020). Additionally, the most commonly prescribed drug classes from 2001 to 2020 were statins followed by calcium channel blockers. These two drug classes are usually used as a combination especially for patients with high cholesterol and hypertension (Khan et al., 2018).

Moreover, the results demonstrated that the number of drugs used by older patients with cardiovascular disease in five-year snapshots starting in 2001 and ending in 2020. The results showed that most of the older patients were taking between 2 and 4 cardiovascular medications, and there was a sharp increase from 43% in 2001 to 64% in 2020 in the percentage of patients prescribed 2–4 drugs. The study also showed that there was a statically significant increase in the mean number of total cardiovascular drugs prescribed in 2020 in comparison to 2001. This fact comes in line with the continuous increase in cardiovascular drug prescriptions (Rashid et al., 2014).

In the second evaluation, the same cohort of patients on cardiovascular medications was followed over 20 years (n = 17,075), with only those having constant and continuous follow-up for the entire 20 year period between 2001 and 2020 included. This evaluation found that the most common drug class prescribed from 2001 to 2020 were statins followed by calcium channel blockers. The study also used an Apriori algorithm in R software to compare drug prescription patterns in Snapshot One (in the period between 2001 and 2005) with Snapshot Two (in the period between 2016 and 2020) to compare changes amongst the top 10 patterns over time. This showed that atenolol and nicorandil were associated with co-prescription with aspirin with a high probability of confidence (62%) in the period between 2001 and 2005. Conversely, in the period between 2016 and 2020, amlodipine, atenolol, and clopidogrel were the most frequently prescribed along with atorvastatin, with a high value of confidence at 72%. In 2015, Rosendorff et al study show that these medications are commonly prescribed together to treat coronary artery disease (Rosendorff et al., 2015). Furthermore, aspirin and atorvastatin were less correlated in snapshot one, with 16,183 prescriptions, whereas in Snapshot Two, there was a considerable increase to 58,905 prescriptions, perhaps highlighting confidence amongst prescribers of the evidence base in co-prescription of these medicines in the treatment of cardiovascular disease.

Chapter Three investigated gastrointestinal disease. The study included two groups of patients with gastrointestinal diseases in the period spanning 2001–2020. The first group (n = 111,355) were 50 years of age or older, and had two or more chronic conditions and two or more years of follow-up. The results showed that lansoprazole and omeprazole were the two most commonly prescribed medications which were also found in another study (Y. Liu et al., 2020). In addition, the most commonly prescribed drug classes were proton pump inhibitors followed by corticosteroids. Evaluation of the 5-year snapshots showed that the majority of people were using only one drug while the number of patients using five drugs and above was the lowest during the study period. From 2001 to 2020, there was a statistically significant increase in the mean number of total gastrointestinal drugs prescribed.

For the second evaluation, as with the cardiovascular drugs, a cohort who had constant and continuous follow-up for the entire 20 year period was tracked (n = 3,110), and drug prescribing patterns examined. The results illustrate that azathioprine was associated with prednisolone

prescription with a confidence of 25% in the period between 2001 and 2005. These two drugs combination shows high level of safety and efficiency (Vianna et al., 2006). However, in the period spanning 2016-2020, prednisolone and senna were the drugs most frequently prescribed together with lansoprazole with a confidence value of 100%. In terms of changes in prescription patterns between Snapshot One (between 2001 and 2005) and Snapshot Two (between 2016 and 2020), prednisolone and lansoprazole were prescribed together 611 times between 2001 and 2005, but this increased to 2089 in snapshot two, reflecting changes in guidelines on the need to use gastro-protectant agents in people who are on gastric irritant drugs such as prednisolone (Munson et al., 2012).

4.3 Strengths

This thesis illustrates a number of strengths in relation to using CPRD data. These include the ability to study a large sample size of both male and female patients. Furthermore, the study also succeeded in tracking patients and prescription patterns over a 20-year period. This has enabled an accurate assessment of how the use of drugs has changed over 20 years, how the polypharmacy has grown, and how the pattern of prescription combinations has evolved. Although CPRD only covers a proportion of the UK population, the results are generalisable to the whole UK population.

4.4 Limitations and Future Studies

The studies described in this thesis have some limitations. Firstly, there is the issue of missing data. Although general practitioners (GPs) can manually enter secondary care data, including important diagnoses, this information is frequently incomplete in primary care records. Researchers are unable to access any additional data that may be present in free text entries or letters received by GPs from secondary care facilities due to data governance concerns. However, linkage to other data sources can be used to obtain additional information on patient journeys, although this does not include information on secondary care prescriptions, medicines dispensed, and over-the-counter (Wolf et al., 2019).

A variety of ethnic classification systems are used in different healthcare settings (such as GP offices, hospitals, etc.) and across various geographic regions in the UK, which may also be considered a limitation. There are probably non-standardised policies and practices for gathering ethnicity data at various facilities, which leads to the variable quality of ethnicity data, such as a lack of agreement between self-reported and health worker coded ethnicity data. (Rees et al., 2016; Shiekh et al., 2023; van Staa et al., 2014).

Another limitation of CPRD data is that CPRD coding in general practices and hospitals may be different. Such coding issues might lead to confusion such as coding stable angina as heart attack. Therefore, reviewing the GP record only may not be sufficiently accurate and it would useful to review hospital records, but this is not currently possible (Herrett et al., 2015; Nicholson et al., 2013).

Finally, a major limitation of the thesis is that we have only concentrated on cardiovascular and gastrointestinal drugs, and did not take into consideration the non-cardiovascular and non-gastrointestinal drugs, which patients were taking. Thus our studies do not give a full picture of the polypharmacy burden, but only of the polypharmacy associated with cardiovascular and gastrointestinal drugs. To undertake an evaluation of all drugs would have been too time-consuming because of difficulties in coding of medicines in CPRD, but clearly this is important to pursue in the future.

Future research could also investigate and evaluate how multimorbidity and polypharmacy affect the healthcare system, and the burden posed by individual patients on the healthcare system, but also to assess the burden on patients themselves of repeated attendances to outpatient clinics, GP appointments, and sometimes, admission to hospital. Such data is important to understand how clinical pathways can be modified in the future to help the healthcare system cope with the growing burden of polypharmacy and multimorbidity.

4.5 Conclusion

To summarise, there are increasing concerns about multimorbidity and polypharmacy in older people. The main purpose of the current study was to illustrate the changing patterns of medication prescribing practice in older people over the past 20 years with an emphasis on cardiovascular and gastrointestinal diseases. It provided a comparison of the prescription patterns between the beginning of the study period (2001–2005) and the end (2016–2020). Additionally, we compared the number of total cardiovascular and gastrointestinal drugs received in the period between 2001 and 2020, which showed a significant difference in prescription patterns over the last 20 years. Clearly part of this polypharmacy is appropriate because of advances in medicine and physician adherence to the latest guidelines. However, there is also a significant burden of inappropriate polypharmacy which can lead to patient harm, as seen in the recent evaluation from Liverpool, which showed that adverse drug reactions accounted for over 15% of hospital admissions (Osanlou et al., 2022). It is therefore incumbent of researchers and clinicians to better understand polypharmacy patterns in individual patients, and minimise the adverse consequences of polypharmacy which include non-adherence, drug-drug interactions and adverse drug reactions.

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